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EDITORIAL

Is it time to stop starving premature infants?

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The past 40 years have witnessed a near miraculous increase in the survival of extremely premature babies. The common practice in many neonatal intensive care units that includes withholding enteral feedings for days to weeks, and simultaneously providing very low amino acid and lipid intakes prompted the concern for the subsequent growth, neurodevelopment and adult health of these individuals, and was the focus of an NIH (National Institutes of Health) workshop approximately a decade ago.[1] Despite several studies, clinical practice has been slow to change. Could withholding amino acids be tantamount to not providing antenatal steroids, postnatal surfactant, continuous positive airway pressure or mechanical ventilation? The immediate results may not be quite as dramatic, but the effects of limiting these nutrients could be devastating. The two articles in this edition of the *Journal of Perinatology*[2,3] aptly augment the burgeoning evidence, which, for some, is intuitively obvious—it's really ok to nourish premature infants.

We have clear indications that the protein accretion rate in the fetus and hence in the premature infant approximates $4\,g\,kg^{-1}$ per day.[4,5] Stress and urinary losses further amplify these requirements.[6] The extremely low birth weight infant on a per weight basis, thus requires approximately three times the amount protein than that required by an adult or even by a term infant. We know from examining the intrauterine growth curves that a 28-week gestation premature infant who remains in the uterus under healthy conditions nearly triples in weight before term birth. During this time, the fetus undergoes major developmental milestones in brain and other organ development. When born prematurely, compared with *in utero* growth, these infants undergo significant extrauterine growth delays,[7] which are known markers for neurodevelopmental impairment[8–10] and are largely because of iatrogenic undernutrition.

Despite this, many neonatal clinicians persist in limiting amino acids shortly after birth. Concerns of high blood urea nitrogen, metabolic acidosis and metabolic imbalances lingering since the early days of neonatal intensive care have largely been obviated by newer amino acid preparations.[11] Studies comparing high vs low intakes of amino acids in the first several days after birth have diminished most of the safety concerns.[12,13] Furthermore, evidence showing decreased catabolism,[14,15] as well as increased growth, head circumference and even neurodevelopment with higher amino acid intakes is emerging.[16] Recently, there have been several important reviews of the topic of provision of amino acids for very low birth-weight infants that make it clear that the time has come for providing gestational age-appropriate intakes to these infants.[17–19]

Of interest is a recent article that might be interpreted as showing a negative effect of higher administration of early amino acids.[20] In this study, a comparison of advancement to 3.5 vs $2.5\,g\,kg^{-1}$ per day did not improve growth. The finding of several blood amino acid concentrations that were outside of the ranges usually found in term infants prompted the authors to state 'we cannot be certain that subtle increases in amino acid levels in the higher-dose group in our study are safe for the developing brain of premature neonates.' This statement should not be misinterpreted to mean that, we should continue with providing low levels of amino acids to premature infants. Studies based on blood amino acid concentrations are difficult to interpret. Altered concentration may occur because of catabolic proteolysis, increased metabolism or limited metabolic capability; term amino acid concentrations also do not reflect normal concentrations in preterm infants.[21] The two studies in this issue of the *Journal of Perinatology*, are pertinent in that they nicely augment earlier research in this area. One supports that a modest rise in BUN (a major earlier concern) is consistent with the utilization of amino acids as a source of energy.[2] The other done partially as a quality improvement project showed that early amino acid supplementation results in the shortening of time to regain birth-weight and the prolonged requirement of parenteral nutrition.[3] These studies combined with the existing literature weigh heavily on the side of providing higher quantities of amino acids to the premature infant.

Another component of intravenous nutrition for the premature infant who is in further need of dogma contradiction pertains to lipid administration for premature infants. Many of these infants undergo prolonged periods wherein no or minimal lipids are provided, despite our knowledge that these infants are highly sensitive to essential fatty acid deficiency.[22] The common practices related to withholding lipids for hyperbilirubinemia, sepsis, ventilatory status, and thrombocytopenia are based on traditions rather than sound scientific evidence. The common practice of frequent monitoring of triglycerides and cholesterol is also based on a poor scientific foundation, and there are no scientifically based guidelines on critical values and what to do with laboratory values once they are obtained.

Additional studies that will fine tune intravenous as well as enteral nutrition for premature infants are clearly needed. However, starving premature babies is no longer an option!

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