A New Milestone in the NICU: New Growth References for Preterm Infants

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Historical view of growth reference in preterm infants

In 1977, The American Academy of Pediatrics Committee on Nutrition published a statement asking for "a prompt postnatal resumption of growth to a rate approximating intrauterine growth because this is believed to provide the best possible condition for subsequent normal development." (1) At that time, at least two growth reference charts have been published. (2,3) These "intrauterine" growth charts were developed by taking measurements at the time of birth from infants born across a range of gestational ages. The measurements were typically grouped by the completed week of gestation (e.g., measurements from infants born between 24 weeks 0 days and 24 weeks 6 days were grouped together). Within each group, the measurement values at each predefined corresponding percentile (e.g., the 3rd, 10th, 50th, 90th, and 97th percentiles) can be calculated and plotted, with the x-axis being the gestational age in weeks and the y-axis being the birth measurement values for the percentiles. The measurement values that belong to the same percentile across gestational age were connected to form a curve for each percentile.

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Under the assumption of a skewed normal distribution of the measurement values (4–6), a power transformation proposed by Box and Cox can be applied to render the distribution of the measurement values normal. (7) The distribution of the measurement values at each completed gestational week can be summarized by three parameters—the Box-Cox power *Lambda* (L), the mean *Mu* (M), and the coefficient of variation *Sigma* (S). All three parameters—the L, M, and S—can then be plotted separately against the completed gestational age in weeks. Using the method of penalized maximum likelihood, the L, M, and S curves can be individually smoothed, and as a result, the percentile lines become smooth curves. (6)

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The LMS method is the foundation of the Fenton growth charts for preterm infants. (8,9) The revised 2013 Fenton growth charts were based on a meta-analysis of six growth chart projects from Germany, the USA, Canada, Australia, the UK, and Italy. (9) Notably, while all six studies were used to generate the weight curves, only two studies (USA and Italy) were used for the length and head circumference curves. The developers of the revised Fenton growth charts connected the percentile curves to the 2006 World Health Organization Child Growth Standards at 50 weeks of gestation by extending the cubic splines between 36 and 50 weeks.

Issues with intrauterine growth charts

There are several significant issues associated with growth references developed using birth measurements:

(1) The growth curves aim to represent intrauterine growth indirectly by measuring "fetal growth at the time of birth." Consequently, infants affected by severe placental insufficiency, leading to growth restriction and being small for gestational age, may be overrepresented in the cohort due to the medical necessity of delivery to ensure maternal and fetal well-being. (10)

(2) Specific to the 2013 Fenton growth charts, mathematically connecting the intrauterine growth curves (with data from 23 to 40 weeks gestation) to the WHO Child Growth Standards (11) (with data from birth to 24 months for the longitudinal component) may be problematic. While done with the intent to extend the growth reference to 50 weeks PMA, it may distort the data reference for values between 36 weeks and 50 weeks. As a result, no data supports the accuracy of these mathematically-derived, smoothed curves between 36 and 50 weeks of gestation. These curves tend to exhibit a bias towards the right, causing an underestimation of infants classified as large for gestational age (>90th percentile) and an overestimation of those classified as small for gestational age (<10th percentile).

(3) Intrauterine growth occurs under low oxygen tension and within a confined intrauterine environment. This contrasts with postnatal growth, which occurs in the isolette in ambient air or at higher oxygen levels if an increased oxygen fraction is blended into the respiratory support modality.

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Postnatal growth charts are available now for clinical use and research.

We have developed a new set of gender- and gestational age-specific growth references for preterm infants, suitable for clinical use and growth/nutrition research. We will now refer to it as **Chou's NICU postnatal growth charts for preterm infants**. The project began to compare postnatal growth under modern nutritional practices to intrauterine growth, utilizing real-world data from the Pediatrix Clinical Data Warehouse. We employed a sophisticated multi-level longitudinal analysis to derive growth estimates in a piece-wise fashion, with Dr. Hung-Wen (Henry) Yeh overseeing the model development process at Children's Mercy Research Institute.

The findings of this project were recently published in Nature Communications, revealing differences between postnatal and intrauterine growth, as well as a common pattern of postnatal growth across different gestational age groups. (12) Specifically, the postnatal growth pattern can be divided into three phases of weight gain, identified by calculating weight gain velocity in gram/kg/day and gram/day. These three phases of weight growth coincide with the three-interval modeling approach that the late Dr. Richard A. Ehrenkranz of Yale University School of Medicine adopted in his 1999 publication in *Pediatrics* on longitudinal growth of hospitalized very low birth weight infants. (13) Although the growth rate values may differ, the consistency in growth patterns between these two studies conducted a quarter-century apart suggests that the pattern does exist and that postnatal growth of preterm infants follows an alternative trajectory compared to their fetal counterparts.

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To make the modeled postnatal growth trajectory curves accessible to the public, we created a series of web applications using R and the Shiny package. Anyone can sign up for an account to fully utilize the web application's functionality.

Figure 1. *Screenshot of the nicugrwoth.app web application portal. The "Simplified Version" link will take the users to abbreviated versions of the web applications for weight, length, and head circumference, allowing measurement data entry, plotting, and trajectory percentile calculation. The Register link will take the users to the Registration page for account sign-up. The "Full Version" link will take the users to the Sign-In page of the full-version web application, which allows data storage and retrieval and other enhanced functions, including recommendations on the timing of transitioning to the WHO Child Growth Standards, as well as z-score/percentile data and plot export.*

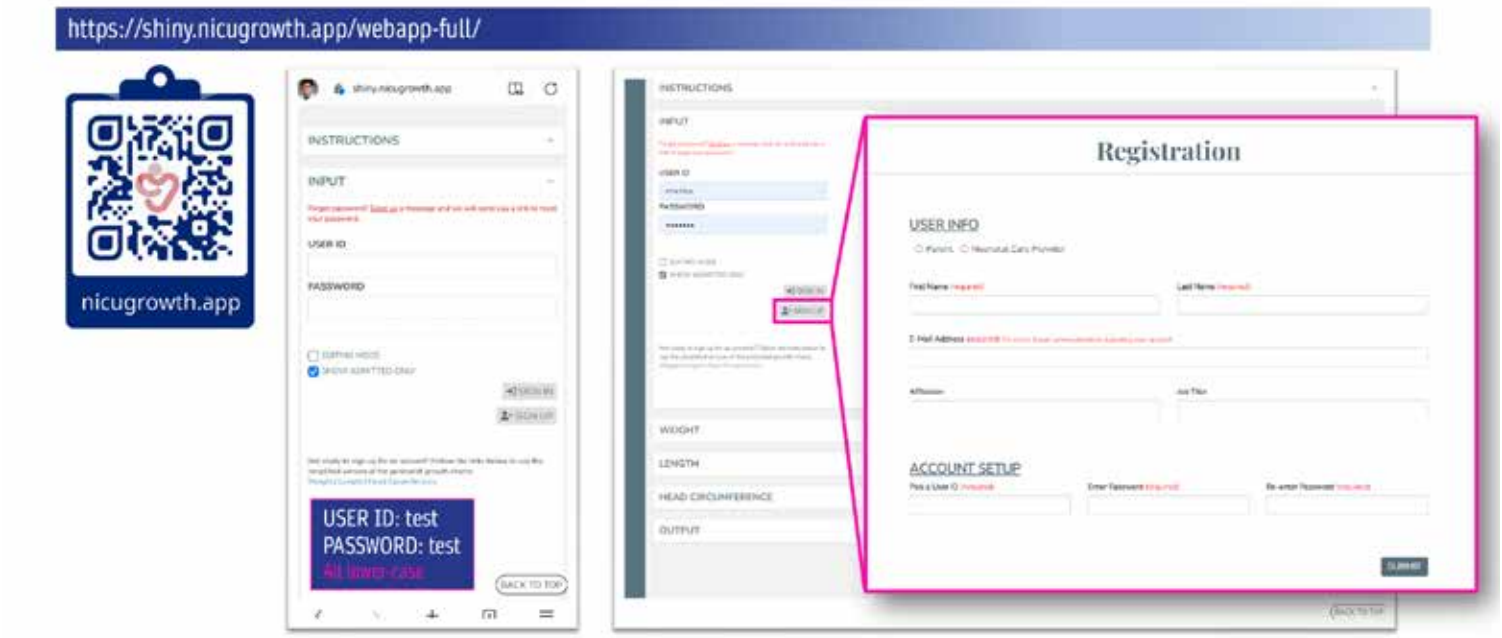

Figure 2. *Full-version web application. The full-version web application can be accessed using the listed URL or the QR code. The full-version web application is optimized for viewing on mobile devices. The users may use the demo account (username/password:test) to trial the web application. The links to the Registration webpage and the simplified version of the weight, length, and head circumference web applications are available on the Sign-In page.*

To access it, please visit https://nicugrowth.app (Figure 1) or use the QR code for direct access to the full-version website (Figure 2). The nicugrowth.app website serves as the portal for web applications. The Media page includes an introductory video and video clips to demonstrate web application use. The web applications have been optimized for mobile devices. These growth charts are suitable for infants born between 22 ⅐ and 34 3/7 weeks' gestation.

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Since these new growth charts were developed using rigorous statistical tools and consider individual variations in birth size and growth rate, we believe this tool will simplify the interpretation of preterm infants' growth. It will make guiding nutrition delivery and necessary interventions to support adequate growth more intuitive.

Furthermore, all or a subset of the growth measurements for each infant can now be automatically summarized into a percentile number using the postnatal growth charts—*a trajectory percentile*. This convenience allows for an easy transition to the WHO Child Growth Standards with a matching percentile (think of the summarized trajectory percentile as the birth percentile). Additionally, when an infant recovers from a significant illness and is ready for nutritional support, clinicians can use the pre-illness trajectory percentile from a subset of measurements taken before the illness to guide post-illness nutrition administration, facilitating genuine "catch-up" growth.

Lastly, even though it remains an ongoing endeavor, we anticipate that we can now accurately redefine postnatal growth failure by enabling peer-to-peer comparisons of growth with this new reference, allowing us to determine whether an infant is deviating from the percentile line.

Summary

Postnatal growth of preterm infants diverges from intrauterine growth following preterm birth. Tracking postnatal growth using user-friendly tools like **Chou's NICU postnatal growth charts for preterm infants** is intuitive and can easily complement the limitations of intrauterine growth charts in clinical settings. Feel free to contact us if you intend to integrate this growth reference tool into your electronic healthcare records.

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