Commentary

Growth charts for preterm infants: Challenging at birth, problematic during growth

Aneurin Young[1, 2] and Mark J Johnson[1,2,3]

Affiliations

1. Human Development and Health, Faculty of Medicine, University of Southampton, Southampton, UK
2. Department of Neonatal Medicine, University Hospital Southampton NHS Foundation Trust, Southampton, UK
3. National Institute for Health Research Southampton Biomedical Research Centre, University Hospital Southampton NHS Foundation Trust and University of Southampton, Southampton, UK

Corresponding Author

Mark J Johnson (Email: m.johnson@soton.ac.uk)

Funding: AY is funded by a National Institute of Health Research Academic Clinical Lectureship. MJJ receives funding from the National Institute for Health Research Southampton Biomedical Research Centre

Disclosures: None

ORCiD: Aneurin Young: 0000-0003-3549-3813 Mark J Johnson: 0000-0003-1829-9912

Word count: 1325

AUTHOR PROOF

The maxim that a preterm infant's growth should mimic that of an equivalent foetus seems simple, elegant, and almost self-evident. It is no surprise that both North American and European authorities recommend such a pattern of growth.[1,2] However, this seemingly common-sense instruction is bedevilled by complications in its application. In this issue of *Paediatric and Perinatal Epidemiology*, Fenton and colleagues[3] make significant progress in addressing one of the thorniest issues: what is the actual normal growth pattern of a foetus? A rigorous understanding of foetal growth is a vital prerequisite for comparing the growth of preterm infants to an equivalent foetus, but the difficulties of understanding their ideal growth trajectories do not end there. In recent years, the desirability of foetus-equivalent growth has repeatedly been called into question.[4,5] Fenton and her co-authors acknowledge that growth trajectories based on real infant growth curves may ultimately prove more valuable if conceptual and technical challenges can be overcome.

Determining foetal growth patterns

The foetus is extremely inconveniently situated for anthropometric assessment, suspended in its amniotic fluid and sequestered within its mother. A recent large WHO study has identified normal patterns of estimated foetal weight by antenatal ultrasound, but these are necessarily based on models relying on spatial measurements rather than direct weighings.[6] The most obvious way to assess the changing weight (or length or head circumference) of the foetus is to take these measurements from preterm infants at birth, in the knowledge that they will reflect the size of a foetus at that gestation. Indeed, that is the method by which current growth charts were created. However, as Fenton elucidates, it is readily apparent that the population of infants born preterm is profoundly unrepresentative of the normally growing foetus. Many (perhaps most) preterm births occur in the context of some

AUTHOR PROOF

aberration in foetal or placental development, or maternal ill health, any of which is liable to impact deleteriously on the growth of the foetus. What is more, foetuses which are exhibiting slow or arrested growth may be deliberately delivered prematurely (by caesarean section or induction of labour), either solely due to their growth deficiency or because of medical conditions which cause that slowing of growth. Therefore, the statistical distribution of the size of preterm newborns will be significantly skewed towards smaller infants compared to the general fetal population. This results in growth-restricted infants being labelled as appropriately grown as they are compared to a significantly growth-restricted cohort rather than the healthy foetal cohort.

Fenton et al. sought to ameliorate this issue by limiting their cohort of preterm newborns to those who they expect to have exhibited normal foetal growth. This was achieved by using large studies measuring infants in developed countries who were the result of pregnancies affected neither by common causes of intrauterine growth restriction (namely, maternal diabetes or hypertension, and foetal abnormalities) nor by medically initiated preterm birth. These exclusion criteria will inevitably leave in the cohort a significant number of infants whose growth was restricted for some other reason. It is notable that most included databases did not exclude infants born to mothers who smoked during pregnancy, and smoking during pregnancy was relatively common during the period in question in some of the countries providing the largest cohorts (Netherlands 18.6%, Australia 24.4%, Finland 22.4%).[7] Nevertheless, the authors provide compelling evidence that their inclusion restrictions normalised the implausibly flat curves and low weight gain velocities at the lower centiles in earlier charts, and brought birthweight data closer to the pattern of

AUTHOR PROOF

ultrasonographic foetal assessments (although the 3rd percentile still appears slightly suppressed compared to WHO ultrasound-based data).

The charts presented by Fenton et al. undoubtedly improve the reliability of preterm growth charts to assess foetal growth at the point of birth. They are a much better guide as to whether an infant experienced intrauterine growth restriction than current charts, and will help to highlight such infants for special attention.

Should preterm infants follow foetal growth patterns?

Conversely, the utility of these charts and others like them in assessing the adequacy of growth trajectories in preterm infants is much less certain. Epidemiological and physiological studies over several decades have identified that preterm infants do not,[8,9] and likely should not,[4] simply follow the centile line on which they are born as they grow. Early weight changes are especially unlike foetal patterns, with normal fluid loss after birth prompting early physiological weight loss (or static weight at earlier gestations). Fenton et al. acknowledge that no inference can be drawn about the optimal pattern of growth as it relates to the cross-sectionally derived centile lines on their charts; early changes are likely to reduce the centile and there is no evidence to support a notion that they should then remain on their new centile, return to their birth centile or exhibit any other particular pattern. Another Canadian group has previously recommended that an infant should follow a trajectory such that their size at 42 weeks postmenstrual age matches the centile on which they were born, although there is limited data to suggest that this growth pattern is associated with favourable long-term outcomes such as neurodevelopment and cardiometabolic risk in adulthood.[4]

AUTHOR PROOF

Towards target growth trajectories

With the advent of web-based platforms capable of carrying out complex statistical tasks quickly, it is now practical to generate target growth trajectories tailored to individual infants. Landau-Crangle et al.[4] used a deep understanding of early postnatal water loss, along with later growth velocities, to create individualized trajectories (based upon an infant's gestation, sex and birthweight) which conform to physiological expectations and cause an infant to reach their birth centile when they can be plotted on WHO charts at 42 weeks postmenstrual age. This was a powerful proof of principle, and they were able to show that growth similar to the target trajectory was associated with a favourable body composition at term equivalent age. However, no association between growth along this trajectory and important long-term neurodevelopment or cardiometabolic outcomes has been identified.

Fenton et al. recommend that growth trajectories should ideally be based on a cohort of healthy infants. However, comorbidities of prematurity are near-ubiquitous in those born significantly preterm, so no truly healthy cohort is available. Given the known association between early growth patterns and later outcomes,[10] it may be possible to retrospectively identify a cohort of infants who had good long-term outcomes and then recommend growth trajectories that mimic theirs. However, such approaches would perhaps need to consider multiple outcomes. Whilst several cohorts support the notion that faster growth is associated with improved neurodevelopmental outcomes, it is well established that growth in early life also influences the risk of cardiovascular and metabolic disease in adulthood, with some patterns of growth, particularly catch-up growth in infancy, associated with greater risk of disease.

AUTHOR PROOF

The charts presented in this issue of *Paediatric and Perinatal Epidemiology* represent a significant step forward in assessing the size of preterm infants at birth. They will be especially useful in assessing those who are growth-restricted and especially vulnerable, and will be important for researchers interested in growth restriction, as the new charts will better identify those with this diagnosis.

Future work in this field is likely to focus on identifying growth trajectories that support infants to reach their developmental potential after preterm birth, whilst at the same time minimising their risk of cardiovascular and metabolic disease in adulthood. As the work here by Fenton and colleagues demonstrates, several large cohorts of growth data for preterm infants exist, and many of these are based on datasets that have paired neurodevelopmental outcomes. However, understandably, no large contemporary cohorts yet exist that also contain data on these infants regarding their markers of cardiovascular and metabolic risk. Whilst an important next step will be to use existing data to generate growth charts based on optimal neurodevelopmental outcomes, it is essential to ensure data on longer-term cardiometabolic outcomes are collected as preterm infants age, so that such charts can continue to evolve over time.

AUTHOR PROOF

REFERENCES

ADDIN EN.REFLIST 1. American Academy of Pediatrics Committee on Nutrition. Nutritional Needs of the Preterm Infant. In: Kleinman RE, Greer FR, eds. Pediatric Nutrition. 8th edition. ed. Itasca, IL: American Academy of Pediatrics, 2019.

2. Agostoni C, Buonocore G, Carnielli VP, et al. Enteral nutrient supply for preterm infants: commentary from the European Society of Paediatric Gastroenterology, Hepatology and Nutrition Committee on Nutrition. *J Pediatr Gastroenterol Nutr* 2010;50(1):85-91. doi: 10.1097/MPG.0b013e3181adaee0 [published Online First: 2009/11/03]
3. Fenton TR, Elmrayad S, Alshaikh BN. Fenton third-generation growth charts of preterm infants without abnormal fetal growth: A systematic review and meta-analysis. *Paediatric and Perinatal Epidemiology* 2025
4. Landau-Crangle E, Rochow N, Fenton TR, et al. Individualized Postnatal Growth Trajectories for Preterm Infants. *JPEN J Parenter Enteral Nutr* 2018;42(6):1084-92. doi: 10.1002/jpen.1138 [published Online First: 2018/02/09]
5. Villar J, Giuliani F, Barros F, et al. Monitoring the Postnatal Growth of Preterm Infants: A Paradigm Change. *Pediatrics* 2018;141(2) doi: 10.1542/peds.2017-2467 [published Online First: 2018/01/06]
6. Kiserud T, Piaggio G, Carroli G, et al. The World Health Organization Fetal Growth Charts: A Multinational Longitudinal Study of Ultrasound Biometric Measurements and Estimated Fetal Weight. *PLoS Med* 2017;14(1):e1002220. doi: 10.1371/journal.pmed.1002220 [published Online First: 20170124]
7. Lange S, Probst C, Rehm J, et al. National, regional, and global prevalence of smoking during pregnancy in the general population: a systematic review and meta-analysis. *The Lancet Global Health* 2018;6(7):e769-e76. doi: 10.1016/S2214-109X(18)30223-7
8. Young A, Cole TJ, Cheng G, et al. Changes in the growth of very preterm infants in England 2006-2018. *Arch Dis Child Fetal Neonatal Ed* 2022 doi: 10.1136/archdischild-2022-324584 [published Online First: 20221028]
9. Rochow N, Landau-Crangle E, So HY, et al. Z-score differences based on cross-sectional growth charts do not reflect the growth rate of very low birth weight infants. *PLoS One* 2019;14(5):e0216048. doi: 10.1371/journal.pone.0216048 [published Online First: 2019/05/08]
10. Belfort MB, Rifas-Shiman SL, Sullivan T, et al. Infant growth before and after term: effects on neurodevelopment in preterm infants. *Pediatrics* 2011;128(4):e899-906. doi: 10.1542/peds.2011-0282 [published Online First: 2011/09/29]

AUTHOR PROOF