REVIEW ARTICLE

Extrauterine Growth Restriction: Need for an Accurate Definition

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Abstract

Neonates show considerable variation in growth that can be recognized through serial measurements of basic variables such as weight, length, and head circumference. If possible, measurement of subcutaneous and total body fat mass can also be useful. These biometric measurements at birth may be influenced by demographics, maternal and paternal anthropometrics, maternal metabolism, preconceptional nutritional status, and placental health. Subsequent growth may depend on optimal feeding, total caloric intake, total metabolic activity, genetic makeup, postnatal morbidities, medications, and environmental conditions. For premature infants, these factors become even more important; poor *in utero* growth can be an important reason for spontaneous or induced preterm delivery. Later, many infants who have had intrauterine growth restriction (IUGR) and are born small for gestational age (SGA) continue to show suboptimal growth below the 10th percentile, a condition that has been defined as extrauterine growth restriction (EUGR) or postnatal growth restriction (PNGR). More importantly, a subset of these growth-restricted infants may also be at high risk of abnormal neurodevelopmental outcomes. There is a need for well-defined criteria to recognize EUGR/PNGR, so that correctional steps can be instituted in a timely fashion.

Keywords: Body fat mass, Cohort of Indonesian PreTerm infants for long-term Outcomes study, Corrected gestational age, Delta-Z, Demographic factors, Extra-uterine growth restriction, Failure to thrive, Fenton growth chart, Genetic make-up, growth charts, Infant growth, Intra-uterine growth restriction, Intergrowth 21st charts, Infant feeding, Linear growth velocity, Maternal metabolism, Maternal and paternal anthropometrics, Medications, Newborn, Neonate, Neurodevelopmental outcomes, Neonatal morbidities, Placental health, Postnatal growth restriction, Postnatal malnutrition, Pre-conceptional nutritional status, Postnatal morbidities, Postnatal growth, Small for gestation, Term corrected age, Total caloric intake, Total metabolic activity, Weight gain velocity, Z-scores.

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Highlights

- Neonates show considerable variation in growth; assessment requires serial measurement of basic parameters such as weight, length, and head circumference.
- Biometric parameters at birth may reflect demographic factors, maternal and paternal anthropometrics, maternal metabolism, preconceptional nutritional status, and placental health. Postnatal determinants of growth include feeding, total caloric intake, metabolic activity, genetic factors, morbidities, and environmental conditions.
- Infants who have had intrauterine growth restriction (IUGR) and are born small for gestational age (SGA) may have low growth potential. Many have suboptimal neurodevelopmental outcomes.
- There is a need to accurately define extrauterine growth restriction (EUGR) so that correctional steps can be instituted in a timely fashion.

Introduction

Advancements in the field of neonatology over last two decades has led to improved survival of premature and low birth weight infants.[1,2] However, the growth of these premature and critically ill neonates remains a cause for concern. To define and monitor the growth faltering of these infants, many terminologies has been used in literature such as EUGR and PNGR,[3,4] failure to thrive,[4] and postnatal malnutrition.[5] Many definitions have been suggested for these terminologies and attempts have been made

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Table 1: Currently available identification tools for EUGR

Criteria	*Mild EUGR*	*Moderate EUGR*	*Severe EUGR*	*When to apply?*
1. Weight-for-age *Z*-scores[a]	Decline of 0.8–1.2 SD	Decline of >1.2–2 SD	Decline >2 SD	Not appropriate for first 2 weeks of life
2. Weight gain velocity[b]	<75% of expected weight gain for that particular age	<50% of expected weight gain for that particular age	<25% of expected weight gain for that particular age	Not appropriate for first 2 weeks of life
3. ≥2 of the following				Not appropriate for first 2 weeks, can be used subsequently in conjunction with other parameters if accurate length measurement is available.
• Length-for-age *Z*-scores[a]	Decline of 0.8–1.2 SD	Decline of >1.2–2 SD	Decline >2 SD	
• Length gain velocity[b]	<75% of expected length gain for that particular age 15–18 days	<50% of expected length gain for that particular age 19–21 days	<25% of expected length gain for that particular age	
• Days to regain birth weight (in conjugation with nutrient intake)	(>3–5 consecutive days of <75% intakes of estimated protein/calorie)	(>5–7 consecutive days of <75% intakes of estimated protein/calorie)	>21 days (>7 consecutive days of <75% intakes of estimated protein/calorie)	Preferred for first 2 weeks of life

[a]Expected *Z*-score for weight for age and length for age. [b]Weight gain velocity and linear growth velocity were estimated using online calculator (www.peditools.org). In this calculator, weight gain velocity is estimated by using the World Health Organization (WHO) methods; weight increments are classified by birth-weight category presented in 1-week and 2-weeks intervals from birth to 60 days.[21]

to correlate these with neurodevelopmental and other clinical outcomes,[3,6–8]

Infant growth rates have been followed on charts such as the Fenton,[9] British,[10] and Italian.[11] Growth parameters have been studied in greater detail at some time points such as at a postnatal age of 28 days, postnatal and/or corrected gestational ages of 36–40 weeks, or at the time of discharge from NICU. Similar to full-term infants, preterm infants also grow along these growth curves.[12,13] The growth trajectories may get altered during periods of high-acuity illness, which might cause one or more anthropometric parameters to drop in terms of centile ranks at discharge or at term corrected age.[14,15]

Many studies have shown that drops in weight centiles may predict suboptimal neurodevelopmental outcomes.[4,6,7] Altered length[16,17] and head circumference[14,18–20] at corrected 36 weeks, at discharge, and/or and poor weight gain post-discharge have also been associated with poor developmental outcomes. However, we still have not been able to identify critical thresholds of these parameters. There is a need to define EUGR in terms of weight alone or in combination with length, head circumference, body composition, and genetic markers, and genetic potential based on parental anthropometric indices. Growth monitoring is also important for interpretation of postnatal weight loss and loss of growth centiles during high-acuity illness; we currently interpret our findings by comparing with the reference fetus and arbitrary statistical growth percentile cut offs. The objective of this article is to extensively review the current literature and provide uniform definition of EUGR postnatally,[21,22] while answering few important questions which lead the way.

We Still Need to Agree on a Single Definition of Extrauterine Growth Restriction

To assess the appropriate medical and nutritional interventions and to predict auxological long term outcomes, a consensus definition of EUGR is still needed. We recommend rectification, not only in the criteria to define EUGR but also the method and tool for growth monitoring. Until a consensus defines EUGR, the recommendations from "Identifying Malnutrition in Preterm and Neonatal Populations: Recommended Indicators" (Table 1)[5] and "Extrauterine Growth Restriction: Definitions and Predictability of Outcomes in a Cohort of Very Low Birth Weight Infants or Preterm Neonates,"[23] which defines EUGR as longitudinal (if the weight loss is more than one standard deviation (SD) between birth and a given *t*-time and cross sectional (if weight was below the 10th centile at a given *t*-time). A recent prospective cohort study from Jakarta, Indonesia [the Cohort of Indonesian PreTerm infants for long-term Outcomes (CIPTO) study] to study preterm infants born at the Cipto Mangunkusumo General Hospital has also provided important information.[24] They defined EUGR (as in Table 1) as a decline in the weight-for-age *Z*-score of above or equal to 1.2 and have reported related outcomes.

Are we Using Appropriate Metrics to Define Extrauterine Growth Restriction?

We are not sure if it is appropriate to assess growth using a single-point, single-parameter measurement such as weight. Weight measurements show high variability, and we have still not identified one growth chart as better than others for plotting growth of preterm infants. We are also not certain whether a specific set of growth charts can better assess the initial postnatal weight loss and post discharge catch-up. These questions are important in identification of EUGR.

Most studies still use a single point, single-parameter measurement such as weight at corrected 36 weeks' gestation or at discharge.[25–29] This is a convenient way to define EUGR but many studies have identified that there is a good catch-up between 36–40 weeks' gestation;[11,30,31] EUGR has been defined in literature using the following:

- Percentile ranks (<3rd and <10th percentiles) at 36 weeks/discharge,[32]
- The *Z*-scores (*Z*-score of 1 or 2) for weight loss from that at birth,[33]
- The *Z*-score at discharge of < −1.5 of intrauterine growth or standard postnatal growth,[26,34,35]

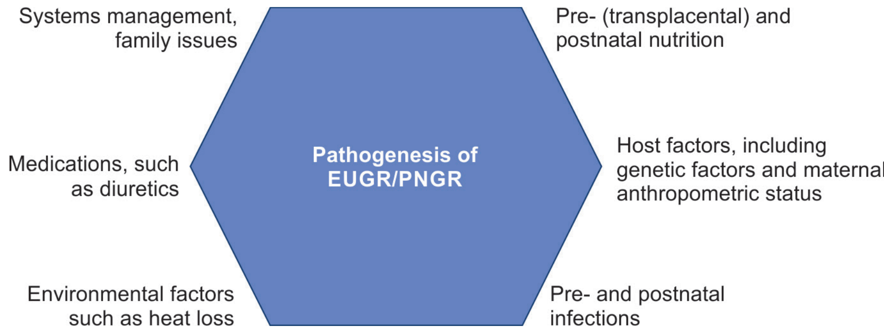

Fig. 1: Multiple factors are likely involved in the pathogenesis of EUGR/PNGR

- Drop in *Z*-score (delta-Z) from birth to 36 weeks corrected gestational age or at discharge.[36,37]

Shah et al.[6] compared the definitions related to both percentiles (<3rd and <10th percentiles) at 36 weeks' discharge, and *Z*-score (1 or 2 *Z*-scores) losses from birth weight. Zozaya et al.[7] compared *Z*-scores at discharge of below −1.5 of intrauterine growth or standard postnatal growth and drop in *Z*-score (delta-*Z*) from birth to corrected 36 weeks' gestational age or at discharge. Both studies concluded that the drop in *Z*-scores has a higher predictive value in relation with neurodevelopment outcome than a single time point measurement of weight less than 10th percentile.

Currently there is no consensus about which growth monitoring tool is better for assessment of growth in preterm infants during postnatal period. There are two following standard growth charts available: (A) the Fenton growth chart is a reference chart based on a cross-sectional study population[9] and (B) the Intergrowth 21st charts (IG-21)[38] that are based on a postnatal longitudinal study population. In accordance with the available literature, growth failure defined as a *Z*-score drop of >1 from birth to discharge in terms of weight, length and head circumference[7,23,39] has shown that that PNGR was less common with IG-21 as compared to Fenton[40–45] and is strongly associated with poor long-term outcome. Larger studies are still required to identify the most optimal growth assessment tool.

We Need to Consider Body Composition in Addition to the Conventional Anthropometric Measurements to Define Extrauterine Growth Restriction/Postnatal Growth Restriction

Weight gain, as an isolated index, may not be the most appropriate method to assess growth because weight is an indirect indicator of body composition (lean body mass + fat tissue + body fluid).[22] The lean body mass is likely to be more accurate as a predictor, and fat tissue may be the least important. In a systematic review and meta-analysis, Johnson et al.[46] and Gianni et al.[47] showed that preterm infants at corrected term gestational age of 40 weeks had a higher proportion of body fat than comparable full-term infants. The preterm infants in this cohort had less lean body mass, and this continued to be a matter of concern until 5 years of age. In another consideration, all preterm infants show a variable degree of physiological weight loss in the first few days after birth due to loss of extracellular fluid. This is reflected in growth charts as loss of growth percentiles.[12] This fluid loss is important for hemodynamic and physiological stability of these infants.[48,49] If a preterm infant is discharged from the hospital during this period of physiological weight loss, these changes will be documented as EUGR but Rochow et al.[12] showed that they subsequently regain normal growth trajectories. The WHO recommends body mass index (BMI) and weight-for-length as better standards for monitoring growth during childhood,[50] but these guidelines cannot be readily extrapolated for preterm infants. In these patients, the body composition will remain concerning even if they gain weight because the length will likely not change proportionately.[51,52] We believe that instead of using a single-point, single-parameter measurement such as weight, following the three most commonly used anthropometric parameters (weight, length and head circumference) over time might be better.

The Impact of Suboptimal Growth goes Beyond Somatic Consequences

In premature infants, neurodevelopmental outcomes are an important indicator of the quality of care. Many recent studies emphasize the effect of nutrition on neurodevelopmental outcome of premature infants.[53–55] Others suggest that preterm infants with multiple morbidities grow slower than controls who have been relatively healthy.[14,15,56] Hence, optimization of nutrition can potentially improve both growth and developmental outcomes. However, weight below 10th percentile at a single time point (36 or 40 weeks' corrected gestational age, or at discharge) is not the only growth indicator that is associated with poor developmental outcome;[4,6,7] length[16,17] and head circumference[16,18–20,57–59] may also be important predictors.

Infants who are born SGA[60] have shown slower growth during their hospital stay.[7,14,57–59] They are at increased risk of multiple neonatal morbidities,[5,56] neurological injury such as intraventricular hemorrhage and periventricular leukomalacia,[14] and are at risk of developmental delay. However, these are complex issues that extend beyond infant health; parental cognitive capacity, involvement, education, and socioeconomic status are also important predictors of developmental outcome.[61–63] A cursory look at the host–infections–environment–therapy–nutrition–systems management hexagon that we have been using in this journal to study disease pathogenesis suggests that there is a clear possibility of multifactorial origin (Fig. 1).[64] There is a need for an in-depth, careful analysis to determine the relative weightage of each of these nodes.

Conclusion

Extrauterine growth restriction/PNGR is an important problem in recovering premature/critically ill infants and cannot be ignored. To define EUGR appropriately is the need of the hour and growth monitoring of preterm infants using appropriate growth charts should be encouraged to identify early deviance in growth trajectories. Only then we will be able to institute relevant interventions in a timely fashion. The association with neurodevelopmental outcomes increases its importance even further; it may enrich our currently used single-point, single-parameter measurement at 36 weeks or at corrected term gestational age. If we do not have an optimum way of measurement, it will remain difficult to compare the impact of many prophylactic/therapeutic interventions.

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