Small Beginnings, Complex Outcomes: Understanding Birth Size and Health Consequences

Ashish Jain, Shoham Majumder

Department of Neonatology, Maulana Azad Medical College, and Lok Nayak Hospital, New Delhi 110002, India
neoashish2008@gmail.com

INTRODUCTION

The neonatal period is a critical phase characterized by rapid growth and development, yet it is also a time of heightened vulnerability. Neonatal mortality, defined as death within the first 28 days of life, remains a pressing public health concern globally, with an estimated 2.3 million neonatal deaths occurring annually [1]. In India, despite notable improvements in maternal and child health in recent years, neonatal mortality rates remain high at 25/1000 live births, accounting for more than half of under-five deaths [2]. The intrauterine course and the point of transition to extrauterine life are the most critical determinants of immediate neonatal course as well as long term health. Within this context, birth size and gestational age play the most pivotal roles in shaping the trajectory of neonatal health outcomes. Low birth weight (LBW), typically defined as weighing less than 2500 grams at birth, and preterm birth, occurring before 37 weeks of gestation, are two key statistical thresholds. A significant proportion of neonatal illnesses can be attributed to complications related to LBW, and prematurity or a combination of the two.

The impact of intrauterine growth and prematurity extends beyond neonatal mortality to encompass a spectrum of morbidity patterns. The burden of neonatal mortality and morbidity associated with LBW and prematurity is influenced by a myriad of factors, including maternal health status, access to quality antenatal care, socioeconomic disparities, and environmental factors. Addressing these determinants requires a multifaceted and congruent approach encompassing interventions aimed at improving health of the adolescent girls, preconception care and counseling, maternal nutrition, enhancing antenatal care services, promoting safe delivery practices, and strengthening neonatal healthcare and referral infrastructure.

Fifty years back Bhargava et al published a paper in Indian Pediatrics wherein they explored the complex interplay between birth size, prematurity, and neonatal mortality and morbidity, drawing on prevalent Indian data to provide insights into the magnitude of the problem [3]. The study was conducted in Safdarjung Hospital, Delhi, over 6-months (January 01, 1973 to June 30, 1973) on 4748 consecutively born infants. Gestational age was estimated from day of last menstrual period and confirmed by a postnatal physical and neurological examination and neonates were classified into preterm (gestational age less than 37 weeks), term (gestational age 37-41 weeks) and post-term (gestational age 42 weeks or more) categories. Depending on their position in the intrauterine growth curves obtained from previous studies by the same authors [4], the term infants were classified based on their birth weight and the expected weight for gestation: (*i*) Group I: within 1 SD, (*ii*) Group II: between -1 SD and -2 SD (*iii*) Group III: below -2 SD and (*iv*) Group IV: above +2 SD. Prevalent to the practices of the time, group II was named by authors as Intrauterine Growth Retardation (IUGR) and group III was also called as small for dates (SFD). A total of 421 infants were preterm while 4327 were term and a distinct pattern of morbidity was observed in the various study groups. While the former had an overall morbidity of 62.7%, the later had a morbidity of 11.2%. In preterms, infections and intracranial and pulmonary hemorrhages constituted major causes of morbidity while in term infants the leading causes were anoxia, pneumonia and hypoglycemia. While 8% of the

preterms had hyperbilirubinemia, only 0.6% of the term babies suffered from the same. The incidence of infections in preterms was 18 times higher than in term infants. Among term infants, morbidities were higher in those with aberrant growth patterns. Additionally, there was a correlation between intrauterine growth and type of morbidity. Infants in the IUGR group showed higher incidence of infections, hypoglycemia and hyperbilirubinemia whereas SFD babies had higher infections, pulmonary hemorrhage and hypoglycemia. Large-for-date babies were predominantly afflicted with hypoglycemia likely due to maternal diabetes or prediabetes, and intracranial hemorrhage attributed by the authors to their sheer large size. Among babies with similar birth weights, preterm infants were more likely to have intracranial hemorrhage and hyperbilirubinemia whereas SFD babies suffered more from hypoglycemia and pneumonia.

THE PAST

That premature delivery and small size at birth reduced chances of neonatal survival was well known since ancient times and is mentioned in extant texts like the Bible. The fascination with fetal development dates back to ancient civilizations, where rudimentary observations of pregnancy and childbirth laid the foundation for understanding intrauterine growth. Early scholars such as Hippocrates and Galen documented prenatal growth patterns, albeit through qualitative descriptions rather than standardized classifications. The 19th century witnessed significant advancements in obstetrics and fetal medicine, leading to more systematic approaches to intrauterine growth assessment. The idea of plotting a child's anthropometric parameters on a chart to illustrate the pattern of growth was first conceived by Count Philibert de Montbeillard of France in the 18th century. He plotted his son's height every six month from birth till the age of 18 years. Henry Bowditch was the first to use the centiles to describe the growth of Massachusetts children in 1891 [5]. Utilising similar concept and taking advantage of the developing science of obstetric ultrasonography, Lubchenco's chart from 1963 was amongst the first intrauterine growth chart to be widely used in neonates [6]. Based on nearly 5000 babies of white ethnicity, it also classified newborns based on size at birth for the first time into SGA, AGA and LGA. Ehrenkranz used a multicentre prospective cohort study of 1660 neonates to develop postnatal growth charts based on actual longitudinal postnatal growth patterns of neonates [7]. Combining the cross-sectional anthropo-metric measurements of preterms at birth with the longitudinal postnatal data of term infants, fetal-infant growth charts were developed by Babson and Benda [8]. To harmonize the preterm growth charts with new WHO growth standards, Fenton and associates analysed 6 studies with 4 million infants to devise growth chart for preterm infants [9]. With the understanding that using the prescriptive, population-based and longitudinal charts for babies with optimal maternal health and intrauterine environment would be more appropriate rather that the charts derived out of the cross-sectional data of babies born at different gestations, a number of standard charts have been developed like the World Health Organization (WHO) Multicentre Growth Reference Study (MGRS) and INTERGROWTH-21. As survival has improved in smaller neonates, more minute subdivisions have been suggested to reflect the changing vulnerability of various gestational ages and birth weight [10].

THE PRESENT

The duration of pregnancy plays a vital role in evaluating prenatal development, with all existing definitions of fetal growth being specific to gestational age. Yet, accurately determining gestational age can pose challenges, and any mistakes in dating can result in mislabeling the infant, carrying potentially significant clinical consequences [11]. Similarly, a lack of consensus haunts the definitions in fetal growth patterns. Normally neonates with birth weight that falls between 10th and 90th centiles for gestational age are deemed "appropriate" for gestational age (AGA). Those falling below 10th are small for gestational age (SGA) whereas those beyond 90th are termed large for gestational age (LGA). However, this is a statistical quotient vis-à-vis population norms and does not consider the actual growth potential of the neonate in context, which is unique to every neonate. IUGR is a pathological diagnosis of true in utero growth faltering and may include newborns with birth weight above the 10th centile. Thus, neither do all SGA babies have IUGR, nor are all IUGR babies SGA. Historically the IUGR babies were divided into symmetrical and asymmetrical anthropometric types. The less common symmetrical type of IUGR have an earlier typical period of insult (usually genetic, chromosomal, or early pregnancy infections), proportionate reduction in weight, length and head circumference, less pronounced features of malnutrition but poorer prognosis. The asymmetrical type of IUGR is more common, with a disproportionately higher head circumference compared to weight or abdo-minal circumference (misleadingly termed as "head sparing") and with more pronounced features of mal-nutrition.

Due to the challenges in defining IUGR, its actual prevalence remains uncertain. However, it is believed that the prevalence is 10% in high-income countries, 19% in low-income countries, and the total neonatal deaths in low- and middle-income countries as a result of IUGR are 21.9%, and this rate is likely higher for stillborn infants [12]. Globally, IUGR ranks as the second most common

cause of perinatal health issues and deaths, following prematurity [13]. Risk of fetal death rises with the severity of growth restriction. While an SGA fetus less than the 10th centile faces a 1.5% risk of fetal death, risk increases to 2.5% for fetuses with a weight below the 5th percentile [14]. IUGR babies are also more likely to require admission to the intensive care unit after birth, where they need close monitoring and treatment for various complications associated with IUGR. It starts from increased need for operative delivery and higher possibility of resuscitation at birth as the chronically hypoxic fetus is unable to tolerate the acute stress imposed by transition at delivery. The maladapted intrauterine survival mechanisms cause hormonal and metabolic alterations that render the neonate susceptible to various complications postnatally. With suboptimal glycogen stores, poor muscle reserve and fatty tissues as gluconeogenesis substrates and increased sensitivity to insulin, nearly half of SGA babies develop hypoglycemia whereas a third of them have severe, prolonged, or recurrent hypoglycemia [15]. Poor brown fat depositions also increase the risk of hypothermia, which in turn exacerbates hypoglycemia. Respiratory vulnerabilities include respiratory distress syndrome. While chronic stress hormone exposures may accelerate lung maturity, this effect is negated by decreased alveolar number and function. Vascular remodeling and chronic lung diseases increase risk of pulmonary hypertension [16]. There is contradictory evidence whether IUGR by itself increases vulnerability to necrotizing enterocolitis, but incidence is particularly high in preterm babies with altered antenatal doppler flows. A myriad of other vulnerabilities including hematological (polycythemia and jaundice) and abnormal immunological responses are reported in IUGR babies.

In the long term, in-utero adaptations engender neurodevelopmental as well as cardiometabolic changes. IUGR babies have higher risk of cerebral palsy, lower neurocognitive scores, poorer attention, lower social coping skills and higher incidence of Alzheimer's disease [17]. Contrary to the previously believed "brain-sparing" response, neurodevelopmental prognosis may in fact be worse in such babies. The increased blood supply is suggestive of more severe brain injury and persists postnatally despite withdrawal of hypoxic environment. The developmental origins of health and disease (DOHaD) hypothesis suggests that the alterations in vascular architecture and hormonal axis in-utero increases the risk of insulin resistance, diabetes mellitus type 2, hypertension, obesity, and cardiovascular diseases (metabolic syndrome or syndrome X). Adults, born IUGR, have higher incidence of cancer, immune dysfunction, and shorter life span [18].

THE FUTURE

With increasingly better care available for lower gestational ages, the growth retarded fetuses represent a crucial arena of intervention for prevention of stillbirth, and neonatal death as well as morbidities, short and long term. Appropriate standards are still being debated and apprehensions are abundant about the one-size-fits-all nature of international growth standards. Customized growth charts, designed initially by Gardosi and colleagues, take in to account the individual growth potential of the neonate and have been rolled out in United Kingdom as part of the Growth Assessment Protocol and is geared to differentiate between IUGR and smaller fetal size due to physiological variation [19]. Apart from general improvement in maternal health and nutritional status, which is still the main reason of poor neonatal outcomes in developing countries, and some benefits of antithrombotic therapy when started early in women with risk of placental dysfunction, there is yet inadequate evidence for increasing fetal weight through targeted interventions or vasodilatation therapy. Since etiology of IUGR points to disruption in fetal energy source and metabolism, structural functions of cell surface membrane, cell proli-feration and apoptosis, and dysfunction of neuro-transmitter pathways, metabolomic studies to appraise maternal and fetal adaptive responses to the intrauterine environment in different populations may help in setting the ideal thresholds for prediction and diagnosis of fetal growth retardation [20].

CONCLUSION

Intrauterine growth restriction presents an enigma in obstetrics, as its causes and management remain elusive in many cases. In the fifty years since the article under review was published, despite several advances, questions linger regarding the etiology, and the variability in fetal response to compromised growth, confounding diagnosis, and treatment strategies. While doppler ultrasound aids in assessing fetal well-being, its predictive accuracy and optimal timing for intervention are unresolved. Additionally, interventions to mitigate postnatal consequences and longterm outcomes remain under investigation. Such studies in different populations may offer clues about specific prevention and early treatment and help these fetuses reach their destined optimal growth.

Funding: None; *Competing Interests*: None stated

REFERENCES

1. UNICEF. Neonatal mortality. Accessed on Mar 30, 2024. Available from: *https://data.unicef.org/topic/child-survival/neonatal-mortality/*
2. Ministry of Health and Family Welfare, Government of India. National Family Health Survey (NFHS-5), 2019-21,

India Report. Accessed on Mar 30, 2024. Available from: *https://dhsprogram.com/pubs/pdf/FR375/FR375.pdf*
3. Bhargava SK, Lall UB, Kumar A, Kumari S, Ghosh S. Morbidity pattern in newborns by gestation and intrauterine growth. Indian Pediatr. 1974;11:481-5.
4. Ghosh S, Bhargava SK, Madhavan S, Taskar AD, Bhargava V, Nigam SK. Intra-uterine growth of North Indian babies. Pediatrics. 1971;47:826-30.
5. Cole TJ. The development of growth references and growth charts. Ann Hum Biol. 2012;39:382-94.
6. Lubchenco LO, Hansman C, Dressler M, Boyd E. Intrauterine growth as estimated from liveborn birthweight data at 24 to 42 weeks of gestation. Pediatrics. 1963;32:793-800.
7. Ehrenkranz RA, Younes N, Lemons JA, et al. Longitudinal growth of hospitalized very low birth weight infants. Pediatrics. 1999;104:280-9.
8. Babson SG, Benda GI. Growth graphs for the clinical assessment of infants of varying gestational age. J Pediatr. 1976;89:814-20.
9. Fenton TR, Kim JH. A systematic review and meta-analysis to revise the Fenton growth chart for preterm infants. BMC Pediatr. 2013;13:59.
10. World Health Organization. Born too soon: Decade of action on preterm birth. World Health Organization; 2012. Accessed on Mar 30, 2024. Accessed on Mar 30, 2024. Available from: *https://www. who.int/publications/i/item/9789240073890*
11. Savitz D, Terry JW Jr, Dole N, Thorp JW Jr, Siega-Riz AM, Herring AH. Comparison of pregnancy dating by last menstrual period, ultrasound scanning, and their combination. Am J Obstet Gynecol. 2002;187:1660-6.
12. Lee AC, Kozuki N, Cousens S, et al; CHERG Small-for-Gestational-Age-Preterm Birth Working Group. Estimates of burden and consequences of infants born small for gestational age in low and middle income countries with INTERGROWTH-21st standard: Analysis of CHERG datasets. BMJ. 2017;358:j3677.
13. Ohuma E, Moller A-B, Bradley E, et al. National, regional, and worldwide estimates of preterm birth in 2020, with trends from 2010: A systematic analysis. Lancet. 2023; 402:1261-71.
14. Getahun D, Ananth CV, Kinzler WL. Risk factors for antepartum and intrapartum stillbirth: a population-based study. Am J Obstet Gynecol. 2007;196:499-507.
15. Harris DL, Weston PJ, Harding JE. Incidence of neonatal hypoglycemia in babies identified as at risk. J Pediatr. 2012; 161:787-91.
16. Morsing E, Gustafsson P, Brodszki J. Lung function in children born after foetal growth restriction and very preterm birth. Acta Paediatr. 2012;101:48–54.
17. Walker DM, Marlow N. Neurocognitive outcome following fetal growth restriction. Arch Dis Child Fetal Neonatal Ed. 2008;93:F322–5.
18. Calkins K, Devaskar SU. Fetal origins of adult disease. Curr Probl Pediatr Adolesc Health Care. 2011;41:158-76.
19. Gardosi J, Francis A, Turner S, Williams M. Customized growth charts: rationale, validation and clinical benefits. Am J Obstet Gynecol. 2018;218:S609-18.
20. Troisi J, Symes SJK, Lombardi M, et al. Placental metabolomics of fetal growth restriction. Metabolites. 2023;13:235.