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EDITORIAL

Extrauterine growth restriction: is it preventable?☆,☆☆

Restrição do crescimento extrauterino: é possível evitar?

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Longstanding recommendations by the American Academy of Pediatrics,[1,2] the Canadian Paediatrics Society,[3] and the European Society of Paediatric Gastroenterology, Hepatology, and Nutrition[4,5] state that the nutritional management of preterm infants, especially of extremely preterm (EPT) infants, should support growth at a rate that approximates the rate of intrauterine growth. However, extrauterine growth restriction (EUGR) continues to be prevalent, occurring in the majority of extremely preterm (EPT) infants.[6–8] EUGR is typically defined as a growth measurement (weight, length, or head circumference) that is ≤ 10th percentile of the expected intrauterine growth for the postmenstrual age (PMA) at the time of discharge;[9] 36 weeks' PMA or 40 weeks' PMA (term-equivalent age) are often used to compare the incidence of EUGR between neonatal intensive care units.

A number of factors are known to contribute to this observation. The major factor is likely the development of significant protein and energy deficits during the first several weeks of life, which prove difficult to reverse.[10] Furthermore, these deficits increase as gestational age decreases. Nutritional practices common during the past 20 years, such as the mean caloric and protein intake provided, have also been shown to correlate with growth.[11–13] Other factors independently associated with EUGR have included intrauterine growth restriction (IUGR or small-for-gestational age [SGA]), male gender, need for assisted ventilation on the first day of life and the prolonged need for respiratory support, length of hospital stay, and the development of neonatal morbidities such as bronchopulmonary dysplasia (BPD), necrotizing enterocolitis (NEC), and late-onset sepsis.[6,9,13]

Efforts during the past ten to 15 years to develop standardized feeding guidelines have begun to show some success in reducing the incidence of EUGR. Such guidelines provide intense nutritional support through a combination of early parenteral nutrition and early enteral nutrition, followed by a progressive reduction of parenteral nutrition, as enteral feeding volumes are steadily advanced to full enteral nutrition.[14–16] Compared with historic controls, benefits of this approach have included an earlier regaining of birth weight, an earlier achievement of full enteral nutrition, reduction in the duration of PN, and improved anthropometrics at 36 weeks' PMA or discharge.[14,17] Furthermore, standardized feeding guidelines have been associated with less NEC and less late-onset sepsis,[15,18] both of which have been associated with EUGR.

The aims of the article by Lima et al. in this issue of Jornal de Pediatria[19] were to determine the frequency of EUGR in very low birth weight (VLBW, < 1,500 g BW) infants managed at four neonatal centers in Rio de Janeiro, and to evaluate the influence of selected perinatal variables, clinical practices, and neonatal morbidities on the incidence of EUGR. Fenton[20,21] growth charts were used to identify appropriate for gestational age (AGA) and SGA infants; AGA infants had a BW for GA z-score > -1.29 (10th percentile) and SGA infants had a BW for GA z-score ≤ -1.29 (10th percentile). For their analyses, IUGR and EUGR were defined by weight or head circumference (HC) z-scores ≤ -2 for corrected GA

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at birth for IUGR and at hospital discharge for EUGR, and EUGR was used as the primary outcome variable. Univariate and logistic regression analyses were used to identify variables that were associated with weight z-scores $\leq$ -2 and head-circumference z-scores $\leq$ -2 at hospital discharge.

Overall, of the 570 VLBW infants included in the study population, 49% were males and 33% were SGA at birth. At discharge, 26% displayed EUGR considering weight and 5% when considering HC. However, 54.2% of the SGA infants had EUGR at discharge considering weight and 7.4% considering HC, while only 12.3% of the AGA infants had EUGR at discharge considering weight and 4% considering HC. In comparison, defining EUGR as anthropometric measurements $\leq$ 10th percentile, Clark et al.[9] reported an incidence of EUGR in infants between 23 and 34 weeks GA of 28% for weight and 16% for HC, Shan et al.[13] reported an incidence in infants < 37 weeks' GA of 56.8% for weight, and Stoll et al.[7] reported an incidence in infants 22 to 28 weeks' GA of 79% for weight. It should be noted that the use of different intrauterine growth curves by these investigators contributed to the variability in the incidence of EUGR.

Univariate analyses demonstrated that maternal hypertension, male gender, SGA at birth, RDS, and length of hospital stay were significantly associated with weight z-score at hospital discharge. Regarding HC z-score at hospital discharge, univariate analyses identified significant associations with mechanical ventilation, oxygen use at 36 weeks, PDA, and length of hospital stay.

Logistic regression analyses were performed using the weight z-score $\leq$ -2 and HC z-score $\leq$ -2 corrected GA at hospital discharge as outcomes. Length of hospital stay, RDS, PDA, and SGA at birth remained in the final weight model, while length of hospital stay, oxygen use at 36 weeks, and SGA at birth remained in the final HC model.

Therefore, the perinatal variables, clinical practices, and neonatal morbidities identified by Lima et al.[19] as contributing to the development of EUGR, are similar to those identified by other investigators.[6,9,13] It should follow then, that if we are attempting to reduce the incidence and severity of EUGR, we need to ask how the influence of any of contributing variables can be reduced or alleviated. Unfortunately, maternal hypertension, male gender, and SGA at birth may not be readily modifiable. However, several of these factors are modifiable. For example, the use of antenatal corticosteroids to stimulate pulmonary maturation will reduce the incidence and severity of RDS. Therefore, it should reduce the need for assisted ventilation on the first day of life, and might contribute to a reduction in the total duration of mechanical ventilation. Administration of antenatal corticosteroids also facilitates closure of the PDA. The implementation of standardized feeding guidelines that provide intense, early parenteral and enteral nutritional support has been shown reduce the incidence of EUGR by improving growth; achieving earlier nutritional milestones, reducing the incidence of BPD, NEC, and late-onset infection; mediating the severity of critical illness; and reducing the length of hospital stay.[13–18] Therefore, while EUGR may be unavoidable for some EPT infants, factors contributing to its development are certainly assailable.

In order to obtain outcomes such as reduced incidence of EUGR, it is important to understand the variables contributing to local outcomes. Lima et al. should be commended for performing such a study.[19] Although antenatal corticosteroid use was one of the perinatal variables collected in this study, a significant difference in its use was not observed in either the univariate or logistic regression analyses; hopefully because of extensive use by their obstetrical colleagues. Furthermore, the indication that nutritional practices were ''standardized in clinical protocols with equal levels of adherence'' at the four study neonatal units suggests that they are already aware of the importance of early, combined parenteral and enteral nutritional support in reducing the incidence EUGR.

Conflicts of interest

The author declares no conflicts of interest.

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