Low-Birthweight Baby: Born Too Soon or Too Small
Nestlé Nutrition Institute
Workshop Series

Vol. 81
Low-Birthweight Baby: Born Too Soon or Too Small

Editors

Nicholas D. Embleton  Newcastle upon Tyne, UK
Joanne Katz   Baltimore, MD, USA
Ekhard E. Ziegler   Coralville, IA, USA
Contents

VII Preface
IX Foreword
XII Contributors

Global Epidemiology

1 Global Prevalence of Small for Gestational Age Births
   Black, R.E. (USA)

9 Global Incidence of Preterm Birth
   Tielsch, J.M. (USA)

17 Nutritional and Reproductive Risk Factors for Small for Gestational Age and Preterm Births
   Kozuki, N.; Lee, A.C.C.; Black, R.E.; Katz, J. (USA)

29 Mortality Risk among Term and Preterm Small for Gestational Age Infants
   Katz, J.; Lee, A.C.C.; Kozuki, N.; Black, R.E. (USA)

37 Prevention of Intrauterine Growth Restriction and Preterm Birth with Presumptive Antibiotic Treatment of Pregnant Women: A Literature Review
   Ashorn, P.; Vanhala, H.; Pakarinen, O.; Ashorn, U. (Finland);
   De Costa, A. (Finland/Sweden)

Catch-Up Growth

51 Should We Promote Catch-Up Growth or Growth Acceleration in Low-Birthweight Infants?
   Singhal, A. (UK)

61 Catch-Up Growth and Metabolic and Cognitive Outcomes in Adolescents Born Preterm
   Embleton, N.D.; Skeath, T. (UK)

73 Role of Specific Nutrients in Low-Birthweight Infants
   Bhatia, J. (USA)
87 Catch-Up Growth: Basic Mechanisms
Griffin, I.J. (USA)

99 Stunting Persists despite Optimal Feeding: Are Toilets Part of the Solution?
Prendergast, A.J. (UK/Zimbabwe/USA); Humphrey, J.H. (Zimbabwe/USA)

111 Feeding Practices – Current and Improved?
Simmer, K. (Australia)

123 Feeding the Larger Low-Birthweight Infant in a Resource-Poor Environment
Kirsten, G.F. (South Africa)

135 Nutrient Needs for Catch-Up Growth in Low-Birthweight Infants
Ziegler, E.E. (USA)

145 Human Milk Fortification in India
Kler, N.; Thakur, A.; Modi, M.; Kaur, A.; Garg, P.; Soni, A.; Saluja, S. (India)

153 Probiotic Supplementation for Preterm Neonates – What Lies Ahead?
Patole, S. (Australia)

163 Concluding Remarks
167 Subject Index

For more information on related publications, please consult the NNI website:
www.nestlenutrition-institute.org
Preface

Low birthweight has long been known to be a strong predictor of morbidity and mortality risks in the first year of life and beyond. Weight is relatively easy to measure and has a long history of being used to triage infants into those at high risk and in need of additional care and support. Infants can have low birthweight because they are born too soon or because they had poor intrauterine growth, or both. Infants born too soon may need different clinical and nutritional interventions and are at risk for different morbidities than those born too small. In addition, the risk factors for adverse outcomes, and the interventions that are effective in preventing adverse outcomes may be quite different. This book presents the content of the 81st Nestlé Nutrition Workshop entitled ‘Low-Birthweight Baby: Born Too Soon or Too Small’ held March 31 through April 2, 2014, in Magaliesburg, South Africa. The workshop was arranged in three sessions: Global Epidemiology, Catch-Up Growth, and Feeding Practices – Current and Improved? In doing so, we aimed to provide a solid contextual basis for the nature and extent of the problem, highlighting changes in prevalence and risk across different healthcare settings in order that the implications of nutritional interventions could be fully appreciated.

From an epidemiologic perspective, low birthweight has not been separated into preterm and small for gestational age (SGA) in low-resource settings until recently. Since gestational age measurement has become more accessible and accurate in such settings, there are now more data available to estimate the burden of preterm and SGA birth in low-income countries around the world, and this has allowed an examination of whether the risk factors and survival trajectories of preterm infants differ from those of SGA infants. In 2010, the burden of low birthweight (18 million), preterm (15 million), and SGA (32.4 million) in 138 low-income countries was significant, and preventing these conditions could reduce neonatal and infant mortality significantly. Maternal nutritional status, infection and reproductive factors account for some of these adverse outcomes. Interventions to increase maternal body mass index and weight gain, to
provide micronutrient supplementation, to treat infection in pregnancy, and to increase the age at first pregnancy are possible ways to reduce the burden of preterm and SGA births.

Sessions on catch-up growth and feeding practices were designed to highlight the importance of defining nutrient needs, growth and nutritional assessment, and the potential advantages and disadvantages of rapid catch-up growth. We aimed to build on the epidemiological evidence that highlights the importance of distinguishing between low-birthweight infants born at term, compared to those born preterm. Sessions on the scientific basis of catch-up growth were designed to promote a greater mechanistic understanding of the phenotypes observed in clinical practice, and how growth in early life is associated with longer-term outcomes. Presentations covered a range of topics including nutrient requirements, the specific needs of infants born SGA, the importance of breast milk, and the benefits (and risks) of breast milk fortifiers. The importance of health care context was exemplified by presentations covering nutritional practices in low- and middle-income settings, and presentations on the role of enteric infections and aspects of hygiene in early life. Taken together, these data strongly suggest that growth is dependent not simply on nutrient intake, but on a multitude of environmental factors that interact with nutrient intakes to determine growth outcomes. Whilst knowledge on nutritional practice has advanced considerably in the last few years, a major theme we wished to highlight was the competing demands in differing health care settings, and a recognition that a ‘one size fits all’ approach to nutritional management will not optimize outcomes.

The design of the workshop specifically allowed for considerable interaction between the presenters and the expert audience, who collectively provided insights from across the world both in scientific understanding and practical relevance of the data. The discussions were lively, challenging and enjoyable. As chairs of the workshop sessions, we would like to extend our thanks to the Nestlé Nutrition Institute, in particular Dr. Natalia Wagemans and Prof. Ferdinand Haschke, for enabling the workshop to take place. The setting and arrangements provided a unique opportunity for interaction and discussion for all the delegates, and we would like to thank the organizing team, the session chairs and the delegates for making this a unique and informative event.

Nicholas D. Embleton
Joanne Katz
Ekhard E. Ziegler
Foreword

The importance of understanding protein requirements in infancy for appropriate growth and long-term health is well known. Thus, to bring together the latest insights and share knowledge on this key issue, the 81st Nestlé Nutrition Institute (NNI) Workshop held in South Africa in April 2014 focused on the theme ‘Low-Birthweight Baby: Born Too Soon or Too Small’.

The NNI ‘protein journey’ started back in 1993 with the 33rd Nestlé Nutrition Workshop on ‘Protein Metabolism during Infancy’ [1], which was also held in South Africa. It continued with the 43rd Workshop on ‘Nutrition of the Very Low Birthweight Infant’ in 1999 [2] and the 61st Workshop on ‘The Window of Opportunity: Pre-Pregnancy to 24 Months of Age’ in 2007 [3], which discussed different aspects of the protein requirements of preterm and term infants.

Low birthweight was chosen as the topic of the 81st NNI Workshop as very little attention has been paid to the growth and nutrition of small for gestational age (SGA) babies in recent years. This workshop also closes the series of the five NNI Workshops on ‘programming for a healthy life’.

For the scientific program, we brought together epidemiology, modern technology and the latest science to promote a better understanding of the short- and long-term needs and outcomes of low-birthweight babies, depending on whether they are born too small or too early.

The first day of the workshop gave us the global estimates of preterm and SGA prevalence, risk factors associated with increased mortality and morbidity in these groups, and possible intervention programs to prevent SGA/preterm birth. The second day attracted intense discussion on the rationale of catch-up growth in preterm or small for age babies, and short- and long-term outcome of inappropriate growth during early and late postnatal period. Session 3 focused on the feeding practices and brought to the audience the value of breastfeeding and fortification of breast milk, and examined the current feeding practices in different parts of the world.
We wish to warmly thank the workshop’s three chairpersons – world acclaimed experts in the area of child growth and development – Prof. Joanne Katz, Prof. Ekhard Ziegler and Prof. Nicholas Embleton for establishing an excellent scientific workshop program.

We are also indebted to the renowned speakers and discussants that have furthered the debate and understanding of this key topic through their presentations and participation. We thank the many experts who came from across the globe to review and discuss the important public health issue related to low-birthweight babies, their growth and development.

Finally, we wish to thank and congratulate Dr. Lindiwe Whati and her team from Nestlé Nutrition Institute Africa for their excellent logistical support that allowed all of us to enjoy the scientific program and beautiful nature in Johannesburg.

References


Prof. Ferdinand Haschke, MD, PhD
Head of Nestlé Nutrition Institute
Vevey, Switzerland

Natalia Wagemans, MD, PhD
Global Medical Advisor Nestlé Nutrition Institute
Vevey, Switzerland
Contributors

Chairpersons & Speakers

Prof. Per Ashorn
Department for International Health
School of Medicine
University of Tampere
Arvo Building, Room B235
Lääkärinkatu 1
FI–33014 Tampere
Finland
E-Mail per.ashorn@uta.fi

Prof. Jatinder Bhatia
Division of Neonatology
Children’s Hospital of Georgia
1120 15th Street, BIW 6033
Augusta, GA 30912-3740
USA
E-Mail jatindeb@gru.edu

Prof. Robert Black
Institute of International Programs
Department of International Health
Johns Hopkins Bloomberg School of Public Health
615 N. Wolfe Street, E8547
Baltimore, MD 21205
USA
E-Mail rblack1@jhu.edu

Prof. Nicholas Embleton
Newcastle Neonatal Service
Ward 35, Royal Victoria Infirmary
Newcastle upon Tyne NE1 4LP
UK
E-Mail nicholas.embleton@ncl.ac.uk

Dr. Ian J. Griffin
UC Davis Children’s Hospital
2516 Stockton (Ticon II)
Sacramento, CA 95817
USA
E-Mail ijgriffin@ucdavis.edu

Prof. Joanne Katz
Department of International Health
Johns Hopkins Bloomberg School of Public Health
615 N. Wolfe Street, W5009
Baltimore, MD 21205-2103
USA
E-Mail jkatz1@jhu.edu

Prof. Gert F. Kirsten
Department of Pediatrics & Child Health
Faculty of Health Sciences
Stellenbosch University
Francie van Zyl Drive
Tygerberg 7505, Western Cape
South Africa
E-Mail gfk@sun.ac.za

Prof. Neelam Kler
Department of Neonatology
Sir Ganga Ram Hospital
Old Rajinder Nagar
New Delhi 110060
India
E-Mail drneelamkler@gmail.com
Ms. Naoko Kozuki
Johns Hopkins Bloomberg School of Public Health
615 North Wolfe Street, W5031
Baltimore, MD 21205
USA
E-Mail nkozuki@jhu.edu

Prof. Sanjay Patole
Department of Neonatal Paediatrics
NCCU Offices, First floor A Block
King Edward Memorial Hospital for Women
374 Bagot Road
Subiaco Perth, WA 6008
Australia
E-Mail skpatole@hotmail.com

Dr. Andrew J. Prendergast
Centre for Paediatrics
Blizard Institute
Queen Mary University of London
4 Newark Street
London E1 2AT
UK
E-Mail a.prendergast@qmul.ac.uk

Prof. Karen Simmer
Centre for Neonatal Research and Education
University of Western Australia (M550)
35 Stirling Highway
Crawley, WA 6009
Australia
E-Mail karen.simmer@health.wa.gov.au

Prof. Atul Singhal
UCL Institute of Child Health
Nutrition Unit
30 Guilford Street
London WC1N 1EH
UK
E-Mail a.singhal@ich.ucl.ac.uk

Prof. James M. Tielsch
Department of Global Health
Milken Institute School of Public Health
George Washington University
950 New Hampshire Ave., NW, Suite 400
Washington, DC 20052
USA
E-Mail jtielsch@gwu.edu

Prof. Ekhard Ziegler
University of Iowa
Department of Pediatrics
MTF, 2501 Crosspark Rd
Coralville, IA 52241
USA
E-Mail Ekhard-ziegler@uiowa.edu

Participants
Peter Fryer/Australia
Melissa Gilroy/Australia
Pieter Koorts/Australia
Nadja Haiden/Austria
Gabriel Anabwani/Botswana
Ishmael Makone/Botswana
Gislayne Nieto/Brazil
Oswaldo Trindade Filho/Brazil
Evelyn Mungyeh Mah/Cameroon
Lizhong Du/China
Qi Feng/China
Wenjun Li/China
Jianxinq Zhu/China
Laeticia Mavinga/Congo
Marie-Therese Mungende/Congo
Ulla Ashorn/Finland
Simon Jonas Mawugnon Ategbo/Gabon
Priscilla Apaloo/Ghana
Serge Dzeukou/Ghana
Frank Serebour/Ghana
A.K. Jaleel Ahmed/India
Soumitra Dutta/India
Sanjeev Ganguly/India
Pankaj Garg/India
Raghu Ram Mallaiah/India
Arunbhai Mehta Ashish/India
K. Pandian/India
Kishore Kumar Rajagopal/India
Hariram Maralakunte Ramchandra Rao/India
Chandan Ray/India
Umesh Vaidya/India
Flore Amon-Tanoh-Dick/Ivory Coast
Lassina Cisse/Ivory Coast
Gildas Stanislas Lewhe/Ivory Coast
Phyllis Obote/Kenya
Roger Andrianasolo/Madagascar
Boo Aik Khoo/Malaysia
Sridevi Kommireddi/Mauritius
Devbruth Sibartie/Mauritius
Jimena de Martino/Mexico
Dagoberto Delgado Franco/Mexico
Raul Garza Bulnes/Mexico
Jose Alfonso Gutierrez Padilla/Mexico
Ana Laura Juarez Lalinas/Mexico
Chioma Emma-Nwachukwu/Nigeria
Victor Idowu Joel-Medewase/Nigeria
Kenechukwu Oguegbu/Nigeria
Ben Onankpa/Nigeria
James Renner/Nigeria
Abdulrahman Al Zahrani/Saudi Arabia
Papa Moctar Faye/Senegal
Theunis Avenant/South Africa
Peter Cooper/South Africa
Anne-Marie de Beer/South Africa
Suzanne Delport/South Africa
Getruida Gericke/South Africa
Michael Harrison/South Africa
Natalie Harrison/South Africa
Johanna Kemp/South Africa
Naazneen Khan/South Africa
Gerhardus Francois Kirsten/South Africa
Yazeed Seedat/South Africa
Radhika Singh/South Africa
Claire Tolmay/South Africa
Arina van der Byl/South Africa
Merete van der Westhuizen/South Africa
Esmarie van Tonder/South Africa
Elise Yssel/South Africa
Laurent Ameye/Switzerland
Jelena Buncic/Switzerland
Riccardo Pfister/Switzerland
Sagar Thakkar/Switzerland
Enid Mbabazi Mwebaza/Uganda
Mohamed Abdelwahab/United Arab Emirates
Nicholas Hays/USA
Randi Kline/USA
Global Prevalence of Small for Gestational Age Births

Robert E. Black
Institute for International Programs, Bloomberg School of Public Health, Johns Hopkins University, Baltimore, MD, USA

Abstract
Fetal growth restriction is found both in babies who are preterm or full-term, and in either case has important adverse effects on subsequent survival, health, growth and development. Fetal growth restriction is usually assessed by comparing the weight of the newborn with the expected weight for the child’s gestational age using less than the 10th centile of a reference population for fetal growth as the threshold for being called small for gestational age (SGA). We estimate that in 2010 32.4 million babies were born SGA in low- and middle-income countries, constituting 27% of all live births. The estimated prevalence of SGA is highest in South Asia and in Sahelian countries of Africa. India has the world’s largest number of SGA births, 12.8 million in 2010, due to the large number of births and the high proportion, 46.9%, of births that are SGA. The prevalence of SGA births is approximately double the prevalence of low-birthweight births (using the common indicator of <2,500 g birthweight) globally and in the world’s regions. Thus, given the adverse effects of being born SGA, even weighing 2,500 g or more, it is important that maternal, neonatal and child health programs seek and use information on gestational age as well as birthweight to appropriately assess the newborn’s risks and direct care.

Introduction
The importance that optimum fetal growth has for survival, growth and development after birth has long been recognized [1]. Newborns weighing less than 2,500 g, the most commonly used definition of low birthweight (LBW), are at risk of poor health and development outcomes as a consequence of being born prematurely, having fetal growth restriction or both. While this definition of an
at risk population has been useful for nutrition programs, it underestimates the size of a population of newborns at risk because it does not include babies who have fetal growth restriction, but weigh 2,500 g or more [1]. The comparison of weight at birth with a fetal growth reference by week of gestation permits the identification of newborns who are small for their gestational age (SGA) for both preterm and full-term births. This chapter will focus on the estimation of the global prevalence of SGA births.

Low-Birthweight Births

LBW has been defined by the World Health Organization as a weight of <2,500 g at birth and very low birthweight (VLBW) as <1,500 g. Births that are <1,000 g are defined as extremely low birthweight (ELBW). Neonatal complications, including hypothermia, hypoglycemia, asphyxia, respiratory distress, fluid and electrolyte imbalances, hyperbilirubinemia, infection and neurological and sensory problems, are more common in LBW births. These complications are accentuated in VLBW and especially in ELBW births. Compared to babies with birthweights of at least 2,500 g, LBW babies have lower survival rates, which decline monotonically with lower birth weights. Lower birthweights are also associated with increased risk of developmental delay and overweight and related noncommunicable disease in adulthood. The outcome of the complications is very influenced by the level of care that is available for the newborn and young infant. In settings with sophisticated neonatal intensive care, most babies of 1,500–500 g survive, although many have lifelong adverse health effects. In low-income countries with much more limited care options, most babies below 1,500 g at birth do not survive.

It has been estimated by UNICEF that 15% of births globally are <2,500 g at birth, resulting in over 20 million LBW newborns annually (childinfo.org) [2]. The regional importance of LBW births is highest in South Asia where the percentage is more than 25%. Half of the LBW births are in just three countries, India, Pakistan, and Nigeria. India alone has nearly 7.5 million births of babies with weight <2,500 g annually, 38% of the global total. In high- or upper-middle-income countries, 5% or less of births are LBW, largely due to preterm deliveries. The percentage of births in these settings has declined historically from the higher rates seen now in the low-income countries, but in some countries has increased recently because of mistimed Cesarean section deliveries leading to more preterm births and increased multiple births due to fertility treatment.

LBW continues to be used in neonatal health programs because it can be measured with reasonable accuracy. Nevertheless, in areas of the world with the
highest rates of LBW births, most newborns are not weighed because of home deliveries, late postnatal visits and insufficient capacity of health workers. Efforts need to be increased to ensure that all births are registered, weighted and medically assessed because the information is useful to direct home care and health services. In addition, the prevalence of LBW births has been adopted as a World Health Assembly [3] nutrition indicator with a global target of 30% reduction in prevalence by 2025, recognizing the importance of LBW for survival, development and health in the lifespan.

Birthweight is largely determined by two factors, the duration of gestation and the rate of fetal growth. Babies can be <2,500 g because they are born prematurely, i.e. before 37 completed weeks of gestation, with or without fetal growth restriction. Or they can be born at or after 37 weeks but have restricted fetal growth. Furthermore, newborns that are ≥2,500 g may also have fetal growth restriction. Fetal growth restriction is assessed by comparing the weight of the newborn with a reference population thought to have normal fetal growth. The assessment of the adequacy of fetal growth requires knowledge of the gestational age of the newborn, usually by documentation of the last menstrual period or ideally fetal ultrasound examination early in pregnancy. Thus, fetal growth restriction is assessed in regard to achievement of the expected weight for a given gestational age. Being small for gestational age (SGA) is usually defined as having a birthweight below the 10th percentile for gestational age compared to an appropriate reference population. Some of these babies will be small at birth because they are constitutionally small, but for many the fetal growth restriction is due to maternal nutritional deficiencies, infections during pregnancy, abnormal placental function or fetal malformations. The various possibilities for classification of status of the newborn are shown in figure 1 which has weight on the y-axis and gestational age on the x-axis. Newborns who are at the expected weight whether preterm or at or after 37 weeks are referred to as appropriate for gestational age; these are above the dashed line in the figure. Newborns who are lower than the expected weight whether preterm or full term are referred to as SGA. LBW referring simply to being <2,500 g at birth includes some newborns who are preterm, some who are SGA and some who are both with the relative proportions in populations varying by setting and other factors. The classification of LBW does not include the newborns who weigh 2,500 g or more but are small for their gestational age. In figure 1, one can also identify the group of newborns who are full term and at least 2,500 g at birth. This group has been referred to as ‘term low birthweight’ which has been used in previous estimates related to fetal growth restriction due to limited data availability on gestational age and thus on the true prevalence of SGA births.
Small for Gestational Age Births

The Child Health Epidemiology Reference Group (CHERG) of the World Health Organization and UNICEF has undertaken analyses in the last decade of global levels and causes of child death, numbers of preterm births and stillbirths, prevalence and consequences of nutritional risk factors, and maternal, neonatal and child morbidity. In the last 2 years, a set of analyses has focused on prevalence of fetal growth restriction and its consequences [4–7]. These analyses have been published in research papers [5–7] and as part of a series of papers on maternal and child nutrition published in *The Lancet* in mid-2013 [4, 8–10]. Detailed methods are published in these papers. Briefly, SGA was defined as birthweight below the tenth percentile of a reference population for a given gestational age and sex [11]. The reference used for these analyses included more than 3 million nationally representative, multiethnic births in the United States in 1991. Preterm birth was considered to be delivery at less than 37 weeks.

In previous analyses, fetal growth restriction was indicated by LBW (<2,500 g) in babies who were full term because of what data were available [12]. This did not allow estimation of the full prevalence of fetal growth restriction (as indicated by SGA) that would include babies who were both preterm and SGA or who were SGA but weighed more than 2,500 g. In new analyses, it has been possible to do estimates of SGA that overcome these limitations and provide the

![Fig. 1. Relationship of birthweight and gestational age for classification of LBW and SGA.](image-url)
results for both term and preterm births [5, 6]. These estimates indicate that in 2010, 32.4 million babies were born SGA, 27% of all births in low- and middle-income countries [6]. About 20% of the preterm births in these countries were also SGA. India has not only the largest number of SGA births of any country, 12.8 million (uncertainty range 11.5–14.3 million), but an extremely high proportion of all births in India are SGA (46.9%) [6]. Figure 2 shows the estimated national prevalence of SGA births in low- and middle-income countries in 2010. The highest prevalences were in South Asia and the Sahelian countries of Africa.

As shown in figure 3, the prevalence of SGA, including both term and preterm births, is approximately double the prevalence of LBW in all the world regions. SGA is largely in babies born at term with only a small proportion of babies being both preterm and SGA.

**Implications for Programs and Research**

SGA is an important global problem with consequences for child survival and development, and an even more critical problem for countries in South Asia, especially India and some countries in Africa. Success in reducing neonatal and child mortality in these countries [13] may depend on addressing the problem of fetal growth restriction. Improved diets for pregnant women, as well as specific interventions, such as targeted balanced protein energy supplementation and multiple micronutrient supplementation in pregnancy, that are proven to reduce SGA should be implemented in ways to achieve high coverage in preg-
nant women who can benefit. Additional nutritional interventions, e.g. in adolescence and before conception, should be evaluated and implemented if effective.

As the evidence accumulates that poor fetal growth has both short-term consequences for survival and linear growth (i.e. stunting) and long-term adverse effects on cognitive and psychosocial development, adult stature and risk of adult metabolic diseases [4, 14], there must be more focus on programs and research to prevent it. However, recognizing that the prevention approaches may for some time remain only partially successful and that some of the determinants of poor fetal growth may take a generation to reduce, there is a parallel need for research on the mechanisms for these adverse fetal effects, how they may differ by the timing and type of nutritional insult during pregnancy and how the adverse effects of SGA can be mitigated after birth.

**Disclosure Statement**

Robert Black serves on the Boards of the Micronutrient Initiative, Vitamin Angels and the Child Health and Nutrition Research Initiative and the Nestle Creating Shared Value Advisory Committee.
References

Global Incidence of Preterm Birth

James M. Tielsch
Department of Global Health, Milken Institute School of Public Health at The George Washington University, Washington, DC, USA

Abstract
Estimating the incidence of preterm birth depends on accurate assessment of gestational age and pregnancy outcomes. In many countries, such data are not routinely collected, making global estimates difficult. A recent systematic approach to this problem has estimated a worldwide incidence of 11.1 per 100 live births in 2010. Significant variation in rates by country and region of the world was noted, but this variation is smaller than observed for a number of other important reproductive outcomes. Rates range from approximately 5% in some northern European countries to over 15% in some countries in sub-Saharan Africa and Asia. Time trends suggest that preterm birth incidence is increasing, but much of this change may reflect changes in medically induced early delivery practices as improvements in survival of preterm infants has improved. Whether there have been major changes in spontaneous preterm birth is unknown. New approaches to classifying etiologic heterogeneity have been proposed and offer the promise of developing specific interventions to address the range of underlying causes of this important health problem.

Introduction
Despite the significant progress over the past 20 years in maternal and child survival, adverse outcomes of pregnancy have been relatively resistant to change. Among these outcomes, the most resistant has been preterm birth. Preterm birth accounts for over one third of neonatal deaths, and in many countries is the leading cause [1]. Serious morbidity and disability are important consequences of being ‘born too soon’ with important impacts on the lung and brain [2]. These functional sequelae often result in lifelong impairments [2, 3]. While
progress has been made in reducing preterm rates in high-income countries, at least one half of this decline can be attributed to reductions in medially induced deliveries and not to changes in the underlying processes that result in preterm birth [4].

Measurement of Gestational Age and Definitions of Preterm

Key to definition and measurement of preterm is an accurate assessment of gestational age at the time of delivery. The most commonly used measurement tool is the first day of a woman’s last menstrual period (LMP). A normal, or term pregnancy, is one that lasts for 280 days following the LMP. Note that this assumes that fertilization occurs concurrently with ovulation, 2 weeks following LMP. Defining gestational age based on LMP depends on a variety of factors that result in compromises to accuracy. These factors include variations in length and regularity of normal menstrual cycles, fertilization and implantation occurring a variable number of days following ovulation, amenorrhea caused by breastfeeding, illness, or physical stress, and a women’s recall. As might be expected, when a woman is asked about her LMP has an effect on accuracy; the earlier in pregnancy, the more accurate this measurement will be. Waiting until delivery will result in less accurate measures. On average, data suggest LMP is accurate to within about 2 weeks [5].

As a result of these concerns with using LMP, a number of other approaches are used as well. Measurement of fundal height can provide information that is objective but slightly lower in accuracy compared to LMP. As with all anthropometric measurements of gestational age, the accuracy of fundal height measurement depends on when it is measured in pregnancy. The later in pregnancy the measurement is taken, the more likely factors such as uterine anatomy and intrauterine growth restriction will limit accuracy. Best estimates of accuracy for this measure are within approximately 3 weeks [5].

Clinical assessment of the newborn at the time of delivery is often used in settings where there are skilled attendants at delivery. There are a variety of these clinical scales including the Dubowitz, Capurro, Ballard and Parkin scales. They all include an external assessment of selected characteristics and some add neurological assessment as well. Accuracy is within approximately 2 weeks [5].

The current gold standard for measurement of gestational age is based on early ultrasound with specific fetal anthropometric measurements. These include fetal crown-rump length, biparietal diameter, and femur length. The most accurate period for ultrasound-based gestational age estimation is prior to 20
weeks in order to avoid the confounding associated with variations in intrauterine growth of the fetus. Ultrasound requires a trained operator and reader and is accurate to within approximately 5 days if done in the first trimester [5].

‘Best obstetrical estimate’ is commonly used in high-resource settings and requires both LMP and early ultrasound. Algorithms are used to estimate gestational age based on the best available information, but there are a variety of algorithms in use, and this approach is unstandardized. Accuracy varies depending on the type of information and the algorithm, but is somewhere between the accuracy of LMP and early ultrasound assessments [5].

As might be expected, there is wide variation in the available information, and therefore accuracy, regarding gestational age at birth across countries. The vast majority of low-income countries do not have routine ultrasound information available nor are vital record systems in place or complete enough to record such information for the majority of births. As a result, the current best attempt to estimate preterm rates by country was forced to use region-specific mathematical models for 171 of the 184 countries in their analysis [6]. Therefore, all worldwide estimates and many national and regional estimates of preterm birth rates and numbers should be used with caution.

The traditional definition of preterm birth is a live-born infant born at less than 37 completed weeks of gestation [7]. The lower end of preterm is variously defined based on livability of the newborn, with most countries using 22 weeks. Some high-income countries set this bound as low as 16 weeks. As the magnitude and severity of the consequences of preterm birth increase significantly at lower gestational ages, the preterm range has been categorized into 4 groups; late preterm (34 to <37 weeks), moderate preterm (32 to <34 weeks), very preterm (28 to <32 weeks), and extremely preterm (<28 weeks).

Recently, a classification system has been proposed that reflects the etiologic heterogeneity of preterm birth in which five components are considered [8]:

- Maternal conditions present prior to delivery
- Fetal conditions present prior to delivery
- Pathologies of the placenta
- Signs of parturition initiation
- The pathway to delivery.

Part of this new classification paradigm redefines the upper bound of preterm birth at <39 weeks [9] justifying this expansion based on increased risks for these infants relative to those born 39–41 weeks [10, 11] (fig. 1). It also calls for setting the lower bound at 16 weeks and including all births, both live- and still-born. This would increase current estimates by about 28% with the size of the increase varying by setting.
Incidence

Variations in measurement of gestational age and completeness and quality of data sources make estimates of the global incidence of preterm birth difficult. The most comprehensive approach to this challenge has been done recently by Blencowe et al. [6] who estimated national, regional, and global preterm birth rates for 2010. Given the lack of national data in many countries, they used information from a variety of sources including vital records systems, registries, national surveys, a systematic literature review of special studies, and unpublished data from the Child Health Epidemiology Reference Group. High-quality, reliable data were available from a small minority of countries, forcing the investigators to model most of the country estimates based on limited country-specific data of preterm rates, associated risk factors for preterm, and more reliable information from other countries in their region. Similar modeling approaches were used to calculate subcategories of preterm birth.

Globally, Blencowe et al. [6] estimated a preterm birth rate of 11.1% for 2010 resulting in almost 15 million preterm births worldwide. Estimates varied by region with a low of 7.4% in central and eastern Asia to a high of 13.3% in southern Asia. Countries defined as ‘developed’ in this analysis did not have the lowest rates (8.6%) and were equivalent to the rate in the Latin America and Caribbean region. Variations by country were larger with the highest rate estimated in Malawi at 18% and the lowest rates found in northern European countries at around 5% (fig. 2).

While there was significant variation by region and country, the variability of preterm rates is significantly smaller than seen for other important reproductive
outcomes such as small for gestational age [12] and the pattern of rates does not fit neatly into preconceived expectations based on socioeconomic status. For example, rates in some developed countries were higher than in some of the poorer countries in a variety of regions. This likely reflects a mix of data quality issues and/or different etiologies of preterm birth with variations in practice patterns related to medical induction of delivery – a prominent source of this variation.

Blencowe et al. [6] also estimated changes in preterm rates between 1990 and 2010 for a selected set of countries (their developed country group and the Latin America and Caribbean regions). This analysis demonstrated an increase from 7.5 to 8.6% over this period. The percentage increase ranged between 9.1 and 25.8% by region (table 1). Of the 65 countries included in this time trend analysis, only 17 had stable or declining rates, all others had increases of greater than 0.5% per annum. However, the cause of these time-related patterns is unclear. In the US, preterm rates increased to 12.8% in 2006, but have since declined significantly as criteria for medically induced early delivery have changed [13, 14] (fig. 3).

Table 1. Preterm birth rates in selected regions, 1990–2010

<table>
<thead>
<tr>
<th>Region</th>
<th>Preterm birth rate (per 100)</th>
<th>Relative change from 1990 to 2010, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1990</td>
<td>2010</td>
</tr>
<tr>
<td>Developed countries</td>
<td>7.2</td>
<td>8.6</td>
</tr>
<tr>
<td>Latin America</td>
<td>7.7</td>
<td>8.4</td>
</tr>
<tr>
<td>Caribbean</td>
<td>8.9</td>
<td>11.2</td>
</tr>
</tbody>
</table>

Data from Blencowe et al. [6].
Conclusion

The lack of comprehensive vital records systems in many countries and difficulties in measuring gestational age make estimating rates of preterm birth a challenging undertaking. Despite these challenges, it is clear that preterm birth remains a highly frequent condition around the world, one with significant vital and developmental consequences, and one that has been relatively resistant to interventions. In fact, in many countries rates of preterm birth have increased significantly over the past 20 years. While there is significant variation from country to country, this variability is less dramatic than seen for other important reproductive outcomes, suggesting that the interventions used for these other reproductive outcomes are not likely to impact a significant proportion of preterm births.

Preterm birth is not a single condition and is one of the only major health conditions that are classified by when it occurs instead of how it occurs. Improvements in this critical outcome will depend on designing strategies that directly address this heterogeneity. In addition, approaches to classification and definition of the group of pregnancies that should be considered as preterm are being developed, which may offer new strategies to address this global issue.

Disclosure Statement

The author declares that no financial or other conflict of interest exists in relation to the contents of the chapter.
References

Nutritional and Reproductive Risk Factors for Small for Gestational Age and Preterm Births

Naoko Kozuki - Anne C.C. Lee - Robert E. Black - Joanne Katz

Abstract

Approximately 32.4 million small for gestational age (SGA) babies and 13.7 million preterm babies are born annually in low- and middle-income countries (LMICs), of whom 2.8 million are both SGA and preterm. These newborns who are born too small and/or too soon not only experience heightened risk of neonatal and infant mortality, but also of long-term morbidities, like adulthood chronic disease. In order to reduce these burdens worldwide, it is critical to identify and understand the epidemiology of the risk factors that contribute to SGA and preterm births. As part of the Child Health Epidemiology Reference Group, we explored nutritional and reproductive health-related maternal risk factors associated with SGA and preterm outcomes in LMICs, including short maternal stature, young/advanced maternal age, low/high parity, and short birth interval. In this chapter, we highlight our findings and relevant existing literature, and also summarize literature on how low/high BMI and low weight gain during pregnancy, respectively, are associated with SGA and/or preterm outcomes.

Introduction

Low-birthweight (LBW) babies, or those born weighing less than 2,500 g, experience higher risk of neonatal and infant morbidity and mortality, as well as long-term impairments like physical and developmental delays [1] and adulthood chronic disease [2]. LBW babies comprise those who are low weight be-
cause they are born too soon (preterm) and/or because they are born too small (intrauterine growth restricted, IUGR). Small for gestational age (SGA), defined as being born below the 10th percentile of a sex-specific birthweight distribution at a specified gestational age, is often used as a proxy to identify IUGR neonates. Approximately 13.7 million preterm babies [3] and 32.4 million SGA babies [4] are born annually in low- and middle-income countries (LMICs), of whom 2.8 million are both preterm and SGA [4]. Those newborns born both preterm and SGA have the highest mortality risk, with a risk ratio (RR) of 16.20 (95% CI: 10.00–26.23) in the neonatal period and 9.59 (95% CI: 4.53–20.29) in the infant period, compared to those newborns who are born term and appropriate for gestational age (AGA; weighing over the 10th percentile of a sex-specific birthweight distribution at the specified gestational age) [5].

There is value in distinguishing LBW babies by whether they were born too soon and/or too small. While preterm and SGA births share some secondary and tertiary preventive interventions such as exclusive breastfeeding and thermal care, there is greater distinction in primary preventive interventions due to some exposures that are linked to preterm and SGA independently. Understanding the distinct epidemiology can help in designing efforts to prevent both. As part of the Child Health Epidemiology Reference Group (CHERG), we explored nutritional and reproductive health risk factors associated with SGA and preterm outcomes in LMICs, including short maternal stature, maternal age, parity, and short birth interval. In this chapter, we highlight our findings and relevant existing literature, and also summarize literature on how low BMI, high BMI, and low weight gain during pregnancy, respectively, are associated with SGA and/or preterm outcomes.

**Nutritional Risk Factors**

*Height*

Impaired linear growth is considered an indicator of chronic malnutrition in children and may result in low attained height in adolescence and adulthood. Low maternal height may in turn lead to, or be associated with, conditions resulting in poor birth outcomes. The existing literature has reported strong associations between maternal short stature and poor birth/neonatal outcomes. The WHO Collaborative Study of Maternal Anthropometry and Pregnancy Outcomes [6], an analysis including data from 25 studies from low-, middle-, and high-income countries, reported statistically significant associations of low
maternal height with LBW [odds ratio (OR) 1.7, 95% CI: 1.6–1.8], SGA (OR 1.9, 95% CI: 1.8–2.0), and preterm birth (OR 1.2, 95% CI: 1.1–1.2), comparing the lowest quintile with the highest quintile of height for each dataset. The Knowledge Synthesis Group recently conducted a systematic review of the literature and showed very similar magnitudes of association for LBW (OR 1.81, 95% CI: 1.47–2.23) and preterm (OR 1.23, 95% CI: 1.11–1.37), using each study’s own definition of short stature. The analysis identified 2 studies reporting an IUGR outcome, for an adjusted OR of 1.39 (95% CI: 1.15–1.68) [7]. We, as members of the CHERG, are preparing to publish associations between maternal short stature and SGA/preterm birth, using data from 12 prospective cohort studies and 23 national surveys from the WHO Global Survey on Maternal and Perinatal Health conducted in LMICs. We analyzed each dataset using standard exposure and outcome variables, and estimated that women with a height <145 cm had adjusted RRs of 1.79 (95% CI: 1.63–1.97) for term-SGA, 1.52 (95% CI: 1.29–1.79) for preterm-AGA, and 2.00 (95% CI: 1.52–2.61) for preterm-SGA compared to the reference height group of ≥155 cm. The RRs followed a dose-response pattern, with the associations for each outcome becoming weaker as the height categories approached the reference group [Kozuki et al., under review]. See table 1a for a comparison of findings across existing meta-analyses.

Short maternal stature may be operating on SGA by limiting the uterine volume for fetal growth [8]. One study reported that girls born SGA have smaller uterine volume in adolescence [9], meaning there may be intergenerational effects of short maternal stature and subsequent SGA outcomes as well. Kramer et al. [8] reported an association between short stature and mild preterm, but not with moderate or severe preterm, hypothesizing that earlier filling of the pelvis may be linked to early labor. Existing literature has suggested that the main exposures that determine linear growth occur during the first 1,000 days, or the fetal period plus the first 2 years of life. Fetal growth restriction and stunting in early childhood have been linked as strong predictors for stunting later in life [10]. There has thus been emphasis on macro- and micronutrient supplementation and exclusive breastfeeding during this early period to target the reduction of eventual stunting. There is now increasing interest in exploring the potential for intervention in childhood or even in adolescence to promote catch-up growth [11].

It is also important to note that nonnutritional interventions may improve linear growth as well; a study from Bangladesh suggests that pregnancy slows or even completely halts a mother’s linear growth trajectory during and following the pregnancy, even if she had yet to attain her projected adult height [12]. Delaying pregnancy among adolescents may be invaluable in as-
Table 1. Comparisons of findings across existing meta-analyses

**a** Summary of meta-analyses examining association between maternal short stature and SGA/preterm birth

<table>
<thead>
<tr>
<th>Publication</th>
<th>Exposure/reference</th>
<th>SGA</th>
<th>Preterm birth</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHO Collaborative Study [6]</td>
<td>lowest vs. highest quartile of height</td>
<td>crude OR 1.9 (1.8–2.0)</td>
<td>crude OR 1.2 (1.1–1.2)</td>
</tr>
<tr>
<td>Knowledge Synthesis Group [7]</td>
<td>varied by study</td>
<td>aOR 1.39 (1.15–1.68)</td>
<td>crude OR 1.23 (1.11–1.37)</td>
</tr>
<tr>
<td>CHERG (under review)</td>
<td></td>
<td>aRR 1.77 (1.61–1.95)</td>
<td>aRR 1.44 (1.20–1.75)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>aRR 1.50 (1.41–1.60)</td>
<td>aRR 1.13 (1.04–1.22)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>aRR 1.31 (1.26–1.36)</td>
<td>aRR 1.10 (1.02–1.18)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ref.</td>
<td>adjusted data mostly not significant</td>
</tr>
</tbody>
</table>

**b** Summary of meta-analyses examining association between acute nutrition indicators and SGA/birth

<table>
<thead>
<tr>
<th>Research group</th>
<th>Exposure/reference</th>
<th>SGA</th>
<th>Preterm birth</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low BMI</td>
<td>WHO Collaborative Study [6]</td>
<td>lowest vs. highest quartile of BMI</td>
<td>crude OR 1.8 (1.7–2.0)</td>
</tr>
<tr>
<td></td>
<td>Knowledge Synthesis Group [14, 15]</td>
<td>varied by study</td>
<td>OR 1.81 (1.76–1.87)</td>
</tr>
<tr>
<td>High BMI</td>
<td>Knowledge Synthesis Group [18]</td>
<td>varied by study</td>
<td>aRR 0.69 (0.63–0.76)</td>
</tr>
<tr>
<td>Low pregnancy weight gain</td>
<td>WHO Collaborative Study [6]</td>
<td>lowest vs. highest quartile of weight gain, month 5–7&lt;sup&gt;a&lt;/sup&gt;</td>
<td>crude OR 2.7 (1.7–4.2)</td>
</tr>
<tr>
<td></td>
<td>Knowledge Synthesis Group [19]</td>
<td>varied by study</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>RR 1.56, 95% CI: 1.26–1.94 (low weekly weight gain)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Measurement of weight gain by other gestational month cutoffs also available in original paper.
suring that women reach their full growth potential. Casanovas et al. [13] summarizes the need for multisectoral approaches to addressing stunting, as factors like maternal education, water, sanitation, and hygiene, and food security all influence stunting. For sustainable, population-level changes to occur, an appreciation for proximate and distal causes of stunting is necessary.

Body Mass Index

BMI [weight in kg/(height in meters)$^2$] is an index of a weight-for-height ratio, and low BMI is considered a representation of acute malnutrition. The WHO uses the range 18.5–25 as normal weight, and categorizes women with BMI <18.5 as underweight. A systematic review examined the association between maternal underweight and preterm and LBW outcomes, respectively [14]. While the review found statistically significantly increased risk of preterm birth when pooling adjusted associations (RR 1.29, 95% CI: 1.15–1.46), a sensitivity analysis revealed no significant association among the 4 developing country studies contributing data (RR 0.99, 95% CI: 0.67–1.45). Underweight women had a statistically significant association with LBW birth, with a similar magnitude for developed and developing country settings (RR 1.52, 95% CI: 1.25–1.85 for developing countries). A more recently published systematic review examined the SGA outcome, and identified 10 studies reporting an association between underweight and SGA [15]. It reported a pooled OR of 1.81 (95% CI: 1.76–1.87). It should be noted that with both of the aforementioned systematic reviews, a variety of BMI cutoffs were accepted to define underweight, and the reference populations used to define SGA were not the same across studies. See table 1b for comparisons across existing meta-analyses.

The associations between low BMI and poor neonatal outcomes can be a direct nutritional link; limited caloric intake may be restricting fetal growth. However, it can also be operating through other mechanisms like infections; malnutrition is a major cause of secondary immune deficiency [16] and could increase maternal susceptibility to pathogens/infections that may lead to preterm birth. Low BMI could also serve as a proxy for negative exposures like hard manual labor during pregnancy and smoking.

With the epidemiologic transition occurring in many LMICs, fetal and neonatal consequences of high maternal BMI will be of increasing interest. The prevalence of overweight and obesity is increasing worldwide, including LMICs, with rates in Africa reaching over 40% and in the Americas and the Caribbean over 70% [17]. A systematic review reported that overweight or obese women had similar or protective risk of LBW and SGA compared to their normal BMI
counterparts. However, they experienced higher risk of other adverse neonatal outcomes, such as preterm (RR 1.24, 95% CI: 1.13–1.37) [18], large for gestational age (above the 90th percentile of birthweight for specified gestational age; RR 1.53, 95% CI: 1.44–1.63 for overweight mothers, RR 2.08, 95% CI: 1.95–2.23 for obese mothers), macrosomia (RR 1.67, 95% CI: 1.42–1.97), and offspring’s subsequent overweight/obesity (RR 1.95, 95% CI: 1.77–2.13, RR 3.23, 95% CI: 2.39–4.37, respectively) [15].

Weight Gain in Pregnancy

Low weight gain during pregnancy is another indicator of acute malnutrition. Han et al. [19] reported in a meta-analysis that both low total weight gain during pregnancy and low weekly weight gain are associated with increased risk of preterm birth (RR 1.64, 95% CI: 1.62–1.54, RR 1.56, 95% CI: 1.26–1.94, respectively). However, there is great heterogeneity in the literature as to how low weight gain is categorized and also whether each study took into consideration the mother’s pre-pregnancy BMI when determining appropriate weight gain in pregnancy. The meta-analysis used exposure cutoffs that were defined by the original studies, and therefore not standardized. Data from the WHO Collaborative Study of Maternal Anthropometry and Pregnancy Outcomes, which examined weight gain curves by birthweight and by clusters of countries contributing data, showed increased risk of LBW and IUGR, but found inconsistent associations with preterm, comparing women of the lowest to the highest weight gain quartile [6].

In addressing acute malnutrition during pregnancy, it is important to be cautious of the potential consequences of increasing fetal size through maternal protein-energy supplementation. In a study conducted in rural Nepal, Lee et al. [20] reported increased rates of birth asphyxia among newborns of women with height <145 cm (aRR 1.5, 95% CI: 1.1–2.0) and particularly high risk among infants weighing greater than 3,300 g, also born to women <145 cm (aRR 3.8, 95% CI: 2.2–6.5). These data underscore potential concerns in South Asia, a region with high maternal stunting rates. Larger fetal size there may potentially increase rates of cephalopelvic disproportion and obstructed labor. A recent systematic review reported statistically significant increases in birthweight and no increase in risk of neonatal mortality and stillbirths with maternal protein-energy supplementation, but the review only included one study from South Asia, where short stature would be of main concern [21].
Reproductive Risk Factors

Maternal Age and Parity

Our team published a meta-analysis of 14 studies from LMICs, examining the association of maternal age and parity with SGA/preterm outcomes [22]. We standardized the exposure definitions in each dataset before pooling by creating exposure categories that matched maternal age categories with parity categories. We created combinations of age <18, 18-<35, or ≥35 with parity 0, 1–2, or ≥3, using those who were both age 18 to <35 and parity 1–2 as the reference group. This allowed us to better differentiate the impact of young/advanced age and nulliparity/high parity on neonatal outcomes, rather than solely depending on statistical control. We found that women who were both age <18 and nulliparous had the highest odds of SGA and preterm when compared to women in the reference category (age 18 to <35 and parity 1–2; table 2). Those who were nulliparous and age 18 to <35 had increased risk of SGA, but not of preterm, implying that young age is likely the driver for prematurity. Those who were parity ≥3 had heightened risk of preterm (in both age groups of 18 to <35 and ≥35), with the magnitude of the risk slightly higher in the higher age group. We saw no impact of advanced age or high parity on SGA. A systematic review examining parity similarly found increased risk of SGA and no increased risk of preterm among nulliparous women. However, in contrast to our findings, it found no increased risk of preterm associated with high parity [23]. Their RRs were not adjusted for age or other confounders.

The association between young age and adverse neonatal outcomes may have multiple biological mechanisms. The mother may have experienced incomplete physical growth prior to pregnancy, leading to lower stature and smaller pelvic dimensions, thus constraining fetal growth. The dual burden of growth (the
adolescent mother and the fetus) may be nutritionally taxing; in rural Nepal, a larger loss of mid-upper arm circumference in pregnancy was noted among adolescent mothers compared to their older counterparts [24]. Young age may also serve as a proxy for poor socioeconomic status and malnutrition; the literature suggests that controlling for socioeconomic status largely attenuates the associations between young maternal age and adverse outcomes [25]. Among mothers with advanced age, there is increased risk of congenital abnormalities and also of maternal morbidities, which may be linked to preterm birth (gestational diabetes, preeclampsia/eclampsia, etc.).

Any reported association between high parity and SGA or preterm may be partially, if not completely, driven by residual confounding. Characteristics correlated with high parity may not be sufficiently controlled by statistical adjustment in the existing literature, and thus, it may not be a biological mechanism driving this association. A study using data from Demographic and Health Surveys found that when examining child mortality rates across all births of mothers with the same completed fertility (the final number of children the mother had), there was no clear increase in the mortality rate with an increase in birth order [26]. Furthermore, for each birth order, children of mothers who had high completed fertility consistently had a higher mortality risk than children of mothers who had low completed fertility. As an example, figure 1a shows the crude under-5 mortality rates by a child’s birth order, stratified by the mother’s completed fertility, using data from the most recent Indian DHS. For each line (stratification by each unit of mothers’ completed fertility), there is no increase in the mortality rate as birth order increases. Figure 1b is a representation of the same data, but without the stratification by mother’s completed fertility. In this graph, we see the ‘parity effect.’ The study concludes that it only appears as if child mortality increases with parity because a larger proportion of children in higher birth orders are represented by mothers who have negative exposures correlated with high completed fertility. Hence, it may not be biological mechanisms but other confounding factors that are driving the association between parity and poor newborn/child outcomes.

**Birth Interval**

Several meta-analyses have reported an increased risk of SGA and preterm among those born after a short birth interval, although there is great variation in exposure definitions used across these analyses. Our meta-analysis, using five datasets from developing countries with standardized exposures and outcomes, estimated an adjusted OR 1.51 (95% CI: 1.31–1.75) for SGA and aOR 1.58 (95%
CI: 1.19–2.10) for preterm, comparing birth intervals (time between birth of previous child and the child of interest) of <18 months with a reference of 24 to <36 months [27]. Conde-Agudelo et al. [28] in their systematic review reported an aOR 1.26 (95% CI: 1.18–1.33) for SGA and 1.40 (95% CI: 1.24–1.58) for preterm, using the interpregnancy interval (IPI, time between birth of previous

Fig. 1. **a** Crude under-5 mortality rates, stratified by mother’s completed fertility and birth order, India DHS (2005–2006). Figure reproduced from Kozuki et al. [26]. **b** Replication of **a**, not stratified by mother’s completed fertility and birth order, India DHS (2005–2006).
child and the conception of the child of interest) of <6 months, compared against
a reference of 18 to <24 months. Long intervals had less consistent results; our
meta-analysis found a weak but significant association between a birth interval
≥60 months and SGA but not preterm, while Conde-Agudelo et al. [28] report-
ed stronger, significant associations for both SGA and preterm, using a cutoff of
IPI ≥60 months. We report in a separate analysis that the effect of short birth
intervals on adverse child outcomes may be modified by the frequency at which
women experience these short intervals. We noted that while all short interval
births had slightly increased risk of neonatal and infant mortality, short interval
births that occurred in later birth orders experienced higher risk [29]. This could
either be driven by an effect modification that occurs between short birth inter-
vals and high parity (supporting the maternal depletion hypothesis), or it could
be that women with characteristics associated with high fertility (e.g. poor socio-
economic status, malnutrition) may not be able to bear the nutritional and/or
physiological burden of repeated short birth interval pregnancies.

Understanding birth interval as an exposure is difficult, particularly when us-
ing data from low-resource settings. IPI is the preferred measure of the exposure,
compared to birth interval because the gestational length of the second preg-
nancy contributes to the interval in the latter. For instance, a preterm birth that
occurs in the latter pregnancy of an interval may make the IPI look arbitrarily
short. However, it is hard to have a proper measure of IPI without ultrasound
dating to get an accurate reading of time of conception. It is also difficult to de-
termine how best to account for spontaneous abortions and early stillbirths in
these intervals, events that may not have as large a burden on the mother as a
full pregnancy, but more than not having conceived at all. Long birth intervals
may be a result of conscious family planning, or may instead be due to infertil-
ity or other poor health exposures. The failure to differentiate these mechanisms
contributing to the length of a birth interval makes it difficult to arrive at con-
clusions pertaining to its impact on neonatal outcomes.

Conclusion

32.4 million SGA and 12.1 million preterm births occur in LMICs each year.
These newborns experience increased risk of short- and long-term health con-
sequences; for instance, newborns who are born both too small and too soon
experience a 16-fold increased risk of neonatal mortality, compared to their
term, appropriately sized counterparts [5]. Understanding causal mechanisms
that lead to SGA and preterm birth is critical for reducing these adverse health
outcomes. Existing literature highlights various nutritional and reproductive
health-related exposures associated with SGA and preterm birth. There are interventions that have demonstrated efficacy in reducing these outcomes, but there is generally less evidence of effectiveness. Chronic malnutrition may require intergenerational intervention, and potential consequences of increasing fetal size need to be taken into account when addressing acute malnutrition. While family planning can reduce the adverse effects of early pregnancy, increased access to contraceptives affects young age at first birth the least out of all reproductive health-related risk factors [30]. This suggests the need for more research on how to maximize the effectiveness of known, evidence-based interventions, but also for uncovering new, efficacious interventions, taking into account the independent and shared causal mechanisms operating on SGA and preterm outcomes.

Disclosure Statement

The authors declare that no financial or other conflict of interest exists in relation to the contents of the chapter.

References


Abstract
Globally, 15% of infants are low birthweight (LBW; <2,500 g) each year. Most LBW infants are either preterm (<37 weeks gestation) and/or growth restricted in utero. These etiologies of LBW have different prevalence, risk factors, health and survival consequences, and are attenuated by different interventions. Birthweight has generally been easier to measure than gestational age in low-resource settings. This is now changing rapidly with access to antenatal care and ultrasound and allows providers, researchers and public health practitioners the opportunity to identify infants born too soon or too small, and to better target interventions to reduce mortality and morbidity associated with these conditions. Understanding the mortality patterns and burden of preterm or small for gestational age (SGA) is important for designing programs to prevent these outcomes and improve survival of these infants. We present here estimates of the increased mortality risk, timing of mortality, and attributable mortality burden associated with these conditions. Such data provide estimates of the potential for proven maternal interventions to reduce SGA burden and its associated mortality, as well as identify infants who would most benefit from clinical and public health interventions to improve their survival and health.

Introduction
Low birthweight (LBW) infants have long been known to have higher mortality than those born 2,500 g or heavier, with mortality estimated to be 20-fold greater than for normal birthweight babies [1]. Sixty to 80% of the 3.3 million neonatal deaths annually are estimated to be attributed to this condition [2–4]. While
a small component of size at birth that results in LBW may be genetic, most LBW arises from being born preterm or growth restriction in utero, or both conditions. Furthermore, the cut point of 2,500 g for defining LBW is arbitrary and was originally used to identify preterm infants rather than as a marker of mortality risk [5, 6]. These conditions and their severity (how preterm or how growth restricted), rather than birthweight per se, will impact mortality risk, and the timing and causes of death.

It is estimated that a total of 120.4 million births occurred in 138 low- and middle-income countries (LMICs) in 2010 [7]. Eighteen million (15%) of these births were classified as LBW (<2,500 g at birth) and 32.4 million as small for gestational age (SGA; <10th percentile of the Alexander reference population of weights for gestational age) [7, 8]. The vast majority of these SGA infants (91%) were born after 37 weeks’ complete gestation. Approximately 15 million infants were born preterm in 2010, including in high-income countries, where preterm is an increasing problem [9], and 13.7 million of these were born in LMICs [7]. These preterm infants have well-characterized mortality risk and causes, especially those born very preterm [3, 10]. SGA infants are considered to have higher mortality risk than appropriate for gestational age (AGA) infants [11–15]. However, the mortality risk, timing and causes of death have not been as well studied in LMICs. To date, it has been difficult to compare SGA prevalence and risks in the literature because many different reference populations have been used to define SGA, and this can result in significant variations in these estimates within the same data set [16]. Furthermore, the mortality risks may be quite different for term and preterm SGA infants, and recent studies suggest there are a significant number of infants born SGA but not LBW whose mortality risks have not been well characterized [17, 18]. In this paper, we discuss recent estimates of early, late and postneonatal mortality associated with term and preterm SGA, as well as being born SGA but not LBW.

**Associations between SGA, Low Birthweight and Preterm**

It has been estimated that 32.4 million SGA infants were born in 138 LMICs in 2010 [7]. Of these, 29.6 million were term and the remainder preterm. This pattern of high SGA burden in LMICs is in contrast to higher-income countries where preterm predominates. SGA has been defined as birthweight for a given gestational age that falls below the 10th percentile of a large population-based reference distribution [8]. The use of a reference population from a high-income country results in very high prevalence in LMICs, especially in South Asia [7]. In order to better appreciate the severity of SGA in such settings, the analy-
ses we present here defined more severe SGA as birthweight below the 3rd percentile of the Oken reference population, which is similar to that of the Alexander reference population which does not provide data at percentiles other than the 10th [8, 19]. In an analysis that examined data from 22 population-based cohorts of over 2 million live births (table 1), studies from South Asia had the highest prevalence of SGA, and Latin America the lowest [17]. Within these 22 studies, over half of SGA infants were born with birthweights ≥2,500 g (table 1; 54% in Asia, 65% in Africa, and 59% in Latin America). Among LBW SGA infants, about 20% were born preterm in Asia and Africa, but 45% were preterm in Latin America, indicating a much higher proportionate burden of preterm in Latin America.

Table 1. SGA infants born normal weight, term and preterm LBW in 22 studies from Asia, Sub-Saharan Africa and Latin America [17]

<table>
<thead>
<tr>
<th>Region</th>
<th>SGA, %</th>
<th>SGA not LBW, %</th>
<th>SGA term LBW, %</th>
<th>SGA preterm LBW, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asia</td>
<td>40</td>
<td>54</td>
<td>37</td>
<td>9</td>
</tr>
<tr>
<td>Africa</td>
<td>25</td>
<td>65</td>
<td>27</td>
<td>8</td>
</tr>
<tr>
<td>Latin America</td>
<td>8</td>
<td>59</td>
<td>23</td>
<td>19</td>
</tr>
</tbody>
</table>

Mortality Risk and SGA

The risk ratios (RR) for neonatal mortality among SGA infants born below the 3rd percentile were 1.91 (95% CI: 1.40–2.60), 2.23 (95% CI: 1.52–3.28) and 4.01 (95% CI: 2.20–7.28), for Asia, Africa and Latin America, respectively, compared with those who were not SGA [17]. RRs among SGA infants from the 3rd percentile to <10th percentile of the Alexander reference population were 1.20 (95% CI: 0.87–1.66), 1.27 (95% CI: 0.95–1.70) and 1.93 (95% CI: 1.02–3.64) in Asia, Africa and Latin America, respectively [16]. RRs were comparable between Asia and Africa but higher in Latin America. This was primarily due to lower neonatal mortality rates in the reference population of AGA infants in Latin America, relative to Asia or Africa. For example, the median neonatal mortality rate in the 4 Latin American studies was 8.8 deaths per 1,000 live births, compared with 12.0 and 21.6 in Asia and Africa, respectively, where there are many causes of death not present in the Latin American studies.

Neonatal mortality risk was lowest among term SGA infants in all three regions, higher in preterm AGA infants, and highest among those born both preterm and SGA (fig. 1). As with SGA, regardless of whether term or preterm, RRs
were comparable in Asia and Africa but higher in Latin America. These higher RRs in Latin America were driven by lower neonatal mortality rates in term AGA infants in Latin America (2.4 per 1,000 live births), compared with 7.9 and 8.4 per 1,000 live births in Asia and Africa, respectively. It should be noted that the neonatal mortality risk was higher for preterm infants, whether SGA or AGA, than term SGA infants.

Patterns of mortality risk varied with timing of death among SGA preterm infants compared to those born term AGA (fig. 2). Mortality risk was comparable for term SGA infants in the early, late and postneonatal periods, with a 3-fold higher mortality risk than among term AGA infants. For those who were preterm but not SGA, mortality risk declined from the early through late through postneonatal periods but remained significant in the latter period. For infants who were both preterm and SGA, mortality risk was comparable in the early and late neonatal periods but declined in the postneonatal period. Regardless of time period, infants born preterm and SGA had the highest mortality risk relative to those born term AGA.

Since the prevalence of term SGA infants whose birthweight was ≥2,500 g was large, we estimated mortality RRs for these infants separately from term SGA LBW infants (table 2). As expected, term SGA LBW infants had higher mortal-
Mortality of SGA Infants 33

Ity risk relative to term AGA infants in both the neonatal and postneonatal periods compared with term SGA infants not born LBW. However, term SGA not LBW infants still had a significantly higher mortality risk compared with term AGA infants [RR: 1.9 (95% CI: 1.3–2.4) for neonatal mortality and RR: 1.5 (95% CI: 1.3–1.7) for postneonatal mortality].

Table 2. RRs for neonatal and postneonatal mortality among term SGA LBW and term SGA normal birth weight infants compared with term AGA infants [17]

<table>
<thead>
<tr>
<th></th>
<th>Term SGA not LBW RR (95% CI)</th>
<th>Term SGA LBW RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Early</td>
<td>Late</td>
</tr>
<tr>
<td>Term SGA</td>
<td>3.12</td>
<td>3.09</td>
</tr>
<tr>
<td>Preterm AGA</td>
<td>0.96</td>
<td>0.89</td>
</tr>
<tr>
<td>Preterm SGA</td>
<td>5.06</td>
<td>4.99</td>
</tr>
</tbody>
</table>

Fig 2. RRs for early, late and post-neonatal mortality by SGA and/or preterm in 22 studies in Asia, Sub-Saharan Africa and Latin America (all regions combined) [17].
Number of Deaths Attributable to SGA

A total of 1.3 million or 26% of the just over 5 million infant deaths that occurred in 138 LMICs in 2010 were attributable to SGA (table 3) [Lee, unpubl. data]. Of these, 1.3 million SGA deaths, ~845,000 (29% of neonatal deaths attributable to SGA) and ~442,000 (20% attributable to SGA) occurred in the neonatal and postneonatal periods, respectively. Comparable numbers were estimated for 2011 (817,000 attributed to SGA in the neonatal period and 418,000 in the post-neonatal period) [18]. 75% of SGA-attributed neonatal and 80% of postneonatal deaths occurred among term SGA infants. This is because the prevalence of term SGA is much higher than that of preterm SGA, even though the mortality risk in preterm SGA infants is much higher than in those born term SGA.

Conclusions

Infants born SGA are at higher neonatal and postneonatal mortality risk compared with infants born term and AGA. SGA infants born preterm are at higher mortality risk than term SGA ones. Over half of SGA infants are not LBW, especially in South Asia, but these infants are at an almost 2-fold higher neonatal mortality risk than term AGA infants. Hence, clinicians and public health professionals need to pay attention to such infants, even though they may be at lower risk than term LBW SGA infants. SGA is a significant underlying contributor to neonatal and infant mortality, contributing to 29 and 26% of these deaths, respectively. These data suggest that interventions to prevent SGA could have a major impact on neonatal and infant survival in resource-limited settings. Such interventions include iron-folate, multiple micronutrient, or balanced energy protein supplementation during pregnancy [20]. These results also demonstrate that research to identify cost-effective interventions to improve the survival and health of SGA infants could save many lives and contribute to meeting Millennium Development Goal 4.

Table 3. Neonatal, postneonatal and infant deaths attributable to term and preterm SGA among 138 low- and middle-income countries in 2010 [A.C.C. Lee, pers. commun.]

<table>
<thead>
<tr>
<th>Components</th>
<th>Neonatal deaths (2,963,794)</th>
<th>Postneonatal deaths (2,187,393)</th>
<th>All infant deaths (5,151,187)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Term SGA</td>
<td>633,504</td>
<td>357,078</td>
<td>990,582</td>
</tr>
<tr>
<td>Preterm SGA</td>
<td>211,362</td>
<td>122,664</td>
<td>334,026</td>
</tr>
<tr>
<td>All SGA</td>
<td>844,866 (29%)</td>
<td>441,686 (20%)</td>
<td>1,324,608 (26%)</td>
</tr>
</tbody>
</table>
Disclosure Statement

The authors declare that no financial or other conflict of interest exists in relation to the contents of the chapter.

References

Abstract
Intrauterine growth restriction and preterm birth (PTB) account for a large share of global child mortality, morbidity and developmental loss. Of the numerous risk factors for these conditions, maternal infections have been most consistently identified. Our aim was to study if presumptive antibiotic treatment of pregnant women before any signs of the onset of labor would promote fetal growth and reduce the incidence of PTB or low birthweight (LBW). In a systematic literature search, we identified 14 clinical trials of sufficient quality. Eight trials concluded that there was a positive effect on one or both of the conditions, and others found no such association. The trials reporting an effect were typically conducted in Sub-Saharan Africa (6 trials) and with broadest spectrum antibiotics, whereas data from India (2) suggested no intervention effect and trials in the US (5) or Europe (1) yielded both positive and negative findings. We conclude that appropriately chosen presumptive antimicrobial treatment of pregnant women, targeting infections in the reproductive tract but also other maternal infections such as malaria, other parasitic diseases, skin infections, and periodontitis, can in selected contexts promote fetal growth and reduce the incidence of PTB and LBW.
**Introduction**

Worldwide, an estimated 20 million babies are born with a low birthweight (LBW) each year, contributing to approximately 10–15% of the global mortality for under-5-year-old children and a large share of childhood morbidity and developmental loss [1–4]. Two factors determine size at birth: the rate of growth during the fetal period and the duration of pregnancy. Thus, an LBW may reflect either intrauterine growth restriction (IUGR), preterm delivery, or both. Whilst the exact molecular mechanisms leading to early-onset labor or restricted fetal growth are largely unknown, a number of risk factors have been identified for both conditions [5, 6]. These factors have often been categorized into maternal conditions (e.g. maternal genetics, nutritional status or chronic illness), placental pathology (e.g. unfavorable location in the uterus or abnormal vascularization), infant characteristics (e.g. genetic aberration) or environmental or other factors (smoking, high altitude, others). Of all the factors, maternal or fetal infections, especially those of the reproductive tract, placenta or amniotic membranes, have most consistently been associated with both preterm birth (PTB) and IUGR [5, 6].

Because of the assumed causative role of infections, there has been a wide interest to study the efficacy of presumptive or targeted treatment of pregnant women with antimicrobial agents as a means to promote fetal growth and prevent PTB. In malaria-endemic areas, especially in Sub-Saharan Africa, intermittent preventive treatment of malaria in pregnancy has indeed proven beneficial in this respect [7] and the World Health Organization now recommends its regular use in moderate-to-high malaria transmission areas in Africa [8]. The results from studies with antibacterial agents aiming at the cure of reproductive tract or amniotic infections or bacterial vaginosis have yielded more conflicting results. The authors of the only reported systematic Cochrane review, published in 2002, found that antibiotic prophylaxis during the second or third trimester seemed to reduce the risk of premature rupture of membranes and also PTB among women with bacterial vaginosis. However, the authors also noted a general scarcity of data and a substantial possibility for follow-up bias in the reported studies. Therefore, they considered the data insufficient to recommend the use of routine antibiotics during pregnancy [9].

Since the 2002 Cochrane report, there have been a number of new trials published, some of which have reported a positive effect on birth outcomes and others observed no association. Authors of a second systematic review and meta-analysis in 2011, concentrating solely on the use of clindamycin antibiotic among women with bacterial vaginosis, concluded that there was a positive impact but emphasized that the effect was evident only if the study population suffered from the targeted infection, if the treatment was given early enough, if the selected...
compound had a favorable antimicrobial coverage, and if its route of administration facilitated a systemic drug distribution in the host [10]. We found the above conditions plausible and decided to summarize the current knowledge on the potential role of presumptive antibiotic treatment of pregnant women for the prevention of IUGR or PTB by applying the same criteria. Hence, we carried out a literature review for published, clinical trials that measured birthweight or the duration of pregnancy as outcomes and in which pregnant women were treated with broad-spectrum antibiotics orally or as an injection before any signs of labor were evident. This report summarizes the findings of the literature review.

**Methods**

We performed a computerized search of Ovid MEDLINE® In-Process & Other Non-Indexed Citations database (1946 to February 2014) which covers the international literature on biomedicine, including the allied health fields and the biological and physical sciences, humanities, and information science as they relate to medicine and health care. The database also includes PubMed-not-MEDLINE records. Three authors (P.A., O.P. and H.V.) approved the search strategy. We searched for both subject headings and their corresponding keywords that are related to pregnancy, premature birth, birthweight, fetal growth and antimicrobial agents. The search was limited to clinical trials. No language restrictions were applied.

We included randomized clinical trials that compared early treatment of asymptomatic pregnant women with broad-spectrum antibiotics before any signs of labor were evident. Only trials primarily aiming at the promotion of fetal growth or extension of the duration of pregnancy were included, i.e. trials that looked e.g. only at a cure of an infection or a change in colonization were excluded. Antibiotics having antimicrobial activity against both aerobic and anaerobic bacteria, both on the Gram-negative and the Gram-positive side were considered broad-spectrum. Early treatment was defined as one starting before 32 gestation weeks, and asymptomatic meant that the participants did not have signs of acute illness or imminent delivery at the time of enrolment. Other inclusion criteria included an oral or intravenous administration of the antibiotics and the use of a control group that received no presumptive antibiotic treatment besides a possible malaria prophylaxis.

The primary outcomes of interest were mean birthweight and the mean duration of pregnancy. Secondary outcomes included the incidence of LBW and PTB. Birth lengths were reported only from one trial, and the proportion of babies who were small for gestational age at birth was not reported at all. Hence, these variables were not used as outcome indicators.

Two authors (H.V. and O.P.) reviewed independently the titles and abstracts of all retrieved articles, unblinded to the author information. They excluded or included articles based on the above-described pre-agreed criteria. After two independent assessments, the reviewers compared the results and reached agreement through discussion and reevaluation. For all potential articles, they obtained full text copies. After full text evaluation and consensus discussion, they chose articles to be included in the review. If
the same data were used in multiple publications, they chose the study that had the most appropriate primary outcome measurements. For the assessment of study quality, we used a modification of a quality assessment tool developed by Lamont and his collaborators [10]. With this tool, we assessed the reviewed articles for defined validity criteria. Some of the quality criteria concerned general methodology (control group, randomization, control group, group balance, blinding, attrition), others looked at how well study-specific criteria were described and fulfilled (participant representativeness, directly observed treatment, quality of birthweight and pregnancy duration measurement). We categorized each item as adequate, inadequate, or not stated. After two independent assessments, the reviewers compared the results and reached agreement through discussion and reevaluation.

**Results**

The details of article retrieval and the flow of the literature selection are shown in table 1 and figure 1. Of the 374 initially identified articles, we excluded none based on the title alone. A total of 360 were dropped after an abstract review and 7 based on full text inspection. Finally, 15 articles from 14 trials were left in the study material. The total number of participants included in these trials was 15,787.

Table 2 shows the summary of our assessment of trial quality. Most trials met well the general methodology quality criteria, i.e. they were randomized, controlled, blinded, and had a reasonable loss to follow-up. Somewhat more variation was observed in the study-specific criteria, especially in the verification of study medication consumption or the method used for estimating the duration of pregnancy (table 2). All trials were, however, considered of good quality.

The summary characteristics and main findings from the included trials are shown in table 3, sorted primarily by region of study (Africa, Asia, America, Europe), secondarily by year of publication. Six trials were carried out in Sub-Saharan Africa (Kenya, Uganda, Malawi, Zambia, Tanzania, total number of participants 10,790), 2 in India (661 participants), 5 in the United States (3,842 participants) and one in the UK (494 participants). Publication year ranged from 1987 to 2013.

The authors of two articles stated that they aimed to test interventions for improved birth outcomes in general; one mentioned both LBW and PTB as the addressed problem and all others emphasized PTB only. The assumed mechanism leading to improved outcomes was an effect of the antibiotic treatment on maternal reproductive tract infections (4 trials), sexually transmitted infections (2), genital ureaplasma or mycoplasma infection (2), bacterial vaginosis (2), urinary tract infection (1), chorioamnionitis (1), preterm rupture of amniotic membranes (1), or malaria (1).

In 6 trials, the inclusion criteria included specified risk factors for adverse birth outcomes; in others, the participants represented a general population of
pregnant women. Participants were enrolled in first and second trimester in 7 trials, at any time point of pregnancy in one (72% were enrolled in the 1st to 2nd trimester) and before 32 gestation weeks in the other trials. The tested antibiotic regimens included erythromycin alone (in 4 trials), erythromycin + metronidazole (in 3 trials), erythromycin + cephalaxin (1), clindamycin (2), ceftriaxone (1), cefetamet-pivoxil (1), azithromycin + cefexime + metronidazole (1), azithromycin (2), and azithromycin + sulfadoxine-pyrimethmine (1). Some trials tested more than one investigative intervention; hence, the provided numbers do not match with the number of included trials.

Of the 14 trials, 4 reported a statistically significant difference in the duration of pregnancy, 2 reported a marginally significant association (p values just above 0.05 or confidence interval for a relative risk just including 1), one did not report on pregnancy duration, and 9 showed no evidence of antibiotic effect. For birthweight outcomes, 5 trials reported a statistically significant effect, one gave no birthweight data, and 8 reported no effect. Looking at the outcome clusters together, 4 of the studies reported a positive effect on both the duration of preg-

Table 1. Retrieval of articles in the search process

<table>
<thead>
<tr>
<th>Search No.</th>
<th>Search strategy</th>
<th>Identified articles</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pregnancy/</td>
<td>680,330</td>
</tr>
<tr>
<td>2</td>
<td>Pregnant Women/</td>
<td>4,951</td>
</tr>
<tr>
<td>3</td>
<td>1 or 2</td>
<td>680,752</td>
</tr>
<tr>
<td>4</td>
<td>pregnan*.tw.</td>
<td>361,787</td>
</tr>
<tr>
<td>5</td>
<td>3 or 4</td>
<td>760,390</td>
</tr>
<tr>
<td>6</td>
<td>Premature Birth/</td>
<td>5,936</td>
</tr>
<tr>
<td>7</td>
<td>(prematurity or preterm birth or preterm).tw.</td>
<td>53,044</td>
</tr>
<tr>
<td>8</td>
<td>Obstetric Labor, Premature/</td>
<td>11,772</td>
</tr>
<tr>
<td>9</td>
<td>(preterm labour or preterm delivery).tw.</td>
<td>7,505</td>
</tr>
<tr>
<td>10</td>
<td>6 or 7 or 8 or 9</td>
<td>59,505</td>
</tr>
<tr>
<td>11</td>
<td>Birth Weight/</td>
<td>31,689</td>
</tr>
<tr>
<td>12</td>
<td>birth weight.tw.</td>
<td>39,499</td>
</tr>
<tr>
<td>13</td>
<td>Fetal Growth Retardation/</td>
<td>12,484</td>
</tr>
<tr>
<td>14</td>
<td>intrauterine growth retardation.tw.</td>
<td>4,883</td>
</tr>
<tr>
<td>15</td>
<td>exp Infant, Low Birth Weight/</td>
<td>25,359</td>
</tr>
<tr>
<td>16</td>
<td>small for gestational age.tw.</td>
<td>5,827</td>
</tr>
<tr>
<td>17</td>
<td>11 or 12</td>
<td>58,957</td>
</tr>
<tr>
<td>18</td>
<td>13 or 14 or 15 or 16</td>
<td>39,574</td>
</tr>
<tr>
<td>19</td>
<td>exp Anti-Infective Agents/</td>
<td>1,229,226</td>
</tr>
<tr>
<td>20</td>
<td>antibiotic*.tw.</td>
<td>223,057</td>
</tr>
<tr>
<td>21</td>
<td>19 or 20</td>
<td>1,314,329</td>
</tr>
<tr>
<td>22</td>
<td>17 or 18</td>
<td>80,636</td>
</tr>
<tr>
<td>23</td>
<td>10 or 22</td>
<td>121,687</td>
</tr>
<tr>
<td>24</td>
<td>5 and 21 and 23</td>
<td>2,980</td>
</tr>
<tr>
<td>25</td>
<td>limit 24 to clinical trial, all</td>
<td>374</td>
</tr>
</tbody>
</table>
nancy and birthweight, 4 reported a positive impact on either of them and 6 found no effect (table 3).

Out of the 6 trials carried out in Africa, all but one reported a positive effect on either birthweight or the duration of pregnancy. All of these trials tested a relatively wide-spectrum antibiotic regimen, i.e. azithromycin, third-generation cephalosporin, a combination of them, or a combination of erythromycin and metronidazole. When observed, the difference between the intervention and control groups was approximately 150 g in mean birthweight and 30% in the

**Fig. 1.** Flowchart of the literature search. Antibiotic treatment not suitable means no antibiotic treatment or only malaria prophylaxis, treatment not enough broad spectrum, no oral or intravenous treatment, treatment given too late.
incidence of LBW (table 3). The respective difference was roughly 0.5 gestation weeks for the mean duration of pregnancy and approximately 20% for the incidence of PTB. In the largest trial, conducted in Malawi, Tanzania and Zambia and employing erythromycin-metronidazole as the antibiotic of choice, a significant difference was observed only among the HIV-negative but not among the HIV-positive participants [14]. The only trial where no effect was found was conducted in Malawi and tested the effect of a two-dose azithromycin regimen, given in combination with sulfadoxine-pyrimethamine (SP) malaria prophylaxis [15]. A contrasting result, i.e. a significant impact on both birthweight and pregnancy duration was reported from another azithromycin trial carried out approximately at the same time in Malawi [16, 17]. The main apparent differences between the two Malawi azithromycin trials were the trial site, burden of

<table>
<thead>
<tr>
<th>First author</th>
<th>Overall quality</th>
<th>General methodology quality criteria</th>
<th>Study-specific quality criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>randomization</td>
<td>control</td>
</tr>
<tr>
<td>Temmerman [11]</td>
<td>good</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Gichangi [12]</td>
<td>good</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Gray [13]</td>
<td>good</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Goldenberg [14]</td>
<td>good</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>van den Broek [15]</td>
<td>good</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Luntamo [16, 17]</td>
<td>good</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Paul [18]</td>
<td>good</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Sen [19]</td>
<td>good</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>McCormack [20]</td>
<td>good</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>McGregor [21]</td>
<td>good</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Eschenbach [22]</td>
<td>good</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Hauth [23]</td>
<td>good</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Andrews [24]</td>
<td>good</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Ugwumadu [25]</td>
<td>good</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

+ = Adequate; − = inadequate; NS = not stated. Quality assessment criteria for adequate performance in the various variables were the following: randomization – random allocation to study groups; control – inclusion of a control group that did not get antibiotics but was otherwise treated in the same manner as the intervention group; group balance – no obvious differences in summary statistics between the intervention and control group at enrolment; blinding – the outcome assessors were not aware of group allocation; attrition – at least 75% of the originally enrolled participants were included in the outcome analysis; participant representativeness – participant characteristics were not markedly different from patients attending primary or secondary clinics in the country of study; directly observed treatment – the study team could observe and verify that the participants took the trial medication; birthweight measure – taken with appropriate scales and within 14 days of birth; pregnancy duration measure – duration of pregnancy determined with obstetric ultrasound at enrolment. Trials scoring ‘inadequate’ on no more than 3 criteria were considered of good quality.
### Table 3. Summary characteristics and findings from the included trials

<table>
<thead>
<tr>
<th>Reference</th>
<th>Location</th>
<th>Target condition</th>
<th>Enrolment criteria</th>
<th>Gest. age, gw</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temmerman et al. [11], 1995</td>
<td>Nairobi, Kenya (n = 400)</td>
<td>sexually transmitted infections, PTB</td>
<td>pregnant women</td>
<td>28–32</td>
</tr>
<tr>
<td>Gichangi et al. [12], 1997</td>
<td>Nairobi, Kenya (n = 320)</td>
<td>poor pregnancy outcomes</td>
<td>history of PTB, LBW or stillbirth</td>
<td>28–32</td>
</tr>
<tr>
<td>Gray et al. [13], 2001</td>
<td>Rakai, Uganda (n = 4,020)</td>
<td>sexually transmitted infections, poor pregnancy outcomes</td>
<td>15- to 59-year-old pregnant women</td>
<td>any time point 1st trim. 39%, 2nd trim. 33%</td>
</tr>
<tr>
<td>Goldenberg et al. [14], 2006</td>
<td>Zambia, Tanzania, Malawi (n = 2,433)</td>
<td>chorio-amnionitis, PTB</td>
<td>86% HIV positive (part of an HPTN 024 trial, on the prevention of mother-child HIV transm.)</td>
<td>20–24</td>
</tr>
<tr>
<td>van den Broek et al. [15], 2009</td>
<td>Southern Malawi (n = 2,297)</td>
<td>genital tract infections, PTB</td>
<td>pregnant women</td>
<td>&lt;24</td>
</tr>
<tr>
<td>Luntamo et al. [16], 2010; [17], 2013</td>
<td>Mangochi, Malawi (n = 1,320)</td>
<td>reproductive tract infections, malaria</td>
<td>pregnant women</td>
<td>14–26</td>
</tr>
<tr>
<td>Paul et al. [18], 1998</td>
<td>New Delhi, India (n = 437)</td>
<td>genital tract infections, LBW, PTB</td>
<td>pregnant women</td>
<td>26–30</td>
</tr>
<tr>
<td>Sen et al. [19], 2005</td>
<td>Kolkata, India (n = 224)</td>
<td>reproductive and urinary tract infections, LBW, PTB</td>
<td>pregnant women</td>
<td>14–24</td>
</tr>
<tr>
<td>McCormack et al. [20], 1987</td>
<td>Boston, Mass., USA (n = 1,105)</td>
<td><em>Ureaplasma or Mycoplasma</em> infection, PTB</td>
<td>positive vaginal culture for <em>U. urealyticum or M. hominis</em></td>
<td>22–32</td>
</tr>
<tr>
<td>McGregor et al. [21], 1990</td>
<td>low-income area in Denver, Colo., USA (n = 229)</td>
<td>preterm rupture of amniotic membranes, PTB</td>
<td>pregnant women</td>
<td>26–30</td>
</tr>
<tr>
<td>Eschenbach et al. [22], 1991</td>
<td>5 university clinics in the USA (n = 1,181)</td>
<td><em>Ureaplasma</em> infection, PTB</td>
<td>positive culture for <em>U. urealyticum</em></td>
<td>&lt;30</td>
</tr>
<tr>
<td>Hauth et al. [23], 1995</td>
<td>public health clinics Alabama, USA (n = 624)</td>
<td>BV, PTB</td>
<td>previous preterm delivery or weight below 50 kg</td>
<td>22–24</td>
</tr>
<tr>
<td>Andrews et al. [24], 2003</td>
<td>Birmingham, Ala., USA (n = 703)</td>
<td>PTB</td>
<td>positive fetal fibronectin test</td>
<td>21–25</td>
</tr>
<tr>
<td>Ugwumadu et al. [25], 2003</td>
<td>London and Surrey, UK (n = 494)</td>
<td>BV, PTB</td>
<td>pregnant women</td>
<td>12–22</td>
</tr>
</tbody>
</table>

n = Number of subjects recruited; gw = gestational weeks; dur. = duration; BV = bacterial vaginosis.
<table>
<thead>
<tr>
<th>Intervention</th>
<th>Control</th>
<th>Effect on birthweight/LBW</th>
<th>Effect on gest. dur./% preterm</th>
</tr>
</thead>
<tbody>
<tr>
<td>ceftriaxone 250 mg i.m.</td>
<td>placebo i.m.</td>
<td>significant; mean BW 3,209 vs. 3,056 g, p = 0.01; LBW incid. 4.0 vs. 9.3%, p = 0.08</td>
<td>none; mean dur. 38.9 vs. 38.9 gw, p = 0.90; preterm % not stated</td>
</tr>
<tr>
<td>cefetamet-pivoxil 2 g single dose</td>
<td>Placebo</td>
<td>significant; mean BW 2,927 vs. 2,772 g, p = 0.04; LBW incid. 19 vs. 33%, p = 0.04</td>
<td>trend; mean dur. 37.9 vs. 37.2 gw, p = 0.06; preterm % not stated</td>
</tr>
<tr>
<td>azithromycin 1 g + cefixime 400 mg + metronidazole 2 g single dose</td>
<td>low-dose multivitamins</td>
<td>significant; LBW proxy 9.1 vs. 11.0%; RR 0.68 (0.53–0.86), mean values not stated</td>
<td>trend; preterm 9.8 vs. 11.8%; RR 0.77 (0.56–1.05); mean values not stated</td>
</tr>
<tr>
<td>metronidazole 250 mg + erythromycin 250 mg daily for 7 days; additional treatment at labor</td>
<td>placebo</td>
<td>none; HIV-pos.: mean BW 2,946 vs. 2,951 g, NS, LBW incid. 14.4 vs. 13.4%, NS; HIV-neg.: mean BW 3,117 vs. 3,082 g, NS; LBW incid. 9.6 vs. 5.9%, NS</td>
<td>none among HIV-pos.; significant among the HIV-neg.: mean dur. 39.4 vs. 38.5 gw, p = 0.04; preterm 16.5 vs. 28.4%, p = 0.04</td>
</tr>
<tr>
<td>azithromycin 1 g at 16–28 gw and at 28–32 gw, SP at the same time points</td>
<td>SP at 16–28 gw and at 28–32 gw</td>
<td>none; mean BW 3,030 vs. 2,990 g, p = 0.08; LBW incid. not stated</td>
<td>none; mean dur. 38.5 vs. 38.4 gw, p = 0.18; preterm 16.8 vs. 17.0%, p = 0.75</td>
</tr>
<tr>
<td>azithromycin 1 g at enrolment and at 32 weeks, SP monthly</td>
<td>SP at enrolment and at 32 weeks or SP monthly</td>
<td>significant; mean BW 3,020 vs. 2,890 g, p = 0.001; LBW incid. 7.9 vs. 12.9%, p = 0.02</td>
<td>significant; mean dur. 38.8 vs. 38.4 gw, p &lt; 0.01; preterm 11.8 vs. 17.9%, p = 0.01</td>
</tr>
<tr>
<td>erythromycin 500 mg ×2 for 6 weeks</td>
<td>placebo</td>
<td>none; mean BW 2,811 vs. 2,887 g, p = 0.08; LBW 21.6 vs. 17.0% (p = 0.37)</td>
<td>none; mean dur. not stated; preterm 13.2 vs. 10.4%, p = 0.53</td>
</tr>
<tr>
<td>metronidazole 200 mg × 3 for 7 days + cephalaxin 500 mg × 2 for 5 days</td>
<td>iron and folic acid capsules</td>
<td>none; mean BW 2,545 vs. 2,584 g, p = 0.51; LBW incid. 40 vs. 36%, p = 0.28</td>
<td>none; mean dur. not stated; preterm 8 vs. 11%, p = 0.06</td>
</tr>
<tr>
<td>group 1: erythromycin 250 mg × 4 for 6 weeks; group 2: clindamycin 150 mg × 4 for 6 weeks</td>
<td>Placebo</td>
<td>none for clindamycin or erythromycin started in 2nd trimester; significant for later erythromycin: mean BW 3,331 vs. 3,187 g (p = 0.04); LBW 3 vs. 12% (p &lt; 0.05)</td>
<td>not stated</td>
</tr>
<tr>
<td>erythromycin 500 mg ×2 for 6 weeks</td>
<td>placebo</td>
<td>none; mean BW 3,132 vs. 3,099 g, p = 0.7; LBW incid. not stated</td>
<td>none; mean dur. 39.3 vs. 39.2 gw, p &gt; 0.05; preterm 7 vs. 8%, p &gt; 0.05</td>
</tr>
<tr>
<td>erythromycin 333 mg × 3 until 35 gw</td>
<td>placebo × 3 until 35 gw</td>
<td>none; mean BW 3,302 vs. 3,326 g, p &gt; 0.05; LBW incid. 8 vs. 6%, p &gt; 0.05</td>
<td>none; mean dur. not stated; preterm 9 vs. 9%, p &gt; 0.05</td>
</tr>
<tr>
<td>metronidazole 250 mg × 3 for 7 days + erythromycin 333 mg × 3 for 14 days; retreatment 2–4 weeks later if BV+</td>
<td>place, retreatment with the same 2–4 weeks later if BV diagnosed</td>
<td>not stated</td>
<td>significant; preterm 26 vs. 36%; RR 1.4 (1.1–1.8), p = 0.01; mean values not stated</td>
</tr>
<tr>
<td>metronidazole 250 mg × 3 + erythromycin 250 mg × 4 for 10 days</td>
<td>identical placebo capsules for 10 days</td>
<td>none; mean BW not stated; LBW incid. 12.7 vs. 14.3%, p &gt; 0.05</td>
<td>none; mean dur. 38.1 vs 38.1 gw, p = 0.96; preterm 14.4 vs 12.4%, p &gt; 0.05</td>
</tr>
<tr>
<td>clindamycin 300 mg × 2 daily for 5 days</td>
<td>placebo</td>
<td>none; mean BW 3,227 vs. 3,239 g, p = 0.84; LBW incid. 8 vs. 10%, p = 0.53</td>
<td>significant; mean dur. 38.8 vs 38.0 gw, p = 0.052; preterm 5 vs. 12%, p = 0.001</td>
</tr>
</tbody>
</table>
malaria (higher in the trial reporting no effect) and the employed malaria prophylaxis (two SP doses in the trial reporting negative results, monthly SP in the one reporting positive impact).

Neither of the 2 trials carried out in India reported any impact on birth outcomes [18–19]. The trials were relatively small and used a narrower-spectrum antibiotic (erythromycin alone or cephalexin – metronidazole) than those on the African continent. The mean birthweights were also significantly lower in the Indian than in the African studies, whereas the proportion of preterm babies appeared lower in the Indian study populations (table 3).

The remaining 6 trials were carried out in the US or UK, with conflicting results (table 3). Of the 3 trials using erythromycin alone, one suggested a positive impact on birthweight, but only if the treatment was given in the third trimester [20], whereas the 2 others showed no effect on any birth outcomes [21, 22]. A combination of erythromycin and metronidazole was tested in 2 trials, one signifying a positive impact on the incidence of PTB and the other one suggesting no effect [23, 24]. The effect of clindamycin was also tested in 2 trials. Of these, one suggested a positive impact on the incidence of PTB, whilst the other one advocated no effect [20, 25].

Discussion

In the current literature review, we aimed to identify and summarize published data on the potential of maternal presumptive antimicrobial treatment to prevent PTB and fetal IUGR. In total, we identified 14 trials, 8 of which concluded that there was a positive effect on one or both of the conditions and others finding no association between the tested intervention and the outcomes. The trials reporting improved outcomes were typically conducted in Africa, whereas data from India suggested no intervention effect and trials in the US or Europe yielded both positive and negative findings. The African trials typically used broader-spectrum antibiotics than the other reported trials.

For article selection, we used broad search terms and predefined selection criteria, and we assessed all included papers for design quality. Although the available data are rather scarce and we cannot exclude the possibility of publication bias, we believe that the retrieved articles appropriately represent the published literature on the study question. Based on the summary findings from these articles, we conclude that presumptive antibiotic treatment of pregnant women may have the potential to promote fetal growth and prevent preterm labor. Not surprisingly, however, the effect size is very dependent on the chosen antimicrobial agent, the context of the intervention, and the prevailing determi-
nants of PTB or IUGR in the target population. Sub-Saharan Africa and an antibiotic that eliminates a wide spectrum of aerobic and anaerobic organisms, including intracellular bacteria and possibly also parasites, appear as a combination where a positive effect is most likely.

In almost all reports included in our review, the prescribed antibiotics were assumed to improve birth outcomes by affecting infections or bacterial colonization in the maternal reproductive tract. The approach is logical since during pregnancy such infections can relatively easily ascend to the intrauterine cavity and lead to chorioamnionitis, weakened amniotic membranes that rupture too early, preterm labor, and small birth size [5]. Local microbial spread is, however, only one of the pathogenic mechanisms that have been associated with infection-related adverse birth outcomes. An alternative pathway is hematogenic dissemination of bacteria that initially cause infections elsewhere in the body, such as urinary tract or oral cavity [26, 27]. A third possible mechanism is a systemic inflammatory response, elicited by a local or distant infection, and predisposing the host to preterm delivery and IUGR through a multitude of biological processes [28].

Although the regulation of the onset of parturition is not identical in different species [5], the molecular mechanisms that link infection and inflammatory response to PTB and especially growth restriction are likely to be similar in humans and other animals. In poultry farming, the idea of using presumptive antibiotic treatment to promote growth was introduced soon after the discovery of many new antimicrobial agents [29]. In a series of elegant trials, antibiotic provision was convincingly shown to increase weight gain in young chicken, but only in unhygienic environments. Birds reared in germ-free conditions grew well without any medication and gained no benefits from antibiotics [30]. Thus, the antibiotics have been concluded to exert their action on chicken growth by limiting the propagation of environmentally acquired bacteria [31].

The avian studies have suggested several possible mechanisms how a bacterial infection may restrict host growth. Most infections elicit an inflammatory response that includes the secretion of compounds called monokines by immunological cells of the monocyte/macrophage lineage [31]. Such proinflammatory monokines, most notably interleukin-1 (IL-1), IL-6 and tumor necrosis factor-α, may decrease skeletal muscle accretion, increase basal metabolic rate and energy utilization, deviate amino acid use from growth to energy production, negatively affect protein synthesis, redistribute critical nutrients and make them less available for growth, impair accretion of cartilage and bone and alter hormonal balance into a direction that favors catabolism and restricts growth [31]. These studies have been carried out in hatched chicken, but similar mechanisms are associated also with IUGR, e.g. among mouse
pups whose dams are carrying a bacterial urinary tract infection [32]. Human data are still scarce, but it has been proposed that infection-elicited and immunologically mediated pathways are associated with growth failure also among infants and young children in low-income settings [33], and we find it likely that in such living conditions they can also restrict intrauterine growth.

Given the possibility for hematogenous spread, the limited efficacy of topical treatment of reproductive tract infections or bacterial colonization in preventing adverse birth outcomes [34], and the likely contribution of a systemic inflammatory response to preterm labor and especially IUGR, we believe that an effective antimicrobial intervention for pregnant women should target maternal infections in general, not only those in the reproductive tract. Human immunodeficiency virus and malaria infections are probably the best known other maternal infections associated with adverse birth outcomes [5], but the list of important infectious conditions is likely to be much longer, including e.g. other parasitic diseases, skin infections, and periodontitis [27]. The trials in Africa are likely to show a positive effect on birth outcomes because of their use of broad-spectrum antibiotics and the high fraction of IUGR and PTB attributable to infectious etiology in the target population [6]. The only African study with a contrasting result may have failed to reach an impact because of the high burden of malaria and insufficient malaria control in the study sample [15]. Likewise, the narrower-spectrum medications used in trials in India, US and Europe may not have covered all important infectious agents. In those contexts, IUGR and PTB may also have been more often caused by noninfectious factors, not amenable to treatment with antimicrobial agents [5].

In conclusion, we suggest that appropriately chosen presumptive antimicrobial treatment of pregnant women can in selected contexts promote fetal growth and reduce the incidence of preterm delivery and LBW. Such a treatment could, however, also have a profound effect on the antibiotic resistance among bacteria colonizing the pregnant women or the composition of their microbiota in general – possibly leading to perturbations in the microbiota assembly and maturation and eventually significant and persistent health effects also in the offspring [35]. Therefore, both mechanistic and further efficacy trials would be needed before presumptive antibiotic treatment in pregnancy could be considered for public health interventions to promote child health.

**Disclosure Statement**

The authors declare no conflicts of interest.
References

Should We Promote Catch-Up Growth or Growth Acceleration in Low-Birthweight Infants?

Atul Singhal

Childhood Nutrition Research Centre, Institute of Child Health, University College London, London, UK

Abstract

The idea that catch-up growth or growth acceleration has adverse effects on long-term health has generated much debate. This pattern of growth is most commonly seen after birth in infants of low birthweight; a global problem affecting over 20 million newborns a year. Faster postnatal growth may have short-term benefits but increases the long-term risk of aging, obesity and metabolic disease. Consequently, the optimal pattern of postnatal growth is unclear and is likely to differ in different populations. In infants born prematurely, faster postnatal growth improves long-term cognitive function but is associated with later risk factors for cardiovascular disease. So, on balance, the current policy is to promote faster growth by increasing nutrient intake (e.g. using higher-nutrient preterm formulas). Whether the same policy should apply to larger preterm infants is not known. Similarly, in infants from impoverished environments, the short-term benefits of faster postnatal growth may outweigh long-term disadvantages. However, whether similar considerations apply to infants from countries in transition is uncertain. For term infants from developed countries, promoting catch-up growth by nutritional supplementation has few advantages for short- or long-term health. Overall therefore, a ‘one size fits all’ solution for the optimal pattern of postnatal growth is unlikely.

Introduction

Normally, growth, defined at the simplest level as the quantitative increase in body mass or size, is closely regulated and follows a regular and predictable path. Consequently, monitoring the rate of growth is one of the best indices of a child’s...
health, and is an essential part of pediatric care. The pattern of growth is not only a marker of the immediate physical and emotional well-being of the child, but has long-term implications for health. Therefore, historically, achieving adequate growth and the prevention of growth faltering has been the highest priority in clinical research and pediatric practice.

Faltering growth has numerous causes, recovery from which is usually followed by a rate of growth much greater than that expected. This recovery phase of growth, or ‘catch-up growth’, has been a focus of intense research and debate, particularly in light of recent evidence that ‘accelerated’ or too fast growth has detrimental effects on long-term risk of noncommunicable disease. Catch-up growth is most commonly seen immediately after birth in infants with low birthweight (LBW), a problem which affects over 20 million newborns a year globally [1]. However, the factors contributing to this pattern of growth and its consequences for long-term health are poorly understood. The risk-benefit of faster postnatal growth may differ in different populations (e.g. in infants born pre-term versus those born at term, or in infants from developed or developing countries). As a result, whether postnatal catch-up growth should be actively promoted (e.g. by increasing nutrient intake) remains controversial. The present review considers the evidence for the effects of faster postnatal growth on long-term health, focusing on the biology and clinical impact in term infants from developed countries. It will not address the causes and consequences of postnatal malnutrition (e.g. stunting), a major global issue, known to have adverse effects on long-term adult health and human capital [2].

**Terminology and History**

The phenomenon of a child growing at a rate faster than expected was recognized in the 18th and 19th centuries as the growth pattern in response to recovery from illness [3]. However, this pattern of growth was confused with faster growth associated with the adolescent growth spurt leading to the belief that for the adolescent growth spurt to occur the child had to be first ill. The concept of ‘catch-up’ growth was first formally described in 1954 by Bauer who noted faster growth in 19 children recovering from the nephrotic syndrome [as reviewed, 3]. This work was extended by the demonstration of catch-up growth in several clinical conditions by Prader in 1963 [4]. Importantly, catch-up growth was defined as the acceleration in growth in response to recovery from illness or starvation [4]. Faster growth following recovery was also known by some as ‘compensatory growth’. However, as pointed out by Tanner [3], this term originally referred to the overgrowth of an organ when a part of the organ had been removed.
or to the excess growth of the remaining member of a pair of organs (e.g. kidneys) when one of the pair had been removed.

Catch-up growth was recognized to occur as a natural phenomenon in infancy in the 1950s [3]. Children who were small at birth grew more quickly postnatally than those who were larger (and vice versa). It was assumed that this pattern of growth was the same as catch-up growth and that the infants were recovering from undernutrition in utero. However, early postnatal growth is strongly influenced by genes, and infants with genes for large size but born to small mothers show faster postnatal growth (and vice versa). This reassortment of size occurs soon after birth, and had been described many years previously in animal models. In the classic experiments of Walton and Hammond, foals born to small (Shetland) horses crossed with large (Shire) horses showed faster growth after birth (and vice versa) [as reviewed, 3]. The same phenomenon is seen in humans (see ‘mechanisms’ below). Therefore, faster growth after birth is a natural pattern of growth and is not necessarily the same as catch-up growth (i.e. a consequence of recovery from a period of undernutrition in utero).

A growth rate much faster than expected can also be seen after birth as a consequence of changes in the plane of nutrition. This was first demonstrated in the 1960s by McCance who showed that overfeeding rats during a critical window in early postnatal life permanently increased later body size [5]. Similar effects of a higher plane of early postnatal nutrition occur in humans. Infants born preterm and randomly assigned to a higher-nutrient diet (nutrient-enriched infant formula) compared to a lower-nutrient diet (human milk or standard formula) were found to have greater propensity to obesity, dyslipidemia, raised blood pressure, and insulin resistance in adolescence [6]. Faster growth in infancy was also associated with insulin resistance, markers of inflammation, higher blood pressure and endothelial dysfunction (an early stage in the atherosclerotic process) [6]. Based on these data, and previous epidemiological studies linking faster postnatal weight gain with greater risk of later obesity, we proposed the postnatal ‘growth acceleration’ hypothesis [6]. This concept suggests that upward centile crossing (for weight or length) could explain, in part, the adverse long-term effects on health seen in infants born small for gestation (SGA; who show ‘catch-up’ growth immediately after birth) and long-term cardiovascular benefits in babies breastfed (who are relatively undernourished and have slower growth compared to those given formula) [6]. The term ‘growth acceleration’ was specifically chosen because it makes no assumption about the causes of faster postnatal growth, and it encompasses several potential causes such as faster growth arising from recovery from illness or starvation (i.e. ‘catch-up’ growth), genetic factors or accelerated growth as a consequence of a higher plane of postnatal nutrition.
The Impact of Growth Acceleration on Long-Term Health

The fact that ‘catch-up’ occurs in animal species as diverse as mammals, birds, fish as well as humans suggests that this pattern of growth must be an evolutionary conserved adaptive response [7, 8]. These beneficial effects may include faster maturity and hence greater reproductive success, and greater likelihood of survival as a result of a larger size in early life (e.g. protection from predators, infectious disease or starvation) [7, 8]. However, the fact that humans and animals do not grow as fast as they are capable of (e.g. as seen during catch-up growth) suggests that faster growth in early life must also have a biological cost. Therefore, there is a trade-off in order to optimize growth trajectories between short-term benefits and long-term costs, the concept of ‘grow now pay later’ [7].

The short-term advantages of faster growth in infancy either in those born LBW or SGA is well recognized and include, for example, a lower risk of hospitalization in poorer environments [9]. The long-term cost of this faster growth, however, is an increased risk of noncommunicable disease. Importantly, because the effects of faster postnatal growth on risk of diabetes, CVD, and even, more rapid aging, are usually manifest later in life, after reproduction, these ‘diseases’ are not greatly affected by selective pressures.

The concept that growth acceleration has adverse consequences for long-term health is now strongly supported by a wealth of evidence. The association is biologically plausible and experimentally reproducible in several animal models [10–12]. In humans, faster weight gain in infancy (upward centile crossing for weight) is associated with a greater risk of later obesity in more than 30 studies (summarized in 5 systematic reviews [13–17]). The evidence is consistent across studies [15, 16] and includes an individual-level meta-analysis in 47,661 participants from 10 cohorts [16]. The association between postnatal growth acceleration is consistent for cohorts during the last 80 years [13–15], is seen in breastfed and formula-fed populations, and has been shown to influence the main components of the metabolic syndrome [6, 18]. For instance, in infants born SGA, faster weight gain in the first 3 months of life is associated with lower insulin sensitivity and HDL cholesterol concentrations, and higher triglyceride concentrations, obesity and markers of atherosclerosis at age 18–24 years [18].

Long-term effects of postnatal growth acceleration are evident in both infants born preterm or at term, infants born small or appropriate weight for gestation, in adults as well as children, and in developed and developing countries [19]. For example, in a cohort study from Delhi, rapid gain in BMI in the first year was associated with development of the metabolic syndrome in adulthood [as reviewed, 19]. The effects of faster growth in influencing, or programming, long-term health appear to be greatest for central or visceral adiposity [19], a key risk
factor for CVD and type 2 diabetes. These effects on visceral adiposity are particularly marked in infants born SGA [18, 20]. Overall, these studies suggest a large effect size. For example, over 20% of later obesity risk can be explained by the rate of infant weight gain [12], and the relative risk of later obesity associated with more rapid weight gain in infancy ranges from 1.2 to as high as 5.7 [14].

Importantly, while observational studies may be confounded by genetic and environmental factors which could both promote faster infant growth and increase the risk of later obesity, follow-up of randomized studies, initially in established trials in infants born prematurely [6] or SGA [as reviewed 19], and subsequently in new prospective trials, support a causal link between infant growth and later risk of obesity and CVD [19]. Infants born preterm and randomly assigned to a nutrient-enriched diet, which promoted faster weight gain in the first few weeks after birth, had higher fasting concentrations of insulin, cholesterol, and C-reactive protein, as well as leptin resistance in adolescence than controls [6]. Similarly, infants born SGA at term and randomly assigned to nutrient-enriched formula that increased weight gain had higher diastolic BP at age 6–8 years and, in 2 trials, 18–38% greater fat mass at age 5–8 years than controls [19]. Interestingly, differences in childhood fat mass or blood pressure between randomized groups were related to the rate of weight gain in infancy suggesting a ‘dose-response’ association between early growth and later CVD risk [19]. These programming effects have been confirmed in experimental studies of term infants with appropriate birthweight for gestation and in low-income countries (e.g. Chile [19]), thereby supporting the concept that programming of metabolic disease by faster early growth is a fundamental biological finding seen across populations.

Nevertheless, despite extensive evidence for the growth acceleration hypothesis, several areas of controversy remain. For instance, many have argued that programming effects of postnatal growth acceleration are a consequence of catch-up growth following a period of prenatal growth restraint. In support of this, a systematic review of 50 studies found an increased risk of the metabolic syndrome in infants born LBW who showed ‘catch-up’ growth postnatally [22]. Although it is difficult to disentangle the effects of LBW from faster postnatal growth, because the two are closely interrelated, earlier [10] and more recent animal studies [11] suggest that faster postnatal growth is an independent risk factor for later disease [11]. Observations that the effects of LBW on the adult phenotype can be reversed by preventing postnatal catch-up growth, and that growth acceleration increases the risk of metabolic disease in animals without prenatal growth restriction, support the concept that accelerated postnatal growth per se is the key independent risk factor for later metabolic disease [11]. Whether LBW or prenatal nutrition further exacerbates the effects of faster post-
natal growth is not clear, but is unlikely in view of the fact that no study in humans has shown a statistical interaction between birthweight and postnatal growth on later risk of obesity (i.e. size at birth does not modify the effects of postnatal growth acceleration on later health) [15, 16]. This observation has important implications for the nutritional management of infants born SGA and suggests that optimizing postnatal growth may be beneficial irrespective of the antenatal environment.

**Mechanisms**

Research into the mechanisms for the growth acceleration concept has focused in two main areas: (1) understanding the causes of faster postnatal growth and the physiological mechanisms involved, and (2) unravelling the coupling mechanisms that link a stimulus (such as growth/nutrition) acting during a critical window in early life with later outcomes such as obesity and CVD.

In a recent systematic review, postnatal growth acceleration was associated with smoking during pregnancy, being first born, being born LBW (particularly as a result of intrauterine growth retardation in the 3rd trimester), formula feeding rather than breastfeeding, and earlier introduction of complementary feeding [23]. In addition to these factors, the large Nourish study from Australia identified high maternal BMI, low maternal education levels, male infant gender, and feeding on a schedule (rather than in response to the baby’s hunger cues) as factors increasing the rate of postnatal growth. As in animal models, genetic factors affect the postnatal growth rate, as highlighted by data from the Avon Longitudinal Study of Pregnancy and Childhood, which found that infants showing faster postnatal growth had taller fathers. While many of the factors associated with faster postnatal growth are not modifiable, this research clearly suggests that prevention of both antenatal growth faltering and postnatal overnutrition may have benefits for long-term health.

Several generic hypotheses have been proposed to explain the ‘coupling mechanisms’ linking early exposures such as growth with later biological effects such as CVD. The first, the role of epigenetic changes that persist throughout life, is supported by evidence in animal models. Plagemann et al. [24] showed that neonatal overfeeding in rats (which leads to development of the metabolic syndrome later in life) was associated with increased methylation of CpG residues in the insulin receptor promoter gene. Although this epigenetic change did not affect insulin receptor gene expression in the short-term, the authors speculated that increased methylation of this allele could predispose to insulin insensitivity under adverse environmental conditions later in life.
The second hypothesis proposes that early growth acceleration permanently affects hormonal axes that regulate body weight, food intake and metabolism, and hence fat deposition. Hormonal changes in infancy (possibly via changes to the hypothalamic circuitry regulating appetite) could influence the satiety response and increase food intake throughout life, thereby increasing the risk of obesity and CVD. Postnatal growth acceleration may program a higher set point for appetite, a hypothesis proposed by Widdowson and McCance in 1975 [21] and now supported by extensive evidence from animal and human studies [10, 11, 19].

The third generic hypothesis suggests an adverse effect of faster growth on aging and biochemical factors predisposing to cellular aging (e.g. increased oxidative stress and altered mitochondrial function), a hypothesis first proposed by McCay in the 1930s and seen in numerous animal species [8, 10, 11, 25]. In fact, it has been argued that the accumulation of cellular damage is an inevitable feature of catch-up growth as cellular resources are invested in growth rather than repair [8].

**Implications for Infants Born Low Birthweight**

The evidence suggesting adverse long-term effects of postnatal growth acceleration has generated considerable controversy and debate. The optimal growth trajectory for LBW infants is currently unclear and is likely to differ in different populations. Therefore, the answer to the question ‘to catch-up or not to catch-up’ must lie in balancing the interests of the child according to the cause of LBW and the child’s environment. In preterm infants, for example, faster postnatal growth is associated with the same metabolic risk factors for CVD as in term infants [26], but improves cognitive function [27]. So, on balance, the current policy is to promote faster postnatal growth by increasing nutrient intake (e.g. using higher-nutrient preterm formulas). However, even in preterm infants the optimal growth pattern for the larger preterm infant (>34 weeks’ gestation) is unclear since most of the evidence for the benefits of faster growth for later cognitive function is based on infants born <31 weeks’ gestation [27].

Part of the difficulty in answering the question to ‘catch-up or not to catch-up’ for the large number of LBW infants born in developing countries is that gestational age may not be accurately known. Nonetheless, current WHO policy recommends exclusively breastfeeding or using standard formulas rather than nutrient-enriched formulas from hospital discharge to age 6 months [1]. For LBW infants in extremely impoverished environments, clearly the priority is to prevent malnutrition and growth faltering [1, 2]. Even in low-income countries,
however, massive changes in diet and rise in urbanization means that large sections of society are at increased risk of obesity and CVD and so susceptible to programming effects of early growth [19]. Therefore, whether postnatal upward centile crossing should be promoted in developing countries (as is common in many cultures by using bovine milks or early addition of solid foods) is unknown but unlikely to be beneficial in view of the well-established benefits of exclusively breastfeeding for 6 months.

For infants born SGA in developed countries, contrary to previous medical and public opinion, promoting catch-up growth by nutritional supplementation is unlikely to have any advantages for long-term health [28]. In fact, nutrient-enriched formulas designed to promote faster growth are no longer recommended [1, 28, 29] and exclusive breastfeeding may be particularly advantageous for long-term cognitive development in SGA infants [30]. Overall therefore a ‘one size fits all’ solution for the optimal pattern of postnatal growth is unlikely, and further research will be required to guide nutritional and public health practice in many populations.

Disclosure Statement

The author declares that no financial or other conflict of interest exists in relation to the contents of the chapter.

References

11 Jimenez-Chillaron JC, Patti ME: To catch up or not to catch up: is this the question? Lessons from animal models. Curr Opin Endocrinol Diabetes Obes 2007;14:23–29.
Abstract
The worldwide rate of premature birth is increasing. Survival has also improved, even for very preterm infants, meaning greater numbers of preterm infants surviving into later life. This has led to greater attention being focused on long-term outcomes. Recent interest in the Developmental Origins of Health and Disease has highlighted the importance of early life growth and nutritional exposures for chronic diseases such as cardiovascular disease, osteoporosis and type 2 diabetes. There is evidence linking preterm birth and poor growth in utero with worse long-term cognitive outcome, but also evidence to link more rapid growth in certain epochs of early life with adverse metabolic outcomes. The current data suggest that a diverse range of metabolic outcomes are affected by preterm birth, and that adult survivors may be more likely to develop certain chronic diseases. There are data to show that catch-up growth during the neonatal period and in infancy may affect these later outcomes, but studies are inconsistent in their findings. In addition, it is clear that lifestyle factors during childhood and adolescence have a major impact on metabolic disease that may be greater in magnitude to the effects of early growth and nutritional exposures.

Introduction
Dramatic improvements in neonatal care over the last 2–3 decades have resulted in increasing numbers of premature infants surviving longer term [1]. In economically advanced countries, survival at 24 weeks’ gestation (16 weeks premature) is now common. Even in less well-resourced countries, survival of very low birthweight (<1,500 g birthweight) infants is increasingly common.
the world, more than 15 million preterm births occur every year, and these rates look set to increase [1]. The reasons for an increase in the preterm birth rate are complex, but reflect changes to maternal age at first pregnancy, increased rates of multiple pregnancies (twins and higher-order multiples) and increasing use of assisted reproductive technologies such as in vitro fertilization. Preterm birth is associated with significant healthcare costs both in the short and longer term and is a major public health issue for all countries. The vast majority of preterm births (<37 weeks’ gestation) are also low birthweight (LBW, <2.5 kg birthweight) but the metabolic and cognitive costs of prematurity compared to LBW are different. This is important because nutritional strategies and their long-term impact need to be optimized to the individual: a ‘one size fits all’ approach to LBW babies will fail to optimize metabolic and cognitive outcomes. Providing the same ‘inputs’, and aiming for the same ‘outputs’ in a 2-kg appropriately grown preterm LBW infant compared to a 2-kg severely in utero growth-restricted (IUGR) term LBW infant will not optimize population outcomes.

Growth is a fundamental characteristic of all mammalian species and implies an increase in auxological measures (weight, length and head size or occipito-frontal circumference) along with changes in body composition. During the process of growth, there are changes to organ structure and function, and changes in response to endocrine stimuli. Adolescence is an important period particularly because of the impact of puberty and changing endocrine signals. Examining growth outcomes in early adulthood is also important. However, there are few studies of young adults born in the ‘modern’ era of neonatal medicine when use of antenatal steroids and artificial surfactant was widespread.

**Developmental Origins of Health and Disease**

Over recent years, the concept of the Developmental Origins of Health and Disease has gained increasing prominence in scientific study [2]. Animal studies in the 1950s demonstrated relationships between early patterns of growth (dependent on nutritional intake) and later size and metabolic outcomes [3]. However, the wider implication of these findings did not gain scientific prominence until the late 1980s and early 1990s when the translational relevance of the early growth impacts on later adult chronic disease (type 2 diabetes and cardiovascular disease) was documented in epidemiological studies. In a series of seminal papers, Barker showed clear relationships between size at birth and later chronic disease risk with term-born LBW infants having substantially increased risks [4]. Size at birth, i.e. LBW in this context, was used as an indicator of fetal growth. These studies predominantly explored outcomes in individuals born at term.
Studies led by the team of Lucas and Singhal extended these concepts, both confirming the associations in randomized controlled trials (RCTs) in preterm infants, but also highlighting the importance of growth patterns in early postnatal life on outcomes in adolescence [5–7]. Whilst data from Barker’s group suggested benefits to being larger in infancy, they concentrate on outcomes in late adult life, whereas Singhal identified that rapid growth in the immediate postnatal period may be the key factor associated with the greatest increase in later metabolic risk. Slower growth in utero may not result in later metabolic harm unless a period of rapid growth followed in the postnatal period.

The relevance to individuals born preterm is enormous, and currently underrecognized. Premature birth is frequently the end result of a compromised pregnancy, and many preterm infants show signs of IUGR when they are born [8, 9]. Premature birth may be induced because of maternal or fetal concerns, for example pregnancy-induced hypertension or preeclampsia. Preterm infants take time to tolerate enteral feeds and have to overcome many challenges including gastrointestinal immaturity that may be manifest as disordered motility, malabsorption or abnormal patterns of microbial colonization [10]. In addition, metabolic limitations such as hyperglycemia and technical challenges of providing parenteral nutrition (e.g. amino acid and fatty acid composition, mineral solubility, etc.) mean that most preterm infants fail to grow adequately over the initial few postnatal days and weeks [11]. Although growth that aims to match in utero references is widely promoted as an important aim of neonatal nutrition, there are no studies that define the optimal pattern of growth in preterm infants, particularly when Developmental Origins of Health and Disease thinking is considered. Nevertheless, most preterm infants are discharged from hospital with weights considerably below birth centiles. Numerous observational studies have shown strong relationships between early growth and later neurodevelopmental outcome [12]. These are supported by long-term follow-up of RCTs that show early nutrient intake to be a key modulator of later cognitive outcome [13].

**Catch-Up Growth, Growth Acceleration and Weight Gain**

The term ‘catch-up growth’ was first used by Prader and Tanner in the early 1960s to describe a period of rapid growth that followed a period of growth inhibition, and was usually referenced to linear growth (or height) [14]. The growth velocity in this period, linear growth in cm/week or weight gain in g/kg per day, will be above statistical norms for either age or developmental stage/maturity. The effect of this period of increased growth velocity is to take the in-
individual back to their growth centile prior to the period of growth restriction. When considered from a preterm neonatal perspective, it becomes clear that it is difficult to define this process in a similar fashion. Fetal growth cannot be directly assessed: although in utero ultrasound may give an indication of change in auxological parameters, it is referenced to population norms that may not apply to the individual fetus. Many preterm deliveries are spontaneous with limited fetal monitoring. Given that there is a circular relationship between genes and the environment, it is similarly not possible to define whether growth is appropriate or restricted in terms of the infants’ ‘genetic potential’. Most often, catch-up growth is defined in terms of position on a growth chart, with upwards centile crossing or an increase in weight (or length) standard deviation score (SDS) taken to indicate catch-up. Even if the centile position at birth is regained, it may not be possible to state that full catch-up has occurred because birth-weight will also be a reflection of any degree of IUGR.

Whilst ‘catch-up growth’ has to involve ‘growth acceleration’, it may help to conceptualize a different scenario where growth acceleration results in the individual attaining a weight or length centile higher than appropriate (in homeostatic or physiological terms). An example of this can be seen in term infants who are formula rather than breast milk fed. Formula-fed infants exhibit greater early weight and length gains than those who are breast milk fed, possibly due to increased quantity or differences in milk quality. Formula milk contains higher levels of protein, so even at the same intake volume formula-fed infants may receive up to 50% greater protein intakes. This excess protein may stimulate IGF-1 and other endocrine processes resulting in faster weight gain, i.e. growth acceleration [15]. It is again important to reemphasize that growth implies both an increase in auxological measures and an appropriate change in body composition. Whilst weight gain is generally used to imply ‘growth’, similar patterns of weight gain can be seen in individuals who experience very different patterns of changes in body composition, i.e. fat and lean mass (LM) accretion. This is particularly important in adolescence where auxological measures and body mass index (BMI) may be insensitive measures of adiposity [16].

According to the above definitions, many preterm infants exhibit catch-up growth after their acute respiratory or gastrointestinal pathologies have resolved during their initial hospital stay. Although many preterm infants are discharged with weights less than the 10th centile, many also demonstrate catch-up in the immediate postdischarge period and during infancy. Catch-up growth in these periods can be accelerated by the use of enriched formula such as postdischarge formula, but the functional benefits of this approach remain unclear [17]. In the long-term, most preterm and LBW infants tend to demonstrate gradual catch-
up throughout infancy and childhood, so that very few remain outside the 95% confidence intervals of the population for weight and length in adolescence, although they are often still smaller than their peers.

It is clear that growth is not the same as weight gain, but weight is easy and precise to measure and tends to reflect changes in linear growth reasonably well especially after the first few postnatal weeks. Linear growth is extremely important, but is infrequently measured in clinical practice, and tends to be less precise. Alternate measures of linear growth such as ‘tibial’ length (or knee-heel length) can be extremely precise in experienced hands, but lack external validity as there are no references. Head growth is simple to measure and reflects brain size. However, many preterm infants’ heads become flattened during ex-utero life on the neonatal unit, and it is difficult to account for changing head shape on growth charts. Body composition is difficult to measure in routine clinical practice, and even in research settings most commonly used techniques (such as dual X-ray absorptiometry, DXA) involve many assumptions and may lack external validity especially when fat mass (FM) is considered. It is not surprising therefore, that studies of catch-up growth in preterm infants tend to use weight as the main indicator.

**Adolescent Outcomes following Preterm Birth**

Preterm birth is associated with an increased risk of a range of adverse growth, metabolic and cognitive outcomes. Whilst many individuals show catch-up growth, preterm born individuals tend to be slightly smaller in adolescence and early adulthood. This may not matter that much to the individual unless their size is well outside 95% confidence intervals, i.e. growth is not a functional outcome. Preterm-born adolescents show an increased incidence of decreased bone density, increased blood pressure (BP), insulin resistance, and abnormal adiposity, although studies demonstrate inconsistent effects [18]. Nevertheless, these are all considered surrogate markers for later life adult chronic diseases such as osteoporosis, hypertension, type 2 diabetes and obesity. Arguably the most important long-term outcome of preterm birth is impaired cognitive outcome. Global tests of developmental quotient (e.g. Bayley Scales of Infant Development) show that many preterm infants are significantly impaired in infancy, with longer-term studies demonstrating a changing pattern throughout childhood and adolescence [19]. Many individuals with moderate disability in infancy would not consider themselves as impaired, or experiencing a poor quality of life as adolescents. The extent to which cognitive or neurobehavioral outcomes are modifiable remains to be
determined, but there is evidence to suggest that nutrition plays a key role. Even though growth is dependent on many factors, there is strong evidence from experimental studies that nutrient quality and quantity determine patterns of growth [13]. Growth may be an important indicator of later outcomes, but growth per se is not the mechanism linking early nutrition and later metabolic or cognitive outcomes.

A recent large systematic review explored the association between preterm birth and later life metabolic outcomes. In a large review of over 17,000 preterm and 295,000 term-born adults, preterm birth was associated with significantly higher systolic and diastolic BP, and increased levels of low-density lipoprotein [20]. However, no significant differences were detected in insulin resistance (using fasting glucose or insulin levels). This may reflect populations studied, or the tests used, but is at variance with a recent systematic review from our group where we demonstrated decreased levels of insulin sensitivity throughout the life course in individuals born preterm [21]. Given the heterogeneity in population and technique, it was not possible to meta-analyze the data into an overall effect, but a series of well-characterized cohorts showed evidence of increased insulin resistance in individuals (including adolescents) born preterm. Necessarily, one of the problems with examining such long-term outcomes are the attritional losses over time, and the fact that adolescents or young adults reflect neonatal care from 20–30 years ago that may not be reflective of current populations and practices.

Although few studies also explored the associations between catch-up growth and adolescent outcomes, a large Dutch cohort study of preterm birth (average 29 weeks’ gestation) [22] showed a weak association between more rapid catch-up weight gain and insulin resistance in late adolescence (age 19 years). This relationship was significant for weight SDS at 3 months after term, but the study did not explore the precise timing of weight gain, i.e. whether it was predominantly before or after discharge. In a similar study, preterm born (average 32 weeks’ gestation) young adults (18–24 years) were compared to term matched controls [23]. Gain in weight-for-length prior to term was associated with adult %FM, and gain in weight-for-length between term and 3 months was associated with adult cholesterol and low-density lipoprotein. There was no significant association of birth-term, term-3 month or later epochs of weight gain with adult insulin sensitivity.

A recent series of papers from Belfort and colleagues have emphasized the association between early childhood growth and later metabolic and cognitive outcome. A follow-up study of 911 preterm-born children (6–8 years) examined the association of 1st-year weight gain, and showed that for each additional unit weight z score (SDS) increase, systolic BP was 0.7 mm Hg higher
and IQ score (measured using Wechsler Intelligence Scale for Children III) was 1.9 points higher [24]. The authors concluded that there appeared to be modest neurodevelopmental advantages of more rapid infant weight gain with only small BP-related effects. Whether similar effects will be seen in adolescence remains to be determined. In a further study, the same authors studied the effect of more rapid infant growth and IQ at 8 and 18 years of age [25]. At both outcome time points, the effects were similar. More rapid earlier linear growth was associated with a decreased risk of low IQ, but a higher risk of overweight/obesity. Perhaps not surprisingly, more rapid BMI gain in all infant time intervals was associated with higher risk of overweight/obesity in later life, but there appeared to be a benefit of greater BMI gain between 4 and 12 months in terms of decreasing the risk of a low IQ. Taking these and other data together, it suggests there may be trade-offs that clinicians will need to assess [26]. Decreasing the chance of a low IQ may come with a metabolic cost. The trade-off will depend on the individual concerned. Rapid catch-up following IUGR may carry the greatest risk for adverse metabolic outcome. Very preterm infants may have greater potential for neurodevelopmental gain than those only born moderately preterm. Whilst there are no data to suggest that IUGR term-born infants have a neurodevelopmental benefit from rapid catch-up, it is clear that a ‘one size fits all’ approach for nutritional management cannot apply to all LBW infants.

Newcastle Preterm Birth Growth Study

We have recently explored the associations between catch-up growth in neonatal life, infancy and childhood, and adolescent outcomes in a well-characterized cohort of preterm infants originally recruited to one of 2 RCTs in the neonatal period [27]. In brief, >200 preterm LBW infants were recruited to either (a) a postdischarge study comparing standard to preterm formula (PTF) after discharge, that included a ‘crossover’ group who converted from PTF to standard formula at term, or (b) a study of PTF with varying protein density commencing in the predischarge period (around 32 weeks’ corrected age) and continuing after discharge until 12 weeks after term [28, 29]. Control groups of infants receiving breast milk were included. Infants were followed closely over the first 2 years of life with regular measures of growth (weight, length and occipitofrontal circumference) and body composition assessed using DXA to give measures of FM, LM and bone mineral mass. Auxological measures were converted to SDS using population growth references and weight gain calculated by subtraction to give a change in SDS over the period in question. Overall, the studies showed higher
rates of growth in infants on enriched formula that was not associated with excess FM deposition. In addition, careful measurement of intake volumes showed that infants on lower caloric densities upregulated intake volumes so that overall energy intakes between the groups (PTF or standard) were the same. This implies that any long-term effects observed in the study of the two main groups may be due to differences in protein intake (because protein:energy ratio differed) and not due to energy. Furthermore, it suggests complex relationships between growth and appetite control.

Children formula fed in the postdischarge trial were reviewed at 10 years of age and cognition assessed (92 out of 113 eligible = 80%). The entire cohort of children were further reviewed at 11–12 years of age (n = 153) and the assessment included growth, body composition (DXA), measures of insulin sensitivity (fasting glucose and insulin) and plasma lipid profile (102 consented to invasive blood testing). Data from these studies are in press or awaiting publication but show: (1) no long-term cognitive benefits of PTF versus standard formula; (2) an apparent cognitive disadvantage for infants who were converted from a PTF to a standard formula abruptly at term (crossover group); (3) positive associations between catch-up weight gain (increase in SDS) or head growth in infancy and specific domains of later cognition; (4) positive associations between catch-up weight gain before discharge and higher insulin sensitivity in adolescence; (5) negative associations between catch-up weight gain and insulin sensitivity immediately after discharge and in childhood; (6) positive associations between infant weight gain and adolescent bone mineral mass.

The data are in keeping with existing literature showing clear associations between early growth and later outcomes, but suggest that there may not be a metabolic disadvantage to more rapid weight gain when the entire predischarge period is considered. They support the notion that the postdischarge period is an important period for longer-term effects, suggesting that energy shortage (decrease in caloric intake) at a critical stage of rapid brain growth may have deleterious effects, but also that rapid weight gain after discharge may result in worse metabolic outcomes. This apparent paradox between the pre- and immediately postdischarge period may be explained by weight gain composition. In the predischarge period spanning several weeks, higher rates of weight gain may reflect better LM deposition and result in improved insulin sensitivity in later life. Alternately, higher weight gain may reflect more healthy infants (even though the effect persisted when adjusted for illness severity). Weight gain in the immediate postdischarge period (around 36 weeks to term-corrected age) spans a relatively short time, and more rapid gains are therefore likely to reflect differences in FM accretion.
**Growth and Inference Causality**

The mechanisms linking early growth and adolescent outcomes are complex, and are likely to be confounded and interacted by several factors, some of which will remain unknown, for example, specific genetic polymorphisms. Whilst there are clear associations with early growth, two of the key questions that remain are interlinked and are: (1) the extent to which growth is a reliable indicator of nutritional intake and status – what does the relationship between early catch-up growth and later metabolic effects imply in mechanistic terms? (2) The direction of the causal link – in observational studies there is a risk of reverse causation.

Whilst nutrition is the key determinant of growth, some of our previous studies have shown that nutrient intake differences can only explain around 50% of the variation in change in weight SDS [11]. It seems likely that there are other equally important factors shaping growth patterns that also affect the long-term outcomes of interest. In the widest sense, many of these factors are nutritional in nature, but may involve nutrient quality (e.g. breast milk components, fatty acids, or methyl donors) and effects on gene function such as epigenetic modification [30]. Additionally, whilst the data from our studies are in keeping with those from other groups, the precise direction of causality cannot be determined in observational studies, even where there is multiple adjustment for confounding factors. In our studies, adjusting for the severity of illness on later insulin resistance (by using mechanical ventilation as a proxy) or of parental factors on cognition (by adjusting for maternal educational level) did not change the significance or direction of the results. Nevertheless, such adjustment may not be adequate. It is quite likely that specific genetic differences, e.g. single-nucleotide polymorphisms, may have an effect on early LM accretion and later risk of insulin resistance. Statistical adjustment may make it appear that there is a direct link between LM and β-cell function, but in reality there may be a 3rd factor (genetic) that explains the association. It is important to recognize this, and be appropriately critical of long-term observational studies.

**Conclusions: Mechanisms and Lifestyle Factors in Adolescence**

A fuller discussion of the mechanisms linking catch-up growth with later outcomes in relation to LBW infants will be provided in other chapters. In brief, there are numerous mechanisms including structural differences, modifications to cellular ageing, and epigenetic effects [18]. Determining their precise roles will be extremely challenging especially given the life course nature of studies.
that attempt to link infant catch-up growth with adolescent metabolic outcomes. Finally, it is important to recognize the importance of other factors, particularly current lifestyle. Dramatic increases in obesity in adolescents reflect changing attitudes and behaviors to physical activity and dietary intake in the whole population. Differences in physical activity may be due to long-term neurobehavioral effects of preterm birth or LBW, or differences in muscle function, and may be confounded by infant nutrient exposures or current nutrient intakes (e.g. vitamin D). The ‘exposome’ of adolescents born LBW and preterm is extremely complex, especially when lifestyle factors are considered. It is clear that early growth is associated with adolescent outcomes, but the magnitude of the effect may be dwarfed by contemporary factors. This should be seen as encouraging, because lifestyle factors may be easier to modify or prevent than early life factors (e.g. poor fetal growth).

Disclosure Statement

Dr. Embleton declares he has received research support from Danone Baby Nutrition, Pfizer, Novo Nordisk, Baxter and Nestec SA. He has acted as a consultant or speaker for some of these companies at scientific and industry sponsored meetings and has received contributions to his travel and accommodation costs in accordance with the Association of British Pharmaceutical Industry guidelines. His institution has received honoraria or payment for some of this activity. He holds no patents or other rights in respect of his work, and has no personal or family financial arrangements to declare. Dr Skeath has no relevant conflicts to declare.

References

Introduction

Low birthweight (LBW) defined as birthweight <2,500 g, remains a major public health problem since it is estimated that over 20 million infants (15.5% of all births) worldwide are born with LBW, and the overwhelming majority of these infants are born in developing countries. The definition adopted by the World Health Organization (WHO) is also based on epidemiological observations that LBW infants are about 20 times more likely to experience mortality compared to larger infants. In developed countries, LBW is largely due to premature birth, whereas in developing countries it is due to intrauterine growth restriction [2]. Moreover, LBW is
associated with fetal and neonatal morbidity and mortality, poor growth, impaired cognitive development and chronic diseases in adult life [3]. According to the WHO report, half of all LBW infants are born in South-Central Asia followed by Sub-Sahara Africa, Middle East and North Africa, Latin America and the Caribbean, Central and Eastern Europe, Commonwealth of Independent States and East Asia and the Pacific [4]. Various maternal factors including poor protein and energy intakes, prepregnancy weight and body mass index determine LBW, and discussion of these factors is beyond the scope of this paper [5]. An intergenerational cycle of growth failure has also been described, making attention to preconception nutrition a very important intervention in preventing LBW [6].

LBW infants are very heterogeneous from being premature to being small for age at term. The strategies to feed these infants differ because the initial goals are different. For example, the LBW premature infant does not get the benefit of placental transport of various nutrients including protein, essential fatty acids, calcium, phosphorus, magnesium, iron and zinc [7]. The delivery of such an infant then causes abrupt cessation of nutrient delivery, and postnatal nutrition practices can result in negative nitrogen balance very early in life. Aggressive nutritional practices including early parenteral and enteral nutrition have been shown to promote positive nitrogen balance and, in addition, shorten the interval to return to birthweight, a critical factor in reducing extrauterine growth restriction [8–10].

**Nutrient Recommendations**

Current nutrient recommendations are summarized in table 1, and table 2 summarizes the macronutrient composition of human milk, term, preterm and donor milk.

---

**Table 1. Nutrient recommendations**

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Unit/kg enteral</th>
<th>Unit/kg ESPGHAN</th>
<th>Human milk, units/dl</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluid, ml</td>
<td>150</td>
<td>135–200</td>
<td>–</td>
</tr>
<tr>
<td>Energy, kcal</td>
<td>120–130</td>
<td>110–135</td>
<td>64.8–86.6</td>
</tr>
<tr>
<td>Protein, g</td>
<td>3.5</td>
<td>3.5–4 (4–4.5 &lt;1 kg)</td>
<td>1.9–2.3</td>
</tr>
<tr>
<td>Fat, g</td>
<td>1–4</td>
<td>4.8–6.6</td>
<td>4.4–4.8</td>
</tr>
<tr>
<td>Calcium, mg</td>
<td>200–220</td>
<td>120–140</td>
<td>24.8–29.6</td>
</tr>
<tr>
<td>Phosphorus, mg</td>
<td>100–110</td>
<td>60–90</td>
<td>6.2–6.8</td>
</tr>
<tr>
<td>Vitamin D, IU</td>
<td>400</td>
<td>800–1,000</td>
<td>trace</td>
</tr>
</tbody>
</table>

Adapted from Schanler [11], Agostini et al. [12] and Bauer and Gerss [13].
As seen in Table 1, preterm milk would have to be fed in excessive quantities to meet the nutrient recommendations set forth, thus highlighting the need for appropriate fortification. In Table 2, the major differences between preterm, term and donor milk are highlighted.

As will be discussed later in this chapter, feeding premature and LBW infants is challenging especially when feeding them human milk, an accepted global standard. The macro- and micronutrients needed have to be provided in the form of fortification.

### Calcium, Phosphorus and Magnesium

Most of the fetal accretion of calcium, phosphorus and magnesium occurs in the third trimester of pregnancy [15]. Fetal accretion of calcium and phosphorus approximates 20 and 10 g, respectively, during the last trimester, which translates to accretion rates of 100–120 mg/kg per day for calcium and 50–65 mg/kg per day for phosphorus [16]. In the blood, calcium ions exist in three forms: nondiffusible complex with protein (∼40%), diffusible complex with citrate, bicarbonate and phosphate (∼5%) and as free ionized calcium (∼55%). The nondiffusible calcium is bound to albumin and is highly pH dependent, and alterations in acid-base homeostasis will affect free ionized calcium. In the fetus, parathyroid hormone (PTH), PTH-related peptide and 25-hydroxy vitamin D play important roles in the transplacental influx of calcium and bone remodeling; the latter is important since 90% of total calcium is found in teeth and bones especially in the adult [17]. LBW infants, either from prematurity or intrauterine growth restriction, have lower calcium and phosphorus stores compared to their term counterparts. Postnatally, optimal calcium and phosphorus homeostasis is important to diminish the incidence of metabolic bone disease, the spectrum of which ranges from osteopenia to frank rickets and fractures. After birth, there is

<table>
<thead>
<tr>
<th></th>
<th>Protein, g/dl</th>
<th>Fat, g/dl</th>
<th>Lactose, g/dl</th>
<th>Energy, kcal/dl</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Term</strong></td>
<td>1.2 (0.9–1.5)</td>
<td>3.6 (2.2–5)</td>
<td>7.4 (7.2–7.7)</td>
<td>70 (57–83)</td>
</tr>
<tr>
<td><strong>Donor</strong></td>
<td>1.2 (0.7–1.7)</td>
<td>3.2 (1.2–5.2)</td>
<td>7.8 (6–9.6)</td>
<td>65 (43–87)</td>
</tr>
<tr>
<td><strong>Donor</strong></td>
<td>0.9 (0.6–1.4)</td>
<td>3.6 (1.8–8.9)</td>
<td>7.2 (6.4–7.6)</td>
<td>67 (50–115)</td>
</tr>
<tr>
<td><strong>Reference</strong></td>
<td>0.9</td>
<td>3.5</td>
<td>6.7</td>
<td>65–70</td>
</tr>
<tr>
<td><strong>Preterm &lt;29 weeks</strong></td>
<td>2.2 (1.3–3.3)</td>
<td>4.4 (2.6–6.2)</td>
<td>7.6 (6.4–8.8)</td>
<td>78 (61–94)</td>
</tr>
</tbody>
</table>

Adapted from Ballard and Morrow [14].
an increase in calcium flux from the bone to extracellular space and if calcium stores are low, as in prematurity, unless exogenous calcium is provided, hypocalcemia will occur. Very LBW infants exhibit the lowest nadirs of ionized calcium, but in most cases, low levels are not associated with symptoms [18]. Calcium absorption depends on calcium and vitamin D intakes as well as absorbed phosphorus. Thus, the calcium to phosphorus ratio may be an important determinant of calcium absorption and retention [16]. Phosphorus accretion is related to both calcium and protein retention; phosphorus absorption is very efficient (~90%) in infants fed either human milk or formula. However, human milk does not have adequate amounts of calcium and phosphorus to sustain bone health in a small preterm infant and will need fortification. If calcium retention of 60–90 mg/kg per day is achieved with a nitrogen retention of 350–450 mg/kg per day, then an intake of phosphorus of 65–90 mg/kg per day along with a Ca:P ratio of 1.5–2:1 will achieve appropriate phosphate levels [19].

Similar to calcium, plasma concentrations of magnesium in the fetus exceed those of the mother [20]. Little is known about the mechanisms of placental magnesium transport, but they appear to be different from those for placental calcium transport [21].

Fetal growth disturbances are seen in diabetic pregnancies, both in humans and in animals. In rats, fetal growth restriction is a consistent finding [22]; however, human infants may be large for gestational age or growth restricted depending on the timing of the diabetes [23]. The pathophysiology of these disturbances in placental transport of calcium and magnesium during diabetic pregnancy is likely a result of altered placental transport and fetal accretion of calcium and magnesium. Both hypo- and hypermagnesemia are common in diabetic pregnancies [24].

In preterm infants, feeding with human milk is a very effective means of intervention, especially for short-term morbidities such as necrotizing enterocolitis and infections. There are however, numerous nutritional challenges in providing human milk to premature infants. These include inadequate supply, variability in nutritional content between and among mothers, and the nutrient limitations in human milk itself. Figure 1 illustrates the limitations of human milk in providing calcium and phosphate. For preterm infants, the suggested enteral requirements for calcium for example, of 25–40 mmol/kg per day cannot be met by preterm or term human milk and must be fortified. In addition, it is well recognized that it is virtually impossible to meet the requirements of these two minerals through parenteral nutrition, and thus infants on prolonged parenteral nutrition and then on unfortified human milk would be at the greatest risk of deficiencies including slower growth. The entire topic of human milk for premature infants is covered elsewhere [7, 26, 27].
The last Cochrane review [28] concludes that multicomponent fortification of human milk is associated with short-term improvements in weight gain, linear and head growth. Further, fortification of human milk for preterm infants after hospital discharge has not been extensively studied. A recent review by Young et al. [29] found limited evidence that feeding preterm infants with fortified milk impacted growth rates during infancy. One study did not find any statistically significant effects on neurodevelopmental outcomes at 18 months. In a cohort of preterm infants, 750- to 1,800-gram birthweight, human milk-fed infants were randomized to receive either half of the feedings with fortified human milk (n = 19) or all their feedings with unfortified human milk (n = 20) for 12 weeks after hospital discharge. The infants fed fortified human milk were longer (p < 0.001) and had a greater bone mineral content (p = 0.02) at 12 months corrected age, and in infants less than 1,250 g, head circumference remained large (p < 0.001) through the first year of life [30]. In long-term studies, very LBW infants attain a suboptimal peak bone mass and subnormal skeletal mineralization [31]. Fewtrell et al. [32] measured whole and regional bone mineral content and bone mineral density using dual-energy X-ray absorptiometry and single-photon absorptiometry and bone turnover in 244 preterm infants at 8–12 years of age. These infants had been fed either banked human milk (n = 87) or preterm formula (n = 96) or expressed breast milk supplemented with preterm formula (n = 36). Preterm children were shorter and lighter than term children and had significantly lower whole-body bone mineral content. However, the bone mineral content was appropriate for bone and body size, suggesting that early diet despite large differences in mineral intake did not affect bone mass at 8–12 years of age.

![Calcium and phosphate in human milk](image_url)
Magnesium

Similar to calcium, magnesium has a high accretion rate in utero during the third trimester. The magnesium requirement estimated to be 8–15 mg/kg per day is higher than that of term infants. It has been calculated that with human milk feeding (Mg content \(\sim 1.3 \text{ mmol/l}\)), preterm infants will receive 5.5–7.5 mg/kg per day, and magnesium absorption is better with human milk than formulas (73 vs. 48%). Effects of the greater magnesium accretion in premature formula-fed infants than intrauterine estimates are not known. No functional criteria of magnesium status have been demonstrated that reflect dietary changes in infants. The recommended intakes are based on an adequate intake that reflects mean intake from human milk \[33\]. Transient hypomagnesemia is associated with both hypocalcemia and hyperphosphatemia and is common in growth-restricted infants and in infants of diabetic mothers.

Vitamin D

Requirements of vitamin D may be affected by the availability of substrates such as calcium, phosphorus, magnesium and vitamin D itself. In humans, 25-hydroxyvitamin D [25(OH)D] is the major circulating form of vitamin D after it is hydroxylated in the liver and is also the form that is involved in transplacental passage \[34\]. The ideal definition of requirement and optimal levels of vitamin D should be based on functional markers, such as absorption, bone mineralization and PTH concentrations. The major biologic function in humans is to maintain serum calcium and phosphorus within the normal range. The vitamin D available to the infant (term) during the first 6 months of life depends on the vitamin D status of the mother during pregnancy and later on the infant’s exposure to sunlight and availability of vitamin D in the diet. Human milk contains low amounts of vitamin D, and colostrum contains an average of 397 ± 216 ng/l of vitamin D. Low vitamin D levels are not uncommon in neonates fed human milk of formula. Although there is no compelling evidence, it is accepted that a serum 25(OH)D concentration of <50 nmol/l is consistent with deficiency, 50–80 nmol/l is insufficiency and >80 nmol/l is considered sufficient. The Institute of Medicine \[35\] defines sufficiency as 50 nmol/l, risk of deficiency <30 nmol/l and inadequacy as 30–50 nmol/l. In premature infants, the requirements and levels are extrapolated from adult studies. Premature infants are at particular risk for developing metabolic bone disease because of the difficulty in achieving adequate intakes of calcium, phosphorus and vitamin D, relative immobil-
ity, prolonged total parenteral nutrition, feeding of unfortified human milk and adverse effects of commonly used medications such as diuretics and steroids. Suggested intakes vary from 400 IU/day [36, 37] to a recommended upper level of 1,000 IU/day from the Institute of Medicine [38]. The American Academy of Pediatrics has recently published new guidelines for premature infants: <1,500 g birthweight: 200–400 IU of vitamin D/day, >1,500 g: 400 IU/day to a maximum of 1,000 IU/day [39]. Evidence from a randomized controlled study demonstrated that 200–400 IU/kg per day maintains normal vitamin D status [40]. Higher doses may accelerate bone turnover [41]. However, the short-term benefits of increased vitamin D intake on bone mineral status in preterm infants disappear at 9–11 years, similar to the effects seen with different doses of calcium [42].

Iron

LBW and preterm infants are at high risk for iron deficiency since iron is an endowment and is transported in the last trimester of pregnancy. The body content of iron in the term infant is estimated to be ~75 mg/kg. Premature infants have higher iron requirements partially because of the rapid postnatal growth and the depletion of iron stores by bloodletting for laboratory determination. Human milk contains 0.5 mg/l of elemental iron, and breastfed preterm infants remain in negative iron balance for at least the first 30 days of life [43]. Iron deficiency is the most common micronutrient deficiency worldwide, and risk factors include LBW, high cow’s milk intake, low intake of iron-rich diets and lower socioeconomic status. Observational studies have shown an association between iron deficiency and poor neurodevelopment in infants [44]. A recent Cochrane review concluded that enteral iron supplementation of both preterm and LBW infants confers an improvement in hemoglobin and ferritin status at 8 weeks of age [45]. A limited number of studies suggest that early iron deficiency may also adversely affect neurologic function and neurodevelopment in preterm infants. Compared with nonanemic, iron-replete infants, preterm infants with anemia (Hgb ≤10 g/dl) and low iron stores (serum ferritin ≤76 μg/l) had an increased number of abnormal neurologic reflexes at 37 weeks’ postmenstrual age [46]. It has also been shown that mild neurologic abnormalities at 5 years of age in preterm infants occur more often in infants who received iron supplementation from 2 months of age, compared with those supplemented from 2 weeks after birth [47].

As stated above, human milk has a low content of iron and must be fortified. Similarly, iron-fortified formulas need to be fed if human milk is not
used. Formulas containing 5–9 mg/l of iron appear to meet the iron requirements of erythropoiesis in healthy preterm infants during the first 6 months of life [48]. However, 18% of the infants receiving the 9 mg/l formula and 30% of those receiving the 5 mg/l formula developed iron deficiency (serum ferritin concentration <10 μg/l) between 4 and 8 months of age in that study [48]. Current recommendations are to provide a dietary iron intake of 2 mg/kg per day for infants with a birthweight of 1,500–2,500 g and 2–3 mg/kg per day in infants less than 1,500 g. Iron should be started after 2 weeks of age. If erythropoietin is used, higher amounts of iron at 6 mg/kg per day will be needed during the period of its use [49]. Another strategy to reduce the risk of iron deficiency is the timing of umbilical cord clamping. Andersson et al. [50] randomized 400 term Swedish infants to delayed (>3 min) or early (<10 s) cord clamping and showed a significant effect on neonatal iron status and also a significant reduction in the proportion of iron-deficient infants at 4 months of age (0.6 vs. 5.7%, p = 0.01). There were no increases in neonatal jaundice or any other adverse effects. A Cochrane analysis, based on studies performed in low-income countries, also concluded that late cord clamping improves infant iron status [51].

Copper

Copper is essential in physiologically important enzymes such as lysyl oxidase, elastase, monoamine oxidases, ceruloplasmin and copper-zinc superoxide dismutase. Copper deficiency is related to the impaired activities of these enzymes. Further, copper transporters have been described (ATP7A, ATP7B, Ctr1) and may have a role in genetic disorders of copper metabolism. Severe copper deficiency is a rare condition associated with anemia, neutropenia, thrombocytopenia and osteoporosis [52]. Human milk contains low amounts of copper, 0.2–0.4 mg/l [53]. The most recent recommendations for copper intakes are between 120 and 150 μg/kg per day [12, 54]. More recently, a calculation based on 9 clinical studies suggested that enteral copper requirements may be 210–232 μg/kg per day if zinc intake is 2–2.25 mg/kg per day to achieve a net retention of copper of 30 μg/kg per day [19].

An x-linked recessive disorder of copper metabolism, Menkes syndrome, is rare, but is manifested soon after birth and is characterized by anemia, steely hair and progressive brain degeneration [55]. Wilson disease is another autosomal recessive disorder of copper metabolism and results in toxic effects of copper; copper accumulates in the liver and brain, and symptoms include cirrhosis, eye lesions (Kayser-Fleischer ring), and neurological problems [56].
Zinc

Zinc is abundant in the human body second only to iron among the trace elements. It is essential for many enzymes and is part of metalloproteins or zinc-binding proteins. Zinc plays an important role in growth, tissue differentiation, apoptosis and signal transduction. Severe zinc deficiency in infants and children is characterized by a typical skin rash, diarrhea and slow growth [57]. Zinc homeostasis is maintained by regulation of zinc absorption and endogenous secretion in the gastrointestinal tract. Marginal zinc deficiency is difficult to diagnose due to a lack of reliable markers of zinc status [58]. Current recommendations for zinc in preterm infants are in the range of 1–2 mg/kg per day. Lot is not known about zinc accretion rate in the fetus, effects of zinc intake on other micronutrients and effect of disease states. A summary of significant findings from supplementation trails has been recently published [19]. The estimated requirement for zinc is approximately 400 μg/kg per day for premature infants 30–32 weeks’ gestation. Extrapolating data from various metabolic studies, an intake of 2.0–2.25 mg/kg per day should achieve zinc retention [19]. Term breastfed infants are relatively protected from zinc deficiency since zinc concentrations are high in colostrum and decline over the next 3 months. However, in premature infants and in those with diarrheal losses due to short bowel syndrome, zinc deficiency is of importance. Complementary foods should be high in zinc similar to iron especially when infants are weaned from breast milk. Domellof [49] recommends an enteral intake of 1.4–2.5 mg/kg per day and a parenteral intake of 400 μg/kg per day.

Long-Chain Polyunsaturated Fatty Acids

During the last trimester of pregnancy and for the first 18 months after birth, arachidonic and docosahexaenoic acids are accumulated in the cerebral cortex [59, http://journal.frontiersin.org/Journal/10.3389/fnhum.2013.00774/full, 60]. This stage of human development with its brain growth spurt [61] is particularly vulnerable to nutritional insufficiencies [62]. Long-chain polyunsaturated fatty acids (LC-PUFA) are critical for neurodevelopment, and the subject has been extensively studied. In preterm infants, the LC-PUFA are of particular importance since they do not get the benefit of placental transfer and are dependent on sources of these fatty acids in their diet. Possible effects of LC-PUFA supplementation include visual and cognitive effects. Numerous studies have reported on the effects of LC-PUFA on the developing brain [63]. A Cochrane review [64] concluded that no clear benefits or harms were demonstrated for preterm in-
fants receiving LC-PUFA-supplemented formula. Various studies reporting outcomes of LC-PUFA supplementation are summarized by Lapapillonne et al. [63]. Studies using higher doses of docosahexaenoic acid supplementation (0.5% total fatty acids compared to 0.2–0.4% previously used) reported improved growth and, in addition, improved neurodevelopment in boys [65]. Other studies have shown controversial effects [66, 67]. In a more recent meta-analysis, LC-PUFA supplementation failed to show any significant effect on early infant cognition [68]. Thus, as stated by Lapillonne et al. [63], the ‘essentiality’ of arachidonic acid and docosahexaenoic acid has been recognized and that the current recommendations should remain [12].

**Feeding Low-Birthweight and Growth-Restricted Infants**

The specific requirements of this cohort of infants are unknown. Therefore, the stated goals [69] are similar to that for premature infants. WHO evaluated studies of infants <2,500 g or gestational ages <37 weeks. Nutritional requirements were not distinguished for growth-restricted infants. Breastfeeding or provision of breast milk was highly recommended.

In summary, nutrition in premature and LBW infants is a continuum from birth through discharge and after. Although this chapter focused on enteral nutrition, particular attention is needed during parenteral nutrition, human milk feedings and choice of formulas appropriate for birthweight. Current recommendations need to be followed as most deficiency states are preventable and the goal is to promote optimal growth and development as much as possible.

**Disclosure Statement**

The author declares that no financial or other conflict of interest exists in relation to the contents of the chapter.

**References**

Role of Specific Nutrients in Low-Birthweight Infants


11 Schanler RJ: Approach to enteral nutrition in the premature infant. UpToDate 2014.


26 Zeigler EE: Meeting the nutritional needs of the low birth weight infant. Ann Nutr Metab 2011;58(suppl 1):8–18.


38 www.iom.edu/...Vitamin-D/Vitamin%20D%20and%20calcium%202010%20Report%20Brief.


Abstract
The neuroendocrine model of catch-up growth has been well studied in a number of animal models. During nutritional inadequacy, which invariably precedes catch-up growth, growth hormone (GH) levels increase under the influence of the oxygenic ‘hunger signal’ ghrelin. This increase in GH would usually be accompanied by an increase in IGF-1. However, malnutrition also induces the nutritionally responsive proteins sirtuin 1 (SIRT1) and fibroblast growth factor 21 (FGF21) that block GH signal transduction in the liver by blocking the JAK/STAT pathway, limiting IGF-1 production. The result is that GH’s action is shifted from hepatic effects to effects in other tissues (for example muscle and adipose) and shifted away from IGF-1-mediated effects and towards GH-mediated effects. Once nutrients become more available, SIRT1 and FGF21 levels, and hepatic GH sensitivity return to normal, and production of IGF-1 resumes. This shifts GH signaling away from GH-mediated effects, and towards IGF-1-mediated effects both in the liver and in other tissues. It presumably leads to greatly increased IGF-1 signaling that would have been expected without the prior episode of nutritional inadequacy. Although much work remains to be done, it does appear that ghrelin is increased in in utero and postnatal malnutrition, that elevations in ghrelin may be prolonged after malnutrition resolves, and that higher ghrelin levels are associated with increased rates of catch-up growth. Prolonged increases in circulating ghrelin and GH, combined with a rapid return in hepatic GH sensitivity would provide an elegant mechanism to drive catch-up growth after periods of nutritional insufficiency.

Introduction
Catch-up growth usually refers to a process that follows a period of growth failure, whereby the specific growth rate increases above the rate that would have been expected had the preceding growth deficit not have occurred. It leads
to a reduction in the growth deficit between the subject and his/her expected body size. Usually, catch-up is incomplete (a growth deficit remains), but sometimes overcompensation can occur and a greater than expected body size result.

The process has been recognized for almost 100 years [1], although the term originated in 1963 in a paper by Prader and Tanner [2]. Tanner described two types of catch-up: type A is a brief period of rapid growth followed by a normalization of specific growth rate; type B is seen when growth continues longer than would be expected [3]. Both forms of catch-up may be seen simultaneously in the same patient [3]. Small for gestational age and preterm infants clearly demonstrate catch-up growth [4], although most studies have considered type A catch-up rather than type B catch-up.

**Models of Catch-Up Growth**

It is not difficult to imagine why reduced nutrient availability would reduce growth, or why reestablishment of nutrient supply would increase growth back to normal. What is more difficult is to explain why subsequent growth would be greater than normal. Three main hypotheses have been described that seek to explain this [3].

*Tanner’s Time Tally Hypothesis*

In his early writings on catch-up growth, Tanner speculated on a mechanism that is now known as the ‘time tally’ model [3, 5]. He hypothesized the presence of a central marker of ideal body size (the time tally) that increases at a developmentally determined rate. Body tissues produce a counteracting ‘inhibiting substance’. Growth rate is determined by the difference between the central time tally and the inhibiting substance. During periods of growth failure, the time tally would continue to increase at its developmentally programed rate, but the level of the central inhibitor would not increase (as body size was not increasing). At the end of the period of growth arrest, the difference between the time tally and the inhibiting substance is greater than prior to the growth arrest, so growth rate (once sufficient nutrients become available) would also be greater than before the growth arrest, and greater than if that period had not have occurred [3, 5]. Although it is tempting to consider leptin as a potential inhibiting substance, this model suffers from the lack of an obvious mechanism for the central time tally.
Epiphyseal Growth Plate Hypothesis

This model sees the regulation of growth rate being controlled in peripheral tissues (specifically in the epiphyseal growth plate) rather than centrally, and is based on studies of catch-up growth in isolated bones [3, 6]. Explanted rat metatarsals continue to grow in culture, but growth slows dramatically if they are exposed to dexamethasone [6]. In metatarsals taken from rats on postnatal day 8, the specific growth rate after dexamethasone is withdrawn exceeds the rate of metatarsals of the same age that were not exposed to dexamethasone. In other words, catch-up growth occurs [6]. Catch-up does not occur with metatarsals taken on embryonic day 20, or after prolonged courses of dexamethasone [6]. This effect has been explained by delayed senescence of the growth plate [3, 6] and is most similar to type B catch-up, while the time tally mechanism is more similar to type A catch-up [3].

Neuroendocrine Hypothesis

This model (see below) is probably the most popular model of catch-up growth, and has been examined in a number of animals including rodents, birds, pigs, and fish [3, 7]. It explains catch-up growth as resulting from two apparently conflicting actions of growth hormone (GH): (1) a stimulator of somatic growth; (2) a mediator of metabolic adaptation to fasting and two conflicting actions of ghrelin as (1) a stimulator of GH secretion and (2) an appetite-stimulating 'hunger signal'.

The model has been extensively studied in fish [see 7] and is summarized below.

Neuroendocrine Model of Catch-Up Growth

Overview of the Model

A fundamental tenet of the neuroendocrine model is that catch-up growth (or hyperanabolism) can only follow a period of catabolism. It is not possible to move directly from a period of normal growth to one of catch-up growth (fig. 1) as endocrine changes that occur during poor growth are required to enable later catch-up growth [7].

Normal Anabolism

During normal anabolism (normal growth), GH is secreted from the pituitary at a rate determined by the balance between several factors. Ghrelin, produced systemically in the stomach and locally in the hypothalamus, stimulated GH se-
cretion both directly and indirectly. Leptin, derived from adipose tissues, reduces GH secretion. Ghrelin also acts via neuropeptide Y (NPY) and agouti-related peptide (AgRP) neurons to stimulate appetite (orexigenic), while leptin acts on the same neurons to reduce appetite (anorexigenic) [7].

Pituitary-derived GH interacts with receptors on the liver and signals via the Janus kinase/signal transduction and activators of transcription signal (JAK/STAT) pathway to stimulate the production of target genes including IGF-1, ALS (acid labile subunit) and IGFBP-3 (IGF-binding protein 3). These are secreted from the liver and bind to produce the tertiary complex. IGF-1 can affect target tissues (such as muscle and adipose) to stimulate growth via interactions with the IGF-1 receptor and its signaling pathways [7]. The GH/IGF axis therefore produces effects in hepatic and nonhepatic tissues directly via the GH receptor (GHR) and its signaling pathway, and indirectly via IGF-1 and its receptor [7].

Catabolism
During fasting, ghrelin increases as a response to reduced dietary intake, and leptin falls as a response to loss of leptin-producing adipose tissue. This leads to both an increase in appetite (via NPY/AgRP neurons) and an increase in GH

---

**Fig. 1.** Neuroendocrine model of normal anabolism, catabolism, and hyperanabolism (catch-up growth). Reproduced from Won and Borski [7].
secretion. Despite this increase in GH, hepatic production (and serum levels) of IGF-1 falls during fasting due to hepatic GH resistance. The basis for GH resistance is complex. Effects on GHR number and function are possible, but much of the effect appears to be postreceptor, probably within the JAK/STAT signaling pathway (see below). Target tissues now act in response to GH to increase production of free fatty acids and support other GH-mediated fasting adaptations. The action of IGF-1 on target tissues is, however, reduced [7]. The switch from hepatic to nonhepatic effects of GH may also be due to increases in GHR in muscle and adipose tissue during fasting.

**Hyperanabolism**

When refeeding occurs, hepatic GH resistance ends and the elevated GH levels result in elevated IGF-1 levels. These elevated levels act on target tissues to produce greater than normal protein synthesis and cell division, and catch-up growth occurs [7]. Gradually, leptin production rises as adipose stores increase, which leads to greater inhibition of central GH production. At the same time, ghrelin secretion by the stomach (and within the hypothalamus) falls and further decreases GH secretion [7].

In this elegant model, hepatic GH resistance is central to fasting adaptation. The rapid reestablishment of hepatic GH sensitivity (and hepatic GH signal transduction) in the face of persisting and prolonged GH secretion (driven by ghrelin) is responsible for catch-up growth following catabolic stresses.

**Hepatic GH Signaling and Resistance**

Hepatic GH resistance can occur in a variety of conditions including malnutrition, protein deficiency, and deficiency of specific nutrients (including zinc, magnesium, vitamin A and vitamin B₆) [8]. Protein deficiency may also lead to resistance to IGF-1 in target tissues [8].

Fasting leads to hepatic GH resistance by a range of mechanisms, including downregulation of hepatic GHR number and postreceptor effects, for example within the JAK/STAT signaling pathway that mediates many of the effects of GH [8, 9].

**JAK/STAT Signaling and SOCS**

The GHR is a cytokine I receptor and lacks an intrinsic kinase, so it uses the JAK2 to phosphorylate downstream signaling molecules [9]. GH action is mediated via a number of downstream mediators including IRS-1, protein kinase C and STAT proteins (signal transduction and activators of transcription). STAT5
is especially important for GH action. It forms dimers that interact with DNA to upregulate expression of GH target genes including IGF-1, IGFBP-3, ALS, and suppressors of cytokine signaling such as SOCS1, SOCS2, SOCS3, and CIS [cytokine inducible SH2 (Srp-homolog 2)] [9]. The SOCS proteins are critical negative feedback regulators of GH signaling, and the time courses of production of different SOCS proteins vary and are tissue specific. SOCS proteins inhibit GH signaling via a range of mechanisms including inhibition of JAK2, and by marking JAK2 and GHR for proteolytic degradation [9].

Several of the SOCS proteins appear to be associated with GH resistance during sepsis [10], but their role in GH resistance during fasting is less clear. In rats with IUGR without catch-up growth, hepatic IGF-1 production in response to GH is reduced (i.e. they have hepatic GH resistance), JAK/STAT signaling is decreased, and levels of SOCS and CIS are increased [11]. SOCS proteins are also important negative regulators of IGF-1 signaling via the JAK/STAT pathway, and perhaps also via the ERK and PI3K pathways [12].

However, more evidence suggests that the nutrient-sensitive regulators sirtuin (silent mating type information regulation 2 homolog) type 1 (SIRT1) and fibroblast growth factor 21 (FGF21) have important roles in fasting-induced hepatic GH resistance.

Sirtuin 1
Sirtuins are class III deacetylases that require nicotinamide adenine dinucleotide (NAD+) as a cofactor [13]. SIRT1 is the prototypical sirtuin and is involved in the regulation of many transcription factors. SIRT1 is involved in epigenetic deacetylation of histone proteins, and may mediate the effect of calorie restriction on longevity [13]. During periods of malnutrition, NAD+ levels rise and increase the activity of SIRT1 [13]. Low energy levels, and increasing cellular adenosine monophosphate (AMP) concentrations, activate AMP-activated protein kinase (AMPK) and further increase NAD+ and SIRT1 activity [14]. Increased SIRT1 activity leads to deacetylation and inactivation of STAT3 (reducing gluconeogenesis), deacetylation and degradation of CRTC2 (preventing glucagon-stimulated hepatic gluconeogenesis) and deacetylation and degradation of SREBP-1 (reducing lipogenesis and cholesterol synthesis). SIRT1 also deacetylates and activates several transcription factors leading to increased gluconeogenesis (via Fox01 and PGC-1α) and increased fatty acid oxidation (via PGC-1α and peroxisome proliferator-activated receptor-α, PPARα) [13].

SIRT1 also deacetylates and inactivates STAT5 and leads to reduced GHR/JAK/STAT signaling and hepatic GH resistance [8]. SIRT1 knockdowns show elevated hepatic expression of IGF-1, IGFBP-3, ALS and SOCS2 [15], and fail to
develop appropriate GH resistance during fasting [15]. Fasting reduces STAT phosphorylation and acetylation in mice treated with GH, but administration of a SIRT1 antagonist prevents these fasting-induced reductions in acetylated STAT5, and phosphorylated STAT5 were increased back to fed levels [15].

SIRT1 therefore leads to fasting-mediated inactivation of STAT5, and provides a mechanism by which malnutrition (via increased cellular NAD+ and AMP/ATP ratios) can lead to hepatic GH resistance (via inactivation of STAT5).

**Fibroblast Growth Factor 21**

Fasting also leads to increased production of FGF21 under the control of PPARα [16]. PPARα is stimulated by fasting and is responsible for a number of metabolic adaptations including increasing fatty acid oxidation and stimulating ketogenesis [17]. FGF21 is an immediate downstream target of PPARα and is responsible for both increased fatty acid oxidation and increased gluconeogenesis (via PGC-1α) [8]. FGF21 also leads to fasting-induced GH resistance, including downregulation of IGF-1 production in the face of increased GH levels, by reducing phosphorylation (and inactivating) STAT5 [8] via a SOCS2-dependent mechanism [18]. Transgenic mice that overexpress FGF21 have significantly decreased serum IGF-1 concentrations despite elevated GH concentrations [18]. FGF21 transgenic mice also have decreased expression of GH target genes including IGF-1, ALS, IGFBP-1 and SOCS2 [18]. Increased levels of FGF21, either due to overexpression of FGF21 in a transgenic model, or due to pharmacological PPARα activation, lead to similar effects as does fasting, including decreasing hepatic IGF-1 mRNA, decreasing serum IGF-1 protein, decreasing phosphorylation and activation of STAT5 and increasing levels of the JAK/STAT negative feedback regulator SOCS2 [18].

**Relevance to Preterm Infants**

The model combining the neuroendocrine effects of the ghrelin/GH/IGF-1 axis, and fasting-induced hepatic GH resistance (mediated by the nutrient sensors SIRT1 and FGF21) provides an elegant mechanism to explain how adaptations during fasting can allow the development of subsequent catch-up growth (fig. 2). Although evidence in animal models supports such a hypothesis, it is reasonable to ask what evidence exists in humans, and especially in infants.

**GH, IGF-1 and Malnutrition**

Malnutrition, for example in anorexia nervosa, leads to increased GH levels and decreased IGF-1 levels in humans [19]. The elevated GH levels seem to be the result of decreased negative feedback by IGF-1 and a direct effect on the hypothalamus.
In children, GH levels are high in kwashiorkor and fall with treatment, although they may be low in marasmus. However, the effects of nutrition on GH concentration may be misleading, as GH secretion is pulsatile, and intermittent low GH levels (as seen in males) seem to lead to increased phosphorylation and activation of STAT5 compared to more constant levels (seen in females).

Fig. 2. A model of catch-up growth combining the effects of the ghrelin/GH/IGF-1 axis and the actions of the nutrient-regulated proteins FGF21 and SIR1 on hepatic GH signaling. The width of lines is a qualitative measure of their degree of upregulation. AMP = Adenosine monophosphate (or adenosine monophosphate to adenosine triphosphate ratio). Normal anabolism: GH is secreted from the pituitary under the influence of stimulator factors (including ghrelin secreted from the stomach in response to decreased nutrient intake) and inhibitor factors (including leptin secreted from adipose tissue). It binds to hepatic GHR and IGF-1 production via the JAK/STAT signaling pathway. The actions of the GH/IGF-1 axis are due to the effects of GH and of IGF-1. Fasting (catabolism): Ghrelin secretion increases and leptin secretion decreases leading to increased GH secretion. However, low cellular nutrient levels (increased NAD+ and decreased NAHD, increased AMP and decreased ATP) stimulate SIRT1 and FGF21 production. These block the JAK/STAT signaling pathway and lead to hepatic GH resistance. IGF levels are low, and the GH/IGF-1 axis is shifted towards effects in nonhepatic target tissues and towards GH-mediated effects rather than IGF-1-mediated effects. Catch-up (hyperanabolism): Normalization of nutrient supply and cellular NAD+ and AMP levels leads to a reduction in SIRT1 and FGF21 and return of normal hepatic GH sensitivity. However, persisting elevations of ghrelin (and depression of leptin) continue to stimulate higher than normal GH production. This leads to increased GH and IGF-1 levels, increased GH and IGF-1 signaling in liver and other target tissues (such as muscle and adipose), and catch-up growth.
Undernutrition leads to decreased IGF-1 levels, increased production of IGF-binding protein 1 (IGFBP-1, which reduces the effect of IGF-1) and decreased IGFBP-3 production (which increases the effect of IGF-1) [22]. These effects combine to reduce IGF-1 action in malnutrition, and the effect on binding proteins may be more marked in protein malnutrition than in energy malnutrition [22]. Preterm growth-retarded infants have higher GH at birth, and lower IGF-1 and IGFBP-3, than appropriately grown preterm infants, consistent with in utero GH resistance resulting from in utero malnutrition [23].

Ghrelin in Preterm Infants
Ghrelin levels are increased in children with protein energy malnutrition (both marasmus and kwashiorkor) [24]. They are higher in SGA than AGA infants at birth [23, 25], and are negatively correlated with birthweight [25]. At 3 months of age, SGA term infants have higher ghrelin levels than AGA or LGA infants [26], and ghrelin levels are positively correlated with weight, length and head circumference gains [26]. At 12 months of age, SGA and AGA term infants had similar ghrelin levels, and both groups demonstrate reductions in serum ghrelin after an i.v. glucose load [27]. However, among SGA infants, those with catch-up growth had higher ghrelin levels (i.e. failed to suppress ghrelin secretion) than did those without catch-up [27]. Ghrelin levels in the SGA infants 10 min after the i.v. glucose load were positively associated with weight and length at 1 year of age, and with the amount of weight catch-up between birth and 1 year [27].

These findings suggest that poor in utero growth leads to increased ghrelin levels, and that persisting high levels at 3 months, or impaired ability to suppress ghrelin at 12 months, are associated with greater catch-up growth. These findings would be consistent with the model of catch-up growth described in figures 1 and 2.

IGF-1 in Preterm Infants
IGF-1 concentrations are low in preterm infants and begin to increase when catch-up growth begins to occur [28]. Among 64 preterm infants, IGF-1 concentrations were significantly positively associated with rates of weight gain during the initial growth retardation phase (from birth to the time of the lowest weight SD score) and during the later catch-up growth phase (from the time of the lowest weight SD score to 35 weeks’ corrected gestational age) [28].

IGF-1 concentrations in former preterm infants at term-corrected age are correlated with weight and length gain between birth and term, and the same is seen for IGF-1 concentration at 3 months and weight and length gain between
birth and 3 months, and for IGF-1 concentration at 6 months and weight and length gain between birth and 6 months [29].

However, there is no difference between IGF-1 or IGFBP-3 in the first year of life between term SGA infants who did or did not demonstrate catch-up growth, although IGF-2 was higher in those with catch-up growth [30].

Conclusions

The neuroendocrine model and nutritionally mediated hepatic GH resistance provide a compelling mechanism to explain catch-up growth after poor growth caused by nutritional or nonnutritional factors. The model has been well studied in animal models, although more is known about the adaptations and time course of effects associated with the fasting/nutritional insufficiency period than during the catch-up growth period. Although the human data are much more limited, those which are available broadly support the model as a cause of catch-up growth in preterm or small for gestational age infants.

Disclosure Statement

The author declares that no financial or other conflict of interest exists in relation to the contents of the chapter.

References


Abstract

Children in developing countries have an average length-for-age that is already below the World Health Organization standard at birth and show a further decline in linear growth over the first 24 months of life; however, complementary feeding interventions have only a modest impact on growth. Children living in conditions of poor sanitation and hygiene are frequently exposed to pathogenic microbes through feco-oral transmission. Acute diarrhea represents only the tip of the ‘enteric disease iceberg’, with a substantial underlying burden of chronic, subclinical enteropathy. Environmental enteric dysfunction (EED) is characterized by disturbance in small intestinal structure and impaired gut barrier function, enabling microbial translocation and chronic systemic inflammation, which may impair growth. Gut damage appears to arise early in infancy and markers of intestinal inflammation, intestinal permeability and systemic immune activation are inversely associated with linear growth. Reducing feco-oral microbial transmission by improving water, sanitation and hygiene (WASH) may theoretically prevent or ameliorate EED and improve linear growth; ongoing trials are exploring this hypothesis. Given the complex interplay of factors leading to stunting, multisectoral interventions are likely required. Improving WASH in addition to infant feeding may be one approach to improve the growth and developmental potential of infants in developing countries.

© 2015 Nestec Ltd., Vevey/S. Karger AG, Basel

Globally, 165 million children under 5 years of age are stunted [1]. Stunting, defined as a height-for-age more than 2 standard deviations below the World Health Organization (WHO) reference median, is associated with both short- and long-term risks. Stunted children have increased morbidity and mortality, particularly from pneumonia and diarrhea, with an estimated 14–17% of global...
child deaths below 5 years attributable to stunting [2]. Long-term, children who are stunted have reduced motor and cognitive development, poorer performance at school, lower adult economic productivity and an increased risk of nutrition-related chronic diseases [2, 3].

Intrauterine growth restriction is a risk factor for stunting. An estimated 20% of child stunting has in utero origins, based on a recent birth cohort meta-analysis of postnatal growth among infants born small for gestational age [4]. Children in developing countries therefore have an average length-for-age that is already below the WHO standard at birth, then show a further decline in linear growth over the first 24 months of life, with little or no catch-up thereafter [5]. An ambitious global target of 40% reduction between 2010 and 2025 in the proportion of children under 5 years who are stunted is unlikely to be reached; in Africa, where stunting prevalence has remained relatively stable over the past 20 years, the absolute number of stunted children is actually likely to increase by 2025 [6].

Does Inadequate Diet Explain Stunting?

Is the solution to poor linear growth not obvious: children need to consume adequate quantities of a nutrient-rich, varied diet? Whilst this appears logical, the quality and quantity of infant diets does not account for the high prevalence of stunting seen in developing countries. A meta-analysis of 42 effectiveness studies and efficacy trials undertaken in developing countries among children in the 6–24 months age range, when growth faltering peaks, showed only a modest impact of complementary feeding interventions on growth [7]. Generally, studies that provided complementary foods in food-insecure regions such as Africa and South Asia, with or without educational messages about child feeding, showed some benefit; micronutrient fortification alone showed little or no impact on growth. Overall, effect sizes for growth were modest; even the most successful interventions improved height-for-age by only around +0.7 z scores, which is approximately one third of the average growth deficit. Taken together, the sobering fact is that no nutrition trial or program has ever normalized the linear growth of children in developing countries.

The Impact of Enteric Infections on Stunting

Despite its extraordinarily high prevalence, the pathophysiology of stunting remains poorly understood. It is clear that multiple factors contribute to stunting [8], but the relative importance of each is not known, and it remains unclear
which would be most tractable to interventions. Given the high infectious disease burden in developing countries, attention has focused on the impact of recurrent infections on growth. These associations were elegantly demonstrated several decades ago by Leonardo Mata [9] in his rural Guatemalan studies, in which children who thrived in early infancy subsequently showed progressive declines in growth with each episode of intercurrent illness. Diarrhea remains one of the most frequent recurrent infections among children in developing countries, but the impact of diarrhea on both short- and long-term linear growth has been difficult to ascertain. Some studies report a significant impact of diarrhea on height, whilst others indicate that catch-up linear growth occurs between episodes, leading to little or no long-term deficit in height attributable to diarrhea; the discrepancies between findings likely reflect differences in study design and population characteristics. In a recent study of 7 longitudinal cohorts of infants under 24 months of age, cumulative diarrheal burden had a small but measurable effect on linear growth; a child experiencing the average diarrhea burden (equivalent to 23 days per year) was 0.38 cm shorter at 2 years of age compared to a child without diarrhea [10]. Taken together, diarrhea does have an impact on growth, but provided children have a disease-free period for recovery and access to adequate diet, catch-up growth can occur; diarrheal disease is therefore not sufficient to account for the degree of stunting that is typical among infants in developing countries.

**Environmental Enteric Dysfunction – A Role for the Gut in Stunting?**

Children living in impoverished conditions are undoubtedly frequently exposed to pathogenic microbes through feco-oral transmission; it is therefore likely that acute diarrhea represents only the tip of the ‘enteric disease iceberg’ (fig. 1), with a substantial underlying burden of chronic, subclinical enteropathy [11]. Indeed, it has been recognized for many decades that people living in conditions of poverty almost universally have a small intestinal pathology, characterized by villous atrophy and a mucosal inflammatory infiltrate, which has been attributed to living in conditions of poor sanitation and hygiene [12, 13]. Originally named tropical enteropathy, the current preferred term is environmental enteric dysfunction (EED), reflecting the broad disturbance in intestinal structure and function that likely arises from an apparent environmental insult [14].

Studies conducted in the Gambia some 30 years after the original published biopsy findings of tropical enteropathy, refocused attention on the gut and suggested that, rather than being a purely incidental finding, small intestinal enter-
Enteropathy may actually be an important underlying cause of stunting [15–18]. The challenge in investigating EED is that endoscopy and small intestinal biopsy are not feasible or ethical in otherwise healthy infants, so studies have relied almost entirely on surrogate markers. Most have assessed intestinal absorptive capacity and permeability by measuring the ratio of lactulose to mannitol in urine collected over several hours following an oral challenge dose. Mannitol, a monosaccharide, should be passively absorbed by a healthy small intestinal mucosa and reduced mannitol recovery in urine therefore indicates impaired absorptive capacity; lactulose, a disaccharide, should be precluded from absorption by tight junctions between epithelial cells, and increased recovery in urine therefore indicates abnormal gut permeability. Infants in the Gambia were found to have normal lactulose:mannitol (L:M) ratios for the first 3 months of life, then a progressive rise to 12–15 months of age, when the L:M ratio was around 5-fold greater than in age-matched UK counterparts [18]. The elevated L:M ratio was driven partly by impaired absorptive capacity and, to a greater extent, by increased intestinal permeability. Infant length growth was inversely related to the L:M ratio, with the timing of onset of linear growth failure coinciding with the age at which intestinal permeability started to increase. Further studies from the Gambia [15–17] and elsewhere [19, 20] confirmed that abnormal intestinal permeability is common among infants in underprivileged settings; although EED appears to improve from around 15 months of age, L:M ratios remain elevated even in adulthood compared to people living in developed countries.

**Fig. 1.** The enteric disease iceberg. Diarrhea may be conceptualized as being the tip of the ‘enteric disease iceberg’, with a much greater burden of chronic, subclinical enteropathy (termed EED) underlying clinically overt episodes of acute diarrhea. This figure is schematic and is not meant to depict relative proportions of diarrhea and enteropathy.
What would plausibly link impaired intestinal permeability with growth failure in infancy? It is increasingly recognized that intestinal barrier function is critical to health. A single layer of intestinal epithelium separates the ±100 trillion commensal microbes that populate the gut from the systemic circulation. Increased intestinal permeability enables microbes and bioactive macromolecules to cross the gut epithelium (a process termed microbial translocation) and activate macrophages and dendritic cells in local mesenteric lymph nodes and Kupffer cells in the liver. Activation of the innate immune system leads to elaboration of cytokines such as interleukin-6 (IL-6), IL-1β and tumor necrosis factor-α (TNF-α). In response to these proinflammatory cytokines, particularly IL-6, the liver synthesizes acute-phase proteins such as C-reactive protein (CRP).

**Intestinal Barrier Function and Chronic Inflammation**

Fig. 2. The pathway of intestinal microbial translocation. With loss of intestinal barrier function, microbes and microbial-associated products such as flagellin and lipopolysaccharide are able to translocate across the impaired gut epithelium to local mesenteric lymph nodes and to the liver, where they activate pattern recognition receptors on innate immune cells to cause elaboration of cytokines such as interleukin-6 (IL-6), IL-1β and tumor necrosis factor-α (TNF-α). In response to these proinflammatory cytokines, particularly IL-6, the liver synthesizes acute-phase proteins such as C-reactive protein (CRP).
an acute-phase protein produced by the liver, were elevated [15]. Infants also had high concentrations of lipopolysaccharide (also called endotoxin), a major component of the Gram-negative bacterial outer membrane, and antibodies against endotoxin (EndoCAb) in the systemic circulation. It was hypothesized therefore that chronic exposure to bacteria and bacterial constituents due to microbial translocation leads to a state of chronic inflammation that is metabolically expensive, repartitioning nutrients away from growth and towards immune activation.

A series of recent studies has further explored the hypothesis that EED and chronic inflammation underlie stunting [21–24]. The Malnutrition and Enteric Diseases (Mal-ED) study enrolled 8 birth cohorts from countries in South America, Africa and Asia, undertook monthly anthropometry and evaluated three biomarkers of intestinal inflammation (neopterin, myeloperoxidase and α1-antitrypsin) in stool samples from 661 infants collected at 3, 6 and 9 months of age [21]. At all sites, infants had elevated markers of intestinal inflammation, and each of the biomarkers predicted subsequent decline in length-for-age over the following 6 months, highlighting again the association between gut pathology and linear growth deficits. A study of 39 urban and 105 rural Chinese infants (age 5–7 months) evaluated levels of fecal calprotectin, a zinc- and calcium-binding protein abundant in neutrophils, which is a well-validated marker of intestinal inflammation [23]. Fecal calprotectin concentrations were higher in rural compared to urban infants and, in the rural group only, regression analysis using Monte Carlo simulation to account for missing data showed a significant inverse relationship between calprotectin and length-for-age z scores. A study of 202 Zimbabwean infants undertaken by our group evaluated levels of intestinal fatty acid-binding protein, a cytosolic protein in enterocytes that is released into the blood following villous damage [24]. Intestinal damage was evident from 3 months of age, peaked at 12 months, and exceeded levels seen in European children with untreated celiac disease, which has similar biopsy findings to EED. Infants who became stunted by 18 months of age had evidence of chronic inflammation from as early as 6 weeks of age, and the concentration of CRP over the first year of life predicted stunting in multivariate analysis. One mechanism through which inflammation may drive stunting is suppression of the growth hormone (GH) axis. Levels of insulin-like growth factor 1 (IGF-1), which is produced by the liver in response to GH, were inversely associated with each inflammatory marker evaluated [24]. It is well known in children with chronic inflammatory diseases such as Crohn’s disease and juvenile idiopathic arthritis that proinflammatory cytokines suppress IGF-1 levels and impair linear growth, but it appears that in otherwise healthy infants, a similar relationship may exist in the context of low-grade inflammation. Taken together, these recent studies confirm that gut damage occurs early in infancy, that stunting is characterized
by chronic inflammation and is at least partly mediated by suppression of the GH-IGF-1 axis.

What causes such extensive intestinal damage in early life? Studies fairly consistently show that, whichever surrogate marker is used, infants develop enteropathy from around 3 to 6 months of age. Although WHO guidelines recommend exclusive breastfeeding (EBF) for the first 6 months of life, it is well recognized that EBF rates are poor in many settings, with introduction of potentially contaminated non-breast milk liquids and foods early in life. We recently showed that infants, observed in a rural Zimbabwean setting to identify the potential vectors of feco-oral microbial transmission, regularly mouth their own hands (which were frequently visibly dirty and were rarely washed by mothers) and often ingest soil and chicken feces as part of exploratory behavior [25]. There are therefore multiple potential routes of pathogenic microbial exposure for infants living in contaminated conditions, at a time when the normal commensal microbiota is being established.

There is emerging interest in the role of the microbiota in malnutrition. The microbiota emerges from a founding population transmitted from the mother at the time of birth and during breastfeeding, and diversifies over the first 1–2 years of life to form a stable community of organisms [26]. Intestinal commensal organisms may have important functions in energy harvesting, nutrient synthesis and utilization, mucosal immune development and regulation of intestinal inflammation. A recent Malawian study convincingly demonstrated a role for the microbiota in the pathogenesis of severe acute malnutrition (SAM) [27]. Gnotobiotic mice transplanted with fecal microbiota samples from infants with kwashiorkor and fed a typical Malawian diet developed weight loss and metabolic disturbances characteristic of kwashiorkor; introduction of ready-to-use therapeutic food (RUTF) led to a change in the microbiota and weight gain. Another recent study from Malawi recruited clinically stable children treated for SAM with RUTF in the community [28]. Children randomized to a 7-day course of antibiotics in addition to RUTF had lower mortality and better nutritional recovery than children receiving placebo, despite no overt evidence of infection. It is conceivable in this population that antibiotics operate, at least in part, by modulating the intestinal microbiota, thereby improving weight gain. A recent meta-analysis of data from 10 randomized controlled trials enrolling children with a range of underlying conditions in low- and middle-income countries showed a significant impact of antibiotics on both weight and height gain; the authors speculated that the growth-promoting effects of antibiotics may be due to alterations in the intestinal microbiota, although none of the trials specifically investigated this hypothesis [29].

Taken together, there is emerging evidence that both intestinal damage and composition and function of the microbiota may be important factors underlying...
ing malnutrition in early life, although further studies are required to investigate the specific role of the microbiota in stunting. There are multiple potential overlapping causes of enteropathy in developing countries, including persistent diarrhea, HIV, mycotoxin exposure and micronutrient deficiencies, all of which may interact to compound intestinal damage [30]. EED appears to be an almost universal finding among infants living in impoverished conditions and is relatively slow to resolve once established. Could improvements in environmental conditions potentially prevent onset of EED in early life?

**A Role for Toilets in Reducing Stunting?**

Reducing feco-oral microbial transmission by improving water, sanitation and hygiene (WASH) may theoretically prevent or ameliorate EED and improve linear growth. A study from rural Bangladesh, which categorized children as living in ‘clean’ or ‘dirty’ homes based on water quality and sanitary and hand washing infrastructure, found that the height-for-age z score of children in clean homes was 0.54 (95% CI 0.06–1.01) greater than those in dirty homes after adjusting for confounding factors [22]. There was also a trend towards lower L:M ratios and lower EndoCAb concentrations in those from clean homes, suggesting that the height differences between groups may have been mediated by EED.

Several recent studies have explored the association between open defecation and stunting. The starting point for these analyses was the observation that wealth does not adequately explain the prevalence of stunting in different countries. India, in particular, has higher rates of stunting than many African countries, despite individuals on average being wealthier in India. In a regression analysis of data on sanitation coverage and child height from 65 developing countries, the author concluded that differences in height between countries, even after accounting for economic indicators, are explained by rates of open defecation [31]. An ecological analysis from India, where more than 50% of the population still practices open defecation, reported a 0.7% increase in stunting and severe stunting for each 10% increase in open defecation across 112 districts for which data were available [32]. However, despite adjusting for potential founders, these studies are severely limited by the potential for residual confounding inherent in observational and ecological studies.

A recent systematic review of the impact of WASH interventions on child nutritional status identified 5 cluster-randomized controlled trials which evaluated solar disinfection of water, provision of soap or improvement in water quality; there were no trials of improved sanitation [33]. Although no individual
trial showed a significant effect of any intervention on height, a meta-analysis of
data from 4,627 children under 5 years of age showed a small but significant im-
 pact on height-for-age z score (mean difference 0.08; 95% CI 0.00–0.16). The
quality of evidence from these trials was judged to be generally low, and all re-
ported fairly short-term (9–12 months) outcomes, leading the authors to con-
 clude that further high-quality data are required. It is recognized that WASH
interventions can be challenging to evaluate in randomized trials because of dif-
ficulties in blinding, frequent reliance on self-reported outcomes and conse-
quently potential for observer and reporter bias [34].

Two large community-based trials are currently underway to evaluate the
impact of WASH interventions on stunting in developing countries. The San-
itation Hygiene Infant Nutrition Efficacy (SHINE) study in Zimbabwe is a
community-based, cluster-randomized factorial trial evaluating the impact of
improved WASH and/or infant and young child feeding (IYCF) on stunting
and anemia (clinicaltrials.gov identifier NCT01824940). In total, 4,800 preg-
nant women will be recruited from two contiguous districts of rural Zimbabwe
and their infants followed to 18 months of age. WASH interventions include
 provision of a Blair ventilated improved pit latrine and two Tippy Tap hand
washing devices in the homestead (fig. 3), together with chlorination of water
and a clean play space to protect crawling infants from geophagia and inges-

Fig. 3. Tippy Tap hand washing device. A Tippy Tap (www.tippytap.org) is a low-technology, inexpensive, water-saving device to promote hand washing, even among children.
tion of chicken feces. Behavior change interventions promoting use of these hardware items are provided by Village Health Workers. IYCF interventions include education about optimal complementary feeding practices and provision of Nutributter, a lipid-based nutrition supplement that provides additional calories and effectively closes the micronutrient gap, from 6 months of age. The WASH Benefits study (clinicaltrials.gov identifiers NCT01704105 and NCT01590095) comprises 2 parallel cluster-randomized controlled trials, one in Kenya and one in Bangladesh, which are evaluating the impact of individual and combined water quality, sanitation, hand washing and nutritional interventions on child growth and diarrhea. Both SHINE and WASH Benefits have intensive substudies evaluating potential pathways through which these interventions may operate, and the extent to which WASH interventions impact environmental microbial contamination. WASH Benefits and SHINE will be among the few randomized controlled trials of toilets that have evaluated child health outcomes, and aim to provide high-quality evidence to inform public health programming, given that 40% of the global population still lacks access to safe sanitation.

There is increasing interest in multisectoral interventions to tackle stunting, through both nutrition-specific and nutrition-sensitive programs. However, there is currently a paucity of evidence to guide which strategies are likely to be successful. It is hypothesized that interventions need to be targeted to the first 1,000 days to have maximal impact on growth and development (www.thousanddays.org), particularly if the aim is to prevent onset of EED. Improvements in WASH and nutrition are, however, likely only two interventions within a complex interplay of factors that must be targeted to optimally promote healthy growth and improve long-term developmental potential of children in developing countries [8].

**Disclosure Statement**

AJP and JHH are both investigators on the SHINE trial. The authors have no declarations of interest to declare.

**Acknowledgements**

We thank Robert Ntozini for his help with figure production.
References


Feeding Practices – Current and Improved?


Human Milk Fortification

Karen Simmer

Centre for Neonatal Research and Education, The University of Western Australia and NICU King Edward and Princess Margaret Hospitals, Perth, WA, Australia

Abstract

Human milk is the feed of choice for preterm infants. However, human milk does not provide enough nutrition, especially protein, for preterm infants to achieve target growth rates similar to those in utero (15–20 g/kg per day). Fortifiers for human milk, manufactured from bovine milk, are commercially available and routinely used for patients born <32 weeks’ gestation prior to discharge home. Recent recommended dietary intakes (RDI) have been revised. Up to 4.2 g of protein and 135 kcal/kg per day is recommended for infants born very preterm. Additional supplements are needed to current commercial fortifiers to achieve these RDI and reduce the incidence of ex-uterine growth failure. A human milk fortifier that is manufactured from donor human milk is available in some developed countries and may confer some clinical benefits, including a reduction in necrotizing enterocolitis. Fortification can be added in a standardized protocol as per manufacturers’ instructions. Human milk composition can be analyzed and fortification individualized to take into account the large variation from mother to mother. Alternatively, fortification can be increased in a stepwise manner based on assumed composition while monitoring blood urea levels for safety. The current aim is to prevent preterm infants dropping percentiles and falling below the 10th percentile at 36 weeks’ corrected gestational age or discharge home. More data are required on how best to fortify human milk for preterm infants to achieve optimal growth, development and health outcomes in the long term. There is an urgent need for well-designed and informed randomized clinical trials in this vulnerable preterm population.

© 2015 Nestec Ltd., Vevey/S. Karger AG, Basel

The Problem

The majority of preterm infants survive (>95% from 28 weeks’ gestation and >80% from 24 weeks’ gestation; Department of Health, Western Australia). However, their progress in the neonatal intensive care unit (NICU) is compli-
cated by feed intolerance, necrotizing enterocolitis (NEC), infection, broncho-
pulmonary dysplasia and poor growth. Subsequently, neurological disability oc-
curs in about 10%, and the incidence increases with decreasing gestational age
(GA) to 25% infants born <27 weeks’ gestation. In addition, very preterm infants
have a higher incidence of behavioral problems, academic difficulties and hos-
pital readmissions than children born at term. Preterm infants as adults may also
have adverse metabolic outcomes including abnormal insulin sensitivity, lipid
metabolism and blood pressure [1, 2].

Extrauterine growth retardation (EUGR) defined as weight <10th percentile
at discharge home, remains a serious problem. Clark et al. [3] reported an inci-
dence of 28% measured in 24,371 infants born at 23–34 weeks’ gestation from
124 NICU in the United States of America, with an increasing incidence with
decreasing gestation. Dusick et al. [4] reported an incidence of EUGR of 99% in
4,438 very-low-birthweight infants (501–1,500 g; incidence of birthweight <10th
percentile or being small for GA (SGA) was 22%). In Western Australia, the in-
cidence of EUGR at discharge home infants born <28 weeks’ gestation is 50%
(18% SGA at birth, Neonatal Database Women’s and Newborns’ Health Ser-
vice).

EUGR is associated with long-term low growth and cognitive impairment
[4, 5]. Ehrenkranz et al. [6] reported a dose-dependent association between early postnatal growth and neurodevelopmental outcomes. Infants with birth-
weights 501–1,000 g (n = 495) were followed to 18–22 months and divided
into weight gain quartiles for in-hospital growth velocity rates with the lowest
being 12 g/kg per day and the highest 21 g/kg per day. Bivariate analysis dem-
onstrated that as the rate of weight gain increased, the incidence of cerebral
palsy, abnormal neurological examination, and neurodevelopmental impair-
ment fell. Patients in the lower quartile had more NEC, bronchopulmonary
dysplasia, late-onset sepsis and received more postnatal steroids. Logistic re-
gression including variables related to neonatal morbidity suggested that
growth velocity during hospitalization of the ELBW infant was a significant
factor determining neurodevelopmental outcome at 18–22 months’ corrected
age.

The Solution

How we feed these vulnerable patients has a direct effect on their growth,
health and development. Human milk is undoubtedly the best source of nutri-
tion, and the immunological benefits are especially important for the preterm
infant.
The nutrient requirements of preterm infants have been determined by factorial and empirical methods and are well reviewed with recommended intakes by Ziegler [7]. With decreasing GA, the recommended nutrient intakes to match fetal accretion rates increase to over 4 g/kg per day protein and cannot be met with human milk alone. Protein and energy levels in human milk vary widely from mother to mother and across time. McLeod et al. [8] analyzed 336 samples from 36 mothers of preterm infants by laboratory methods and reported median (range) protein 16.1 (13.4–27.6) g/l and energy 730 (630–895) kJ/l.

Fortifiers are available commercially to increase nutrient intakes of very preterm infants with the aim of achieving recommended intakes and growth rates similar to the fetus. In practice, despite efforts, recommended dietary intakes (RDI) are often not met [8, 9]. A recent detailed audit growth of extremely low GA infants in Sweden demonstrated growth falling down percentiles despite early human milk feeds with high levels of fortification [10].

To meet growth targets, it has been suggested that more protein is required than currently available in commercial fortifiers [7]. Miller et al. [11] conducted a randomized clinical trial (RCT) of commercial fortifier (additional 1 g/100 ml) versus an isocaloric high-protein fortifier (additional 1.4 g/100 ml) in 92 infants born <32 weeks’ gestation. Unfortunately, many infants in their study also received preterm formula (2.4 g/100 ml) confounding the results. Median protein intakes (IQR) at weeks 1–4 of the study were 3.6 (3.7–4) versus 4.2 (3.2) g/kg per day. The primary outcomes of length velocity were not significantly different between groups (p = 0.08), neither was there a difference in weight gain or %EUGR at approximately 35% (with 12–16% SGA).

Feeding human milk maximally fortified with a fortifier produced from donor milk also does not prevent EUGR. Hair et al. [12] fed human milk early to patients born ≤1,250 g and fortified when 80 ml/kg per day was tolerated with a product from donor milk. They targeted growth of 20 g/kg per day 1 cm/week and feeding 130–140 kcal/kg per day and 3.6–4.4 g/kg per day. Infants received up to 150 kcal/kg per day and 5.25 g/kg per day protein, with 80% infants gaining ≥20 g/kg per day. With this, the incidence of EUGR was 43% (21% were SGA, and they were all EUGR at discharge, 79% had birthweight appropriate for GA, and 22% were EUGR at discharge).

Body composition is influenced by diet and is emerging as a necessary measure of nutrition adequacy. Air displacement plethysmography technology is a safe and efficient means by which to measure body composition of infants. The data suggest that preterm infants are lighter and fatter than term infants when measured at an equivalent term age [13], but this abnormality may not persist into childhood [14]. However, young adults who were born preterm have cen-
tral adiposity and altered fat distribution measured by detailed MRI studies. The pattern of fat distribution reported in ex-preterm adults has been associated with risk of cardiovascular disease [15].

**The Benefits of Human Milk Fortification for Preterm Infants**

Growth (weight, length and head circumference gain) of infants (<1,800 g) fed fortified human milk (under 2 kg) is better than that of those fed unfortified human milk in the short term (meta-analysis of 13 studies) [16].

Fortified human milk can achieve intakes of protein 4–4.5 g and energy 110–135 kcal as recommended by the ESPGHAN Committee on Nutrition [17].

Fortifiers also supplement calcium, phosphorus and vitamin D with the aim of preventing osteopenia of prematurity, but the data are limited and do not show a benefit.

Improved growth is associated with better neurodevelopmental outcomes [6]. Increasing SD for weight and head circumference from birth to discharge has been associated with neuromotor outcomes at 5 years of age [18]. Increasing protein intake is associated with better growth and better neurodevelopmental outcomes [19].

**The Risks of Human Milk Fortification**

Fortifiers increase osmolality, especially if milk is fortified for a 24-hour period rather than at the bedside immediately prior to the feed (as recommended by the manufacturer). In many busy NICUs, feeds are prepared in a ‘milk room’ under strict management guidelines which may result in slow increase in osmolality as the enzymes in human milk digest nutrients in the fortifier. Osmolarities <450 mosm have been recommended as safe and not increasing the risk of NEC [20].

Adding fortifier to human milk may increase feed intolerance and the risk of NEC compared with feeding unfortified human milk. It has been suggested that cow’s milk protein present in many fortifiers may be a trigger for intestinal inflammation and contribute to the risk of NEC [21].

The added carbohydrate from fortifiers may result in raised plasma glucose levels and diuresis.

For SGA infants, faster weight gain may be associated with higher later blood pressure and risk of obesity [22, 23].

Why?

The aim of human milk fortification is to achieve RDI for preterm infants [17] and achieve growth rates similar to those achieved by the fetus in utero at similar GA [24]. The overall aim is to maintain growth along percentiles feeding human milk. If born SGA, the aim is to prevent further growth retardation. If born lean, it appears best to stay lean.

Who?

Current practice is to fortify human milk for infants born <32 weeks’ GA and sometimes <34 weeks’ GA. Preterm infants born later than this are usually not in hospital long enough to receive nutrient supplementation and often receive some feeds directly from the breast.

There is increasing evidence that ‘late pretermers’ (34–37 weeks’ GA) have increased risk of developmental and behavioral problems, but any effect of human milk fortification in this group has not been extensively studied.

When?

Fortifiers are added at the clinicians’ discretion, and guidelines vary between units. Because of concerns about feed intolerance and NEC, fortifiers are commonly added once ≥100 ml/kg per day human milk is tolerated. As daily protein intakes may fall as patients are transitioned from parenteral to enteral nutrition, some clinicians may add fortifier earlier. Historically, fortifiers may be discontinued when a weight of 2 kg is reached but many units continue fortifying human milk fed by tube or bottle until term or discharge, whichever is earliest. The fortification is weaned as more feeds are taken directly as breastfeeds.

In general, catch-up growth is not promoted, although it may occur naturally for the breastfed infants who regulate their own intake. Supplementing feeds with gastric tube feeding after term rarely occurs unless infants have neurological impairments. Postdischarge fortification is uncommon, although anecdotally some clinicians may recommend alternating breastfeeding with a bottle of fortified expressed breast milk if growth is a concern.
What?

Powder or liquid fortifiers based on cow’s milk proteins (intact or hydrolyzed) and fortifiers manufactured from donor human milk can be used.

Clinicians need to make an informed choice about which fortifier to use for their preterm patients. Protein and energy intakes need to be met at volumes prescribed. Whether energy is provided, a carbohydrate, or carbohydrate and fat, may be important especially for the very preterm infant who may have problems managing plasma glucose levels.

Attention needs be paid to whether the fortifier is supplemented completely with vitamins to meet RDI. Additional vitamin D supplements are often required to meet recent RDI.

Attention needs be paid to whether the fortifier chosen is supplemented with iron or not. Some clinicians prefer to supplement their patients with iron independently and at a later age than when fortifiers are introduced.

Importantly, clinicians should know the osmolality of fortified human milk when fed to their patients as high osmolalities have been associated with NEC. In some NICUs, fortifier is added to human milk at the bedside immediately prior to feeding, and the osmolality will be as stated by the manufacturer. In large busy NICUs, feeds may be prepared daily in the ‘milk room’ and fed over the following 24-hour period. In our NICU, fortifier based on intact cow’s milk protein has an osmolality of 420 mosm after 24 h and one based on hydrolyzed protein, 490 mosm after 24 h. Medications, if added to milk feeds, will further increase the osmolality.

Fortifiers are available that contain intact cow’s milk protein or hydrolyzed cow’s milk protein. In formula-fed infants, hydrolyzed protein has been associated with slower weight gain and higher urinary excretion of essential amino acids [25].

Fortifiers are available as powders or liquids. Liquid fortifiers were introduced because of concerns about bacteria in powered feeds resulting in invasive infection. Use of liquid fortifiers in preterm infants has been associated with acidosis and poor growth [26].

In North America, fortifiers manufactured from donor human milk are available, but these are expensive. Feeding only human milk-based products has been found in an RCT to decrease NEC compared with feeding human milk fortified with cow’s milk products including formula supplements [27]. However, in this RCT, the incidence of NEC was high. The results may not be generalizable to many NICUs where fortifiers based on cow’s milk are used, and donor human milk, not formula, is used when supply of mothers’ own milk is inadequate to meet her baby’s requirements.
How?

Traditionally, fortification of human milk has been standardized. The composition of human milk is assumed and fortifier is added per manufacturers’ instructions. The aim is that assumed plus fortified nutrients meet RDIs. This may not occur for reasons including: volumes of milk fed and tolerated may be less than prescribed; the addition of fortifier may be delayed, or fluids may be chronically restricted.

In our NICU, there may be two levels of standardized fortified human milk with commercial fortifier and supplemental protein: level 1, fortified (2.6 g protein/100 ml) and fed at ≥150 ml/kg per day, and level 2 (3 g protein/100) for infants who are fluid-restricted or failing to thrive. Blood urea is measured at least weekly to provide some reassurance that high protein intakes are tolerated.

A potential problem is that human milk varies over the postnatal period and from mother to mother, so assumed composition may not be accurate [8]. This has led to the suggestion that protein and energy content of human milk should be measured and fortification individualized [28]. Evidence of clinical benefit of individualized fortification has yet to be demonstrated.

One reason for the lack of clinical benefit is that infants receiving standardized fortification may receive more protein than those fed individualized fortified milk. De Halleux and Rigo [29] measured the composition of mothers’ own and donor milk by mid-infrared spectroscopy and targeted fortification in two steps: fat content adjusted to 4 g/dl and addition of fortifier to provide protein 4.3 g/kg per day. Nutrient intakes were calculated for 24 VLBW infants and control infants fed standard fortification. Variability of protein intakes was reduced by 21% but protein intake was lower in infants fed individualized fortification compared with infants fed standard fortifier.

We conducted an RCT of fortifying milk on the basis of milk analysis and by targeting PE ratios and protein intakes according to postnatal age [30]. 40 preterm infants with GAs from 23 to 29 weeks and birthweights from 480 to 1,475 g were randomized to either individualized or standard fortification. Mean milk composition for the intervention infants was determined weekly from daily milk samples using mid-infra-red technology, and milk was fortified with commercial HM fortifier, a protein and/or energy supplement to reach recommended protein and energy RDIs. Control infants received standard fortification as per unit protocol based on assumed composition of HM. Nutrition intakes of both groups were calculated retrospectively using measured composition of milk for all infants. During the intervention period (6 weeks), infants were fed less protein (3.2 ± 0.4 vs. 3.9 ± 0.3 g/kg per day, p < 0.001) and gained less weight, but
there was no difference between the groups in weight or body composition at discharge home ($2,265 \pm 342$ vs. $2,464 \pm 528$ g, $p = 0.175$, and $13.6 \pm 3.7$ vs. $13.6 \pm 3.5$ %fat).

Rochow et al. [31] in Canada conducted a case-control study with similar results. Ten VLBW infants were fed human milk with fortification targeted at final contents of fat 4.4 g, protein 3 g and carbohydrate 8.8 g per 100 ml. Their growth was compared with 20 infants in a matched-pair analysis and was similar.

A totally different approach to fortification was trialed by Arsanoglu et al. [32]. Their feeding guidelines slowly increase fortifier and protein intakes provided blood urea is maintained in the normal range. This results in high nutrient intakes than when feeding standardized fortified human milk (2.9, 3.2 and 3.4 vs. 2.9, 2.9 and 2.8 g/kg per day weeks 1, 2, and 3 adjusted vs. standard fortification), and was associated in their preterm patients with better growth.

**Donor Human Milk**

Preterm infants receiving pasteurized donor human milk (PDHM) grow less well than those fed formula [33]. Michaelsen et al. [34] analyzed by mid-infrared spectroscopy 2,554 samples from 224 mothers donating to human milk bank in Copenhagen and reported relatively low protein levels, mean 9.0 g/l (95% CI 6.3–14.3) with energy 696 kcal/l (95% CI 500–1,155). These levels are similar to those in our human milk bank for pasteurized donor milk of 10.4 ± 2.2 g/l and 667 ± 86 kcal/l ($n = 89$, mean ± SD).

The quality of both protein and fat is altered through pasteurization. Infants fed PDHM may benefit from a higher level of fortification than prescribed for mothers’ own milk. It has also been suggested that the human milk bank may be the best place to introduce individualized fortification. Batches of PDHM could have protein and energy contents measured and fortification added to ensure known composition is dispensed from the human milk bank [29].

In conclusion, higher nutrient intakes are required than commonly delivered with human milk supplemented with commercial fortifiers to meet recent RDIs for preterm infants. Extra protein can be added to fortifiers to reach RDI-based on assumed composition of human milk but the limited evidence suggests that protein alone will not be adequate. Alternatively, supplementation can be increased until growth targets are met as per regime of Arsanoglu et al. [32] of measuring tolerance by blood urea nitrogen.
Individualized or targeted fortification of human milk based on measured composition, although theoretical preferable, has yet to demonstrate a benefit in an RCT. A fortifier produced from human milk rather than bovine products may be beneficial, and results of early trials need to be confirmed before being adopted more generally.

At a more fundamental level, optimal rate of growth and quality of growth (including body composition) needs to be determined. It may not be possible, let alone desirable, for very preterm infants to grow along fetal growth charts. There are some data from ex-preterm children suggesting that relative undernutrition in early life may have beneficial effects on insulin resistance [2]. Further, health outcomes may be worse if growth retardation is followed by a period of rapid catch-up growth. This was suggested from animal studies, when protein deficiency followed by a cafeteria diet reduced longevity significantly [35].

The current aim is to prevent preterm infants dropping percentiles and falling below the 10th percentile at 36 weeks’ corrected GA or discharge home. Moltu’s group randomized 50 neonates <1,500 g to a multipronged intervention of high-protein/-lipid and -vitamin parenteral nutrition and high-protein fortifier and ‘protein shots’ prior to discharge in an attempt to meet RDI and prevent EUGR. Growth velocity and z scores were improved, but the trial ceased prematurely because of an increased incidence of septicemia in the intervention group possibly related to electrolyte disturbances indicative of accelerated protein synthesis.

There is a gap in our knowledge about how best to fortify human milk for preterm infants to achieve optimal growth, development and health outcomes in the long term. A Cochrane review [16] concludes that there is unlikely to be further trials on fortified versus unfortified human milk, but further research is needed comparing different fortifiers with short- and long-term outcomes to determine the optimal fortifier for human milk. There is an urgent need for well-designed and informed RCTs in this vulnerable preterm population.

**Disclosure Statement**

The author declares that no financial or other conflict of interest exists in relation to the contents of the chapter.
References


Feeding Practices – Current and Improved?


Abstract
The high low birthweight prevalence in resource-poor countries (16.5%) places a burden on overstretched resources. Labor ward must have written guidelines to triage these infants for optimal nutritional support to the special care nursery (SCN; 1,500–1,800 g and <34 weeks) and postnatal ward (PW; >1,800 g and ≥34 weeks). Separation of mother and infant should be prevented. Initiating breastfeeding and kangaroo mother care (KMC) in labor ward by skilled nurses in the latter group is a priority and continues in the PW. SCN infants receive an intravenous 10% glucose-electrolyte solution and, if stable, commence with expressed colostrum and breast milk (EBM) feeding and intermittent KMC which progresses to continuous KMC and breastfeeding. Enteral feeding is advanced more slowly in unstable infants. Parenteral nutrition is only administered to infants with bowel obstruction or feeding intolerance. EBM of HIV+ mothers in the SCN is pasteurized. The decision to discharge a mother-infant dyad should be individualized. Infants in the SCN are discharged at 34 weeks, a weight of 1,600–1,800 g and are gaining adequate weight. Discharge from the PW usually takes place after 48 h, often before the infant has regained his birthweight but breastfeeding must be established. Multivitamin- and iron-containing syrup is continued for at least 12 months. The clinics in the community must provide post-discharge nutritional support. © 2015 Nestec Ltd., Vevey/S. Karger AG, Basel

Introduction
More low-birthweight (LBW) infants are born in developing countries (16.5 vs. 7%) than in First World countries, and they are often born to women with serious antenatal risk factors; yet, they are delivered at hospitals with limited facilities and medical and nursing expertise [1].

Feeding the Larger Low-Birthweight Infant in a Resource-Poor Environment

Gert F. Kirsten
Division of Neonatology, Department of Paediatrics and Child Health, Tygerberg Children’s Hospital and University of Stellenbosch, Western Cape, South Africa

Abstract
The high low birthweight prevalence in resource-poor countries (16.5%) places a burden on overstretched resources. Labor ward must have written guidelines to triage these infants for optimal nutritional support to the special care nursery (SCN; 1,500–1,800 g and <34 weeks) and postnatal ward (PW; >1,800 g and ≥34 weeks). Separation of mother and infant should be prevented. Initiating breastfeeding and kangaroo mother care (KMC) in labor ward by skilled nurses in the latter group is a priority and continues in the PW. SCN infants receive an intravenous 10% glucose-electrolyte solution and, if stable, commence with expressed colostrum and breast milk (EBM) feeding and intermittent KMC which progresses to continuous KMC and breastfeeding. Enteral feeding is advanced more slowly in unstable infants. Parenteral nutrition is only administered to infants with bowel obstruction or feeding intolerance. EBM of HIV+ mothers in the SCN is pasteurized. The decision to discharge a mother-infant dyad should be individualized. Infants in the SCN are discharged at 34 weeks, a weight of 1,600–1,800 g and are gaining adequate weight. Discharge from the PW usually takes place after 48 h, often before the infant has regained his birthweight but breastfeeding must be established. Multivitamin- and iron-containing syrup is continued for at least 12 months. The clinics in the community must provide post-discharge nutritional support. © 2015 Nestec Ltd., Vevey/S. Karger AG, Basel

Introduction
More low-birthweight (LBW) infants are born in developing countries (16.5 vs. 7%) than in First World countries, and they are often born to women with serious antenatal risk factors; yet, they are delivered at hospitals with limited facilities and medical and nursing expertise [1].
LBW refers to infants <2,500 g. Small for gestational age (SGA) refers to the infant with a birthweight (BW) <10th centile for gestation while intrauterine growth restriction (IUGR) only to those infants with BW and/or birth length below the 10th percentile for gestational age (GA) with a pathologic restriction of fetal growth. IUGR forms a subset of cases of SGA infants [2].

The prevalence of LBW in India has been reported as 26% with 54% IUGR [3, 4] (prevalence in the United States: 6.9–8.1%) with one third of these suffering from IUGR [5].

This paper will deal with the larger (≥1,500 g) LBW infant who is born prematurely (<38 weeks). Due to limited neonatal intensive care facilities, these infants are predominantly managed in the special care nursery (SCN) and postnatal ward (PW). Readmission to hospital due to feeding difficulties and jaundice is common in LBW infants born preterm as many are discharged at low GAs before lactation is fully established [6].

Management of Low-Birthweight Infants in Labor Ward

Triage in labor ward is essential directly after birth. The triage of the supposedly well infant into those that require incubator care and parenteral glucose administration versus kangaroo mother care (KMC) and breastfeeding is complicated by factors such as uncertain GA, growth restriction, ill mother, etc. Labor ward must have written guidelines for the midwives for triaging LBW infants either to the SCN or PW. The attending pediatric doctor should assess all infants <2,000 g. As many women only attend an antenatal clinic late, GA is often uncertain and an attempt should be made to verify it [7]. To ascertain SGA, the weight of the infant should be plotted on a growth chart [8].

Triage and Transfer from Labor Ward

Only broad guidelines can be provided for triaging these infants into 4 groups of which the management differs substantially:

- Group 1: infants with BWs between 1,500 and 1,800 g and <34 weeks’ gestation. They are transferred by incubator to the SCN, and their mothers follow once they are stable.
- Group 2: infants with BWs between 1,800 and 2,000 g and <34 weeks. They are transferred to either the SCN by incubator (<34 weeks) or the PW (≥34 weeks) in the KMC position once the mother is stable. Teenage
mothers and mothers with multiple births are assessed and transferred individually.

- **Group 3:** infants >1,800 g with a gestation of 34 weeks or those >2,000 g. These infants are transferred in the KMC position to the PW with their mothers.
- **Group 4:** infants who require admission to the NICU. They are not discussed in this chapter.

Due to an increased risk of feeding intolerance, hypoglycemia and hypothermia, infants with severe IUGR, regardless of weight or GA, should initially be transferred to the SCN with their mothers.

If the mother is ill, her infant is immediately transferred to either the SCN or the PW in an incubator.

*Nutritional Management in Labor Ward*

Preventing the separation of mother and infant as far as possible and initiating breastfeeding and KMC in labor ward in the infants who are to be transferred to the PW is a priority. Early skin-to-skin contact increases the success of the first breastfeed [9], allows frequent suckling and prevents hypothermia. Breastfeeding is commenced in the stable HIV– mother’s infant or in the baby of the HIV+ mother who has chosen to breastfeed. Labor ward nursing personnel must be well versed in breastfeeding support of mothers of premature infants [10]. The HIV+ mother who opts for formula feeding will also practice KMC and will be provided with preterm formula for her infant.

*Labor Ward Observations*

Although these infants appear stable as they do not suffer from respiratory distress, etc., they do require close observation as they are sleepy, do not latch and suckle as well as term infants and can become hypothermic and hypoglycemic very quickly [6]. A blood glucose level should be determined on every baby within 1 1/2 to 2 h of age. Earlier measurement has not been shown to be of benefit.

Growth-restricted infants require close observation for hypothermia and hypoglycemia. They should be transferred to the SCN for parenteral glucose administration if they have symptomatic hypoglycemia or a blood glucose level <2.4 mmol/l [11].
**Nutritional Management in the Special Care Nursery**

These infants are nursed in an incubator and receive an intravenous 10% glucose-electrolyte solution on admission at a volume of 70 ml/kg per day. An orogastric tube is also placed.

Breast milk, with its low risk of necrotizing enterocolitis (NEC), can be advanced rapidly to increase enteral protein intake in resource-constrained environments where there is a scarcity of parenteral nutrition (PN).

The infants in the SCN are divided into 2 groups depending on their clinical condition. Those on either nasal CPAP or nasal cannula oxygen are categorized as ‘unstable’. However, they are only kept nil by mouth if there is a medical or surgical contraindication to enteral feeding. Incubator care is continued until oxygen therapy is discontinued and intermittent KMC and expressed breast milk (EBM) feeding can be commenced. Stable infants commence with intermittent KMC, EBM and breastfeeding immediately, which progresses to continuous KMC and breastfeeding once the mother is producing adequate volumes of milk for the intravenous infusion to be discontinued. Infants are weighed daily.

**Colostrum, Expressed Breast Milk and Pasteurization**

Once a mother is stable, she is assisted and instructed in the technique of KMC, the aseptic technique of manually expressing colostrum and breast milk and the correct labelling of bottles and of refrigeration. All colostrum is administered by syringe or teaspoon directly into the mouth of both the stable and unstable baby.

EBM in the SCN is used in the form of unpasteurized own mother’s EBM from HIV− women, pasteurized own mother’s EBM from HIV+ women and donor EBM. Due to the risk of HIV transmission through EBM to her own baby or to another baby in the ward in the event of the inadvertent administration of EBM to the wrong baby, the HIV status of every mother must be known on admission of her baby to the ward [14, 15]. Mothers are supplied with sterilized wide-rimmed glass containers for milk expressing. The use of breast pumps is not allowed as they may be shared, and in so doing HIV, CMV, hepatitis B, etc. may be transmitted [16]. The SCN should have a milk kitchen with ample refrigeration and freezer facilities as well as the necessary equipment for the ‘flash heating’ method of pasteurization.

EBM must be refrigerated immediately after expressing. Human milk may be stored at 4°C for up to 96 h or should be frozen [17]. If cooling or freezing fa-
cilities are not available, preterm EBM may be stored for up to 4 h at room temperature [18].

HIV+ mothers are taught to pasteurize their breast milk immediately after expressing [19]. A wall chart should be available in the milk kitchen for reference.

EBM of mothers who refuse to be tested for HIV must also be pasteurized. The nursing staff must teach the mothers the correct way of labelling the milk bottles. A designated colored sticker is applied to the bottles containing pasteurized EBM from an HIV+ mother. The baby’s name, surname, hospital number, date and time of expressing as well as date and time of pasteurization must be noted on a label applied to the milk bottle.

Only pasteurized EBM from an HIV+ mother may be placed in the refrigerator or freezer. Cooled pasteurized EBM can be used immediately or stored in the designated milk refrigerator for up to 96 h where after it should be frozen. If no freezer facilities are available, pasteurized EBM may be stored at room temperature for 24 h [20].

Strict protocols must be followed to ensure that EBM is administered to the correct baby. Protocols must also be in place for the management of an infant during the inadvertent administration of HIV+ EBM to another mother’s baby.

**Pasteurized Donor Expressed Breast Milk**

As it is a scarce commodity, pasteurized donor EBM is generally only available for VLBW infants and is only an option for LBW infants >1,500 g with feeding intolerance and IUGR whose mothers are unable to provide EBM.

**Formula Feeding in the Special Care Nursery**

If mother’s own breast milk is unavailable due to maternal illness or death, formula is commenced.

Formula milk is associated with complications such as NEC; it does not confer anti-infective properties such as IgG, secretory IgA, oligosaccharides, etc. to the infant [21], is unaffordable to the majority of parents and is associated with gastroenteritis if good sanitation and clean water are not available at home. It is the HIV+ mother’s informed choice to decide whether she is going to breastfeed, feed the baby pasteurized EBM or give formula.
Administration and Advancement of Expressed Breast Milk in the Special Care Nursery

Infants with BWs >1,500 require 60–80 ml/kg per day on day one. For all infants, total fluids (intravenous + enteral) are increased by 25 ml/kg per day to reach 150–160 ml/kg per day by 5–6 days of age. Breast milk intake in the SCN is commenced according to what is available, is advanced by 25–30 ml/kg daily and administered by orogastric tube as a bolus. The daily intravenous glucose volume is decreased as the EBM intake increases. The EBM intake can be increased to a maximum of 180–200 ml/kg per day if the weight gain is <20 g/kg per day once BW is regained. If the weight gain is still suboptimal, a commercially prepared fortifier or coconut oil may be considered. If a fortifier is not available, 2.5 g skim milk may be added to 100 ml of EBM [22]. Hindmilk has a higher fat and caloric content than foremilk and may also be used to increase caloric intake [23].

Special attention should be paid to the infant with severe IUGR as feeding intolerance and an increased risk of NEC may necessitate a smaller daily increment in milk volume and a continuous infusion of EBM by orogastric tube instead of bolus feeding [24]. It may be necessary to supplement caloric intake with PN.

Kangaroo Mother Care and Breastfeeding in the Special Care Nursery

While the infant is receiving intravenous feeding and gavage feeding of EBM and is stable, the mother practices intermittent KMC and begins to initiate breastfeeding. The first step is nipple contact during KMC which stimulates the let-down reflex and assists with manual expressing of colostrum, and later of breast milk.

Once the infant is gaining weight adequately, intravenous fluid has been discontinued, he/she is off oxygen and the nasogastric tube has been removed, he/she is removed from the incubator to his/her mother’s bed for continuous KMC and full breastfeeding. The infant is still weighed daily as there is often a decline in daily weight gain due to the increased activity of full breastfeeding. Feeding by cup is also introduced to provide top-up EBM feeds for the infant with sub-optimal weight gain.

‘Milk handlers’ are designated nursing assistants who obtain colostrum and EBM from a mother separated from her baby (e.g. mother in obstetrical high care, etc.). They also train and support mothers in manual expressing of breast milk and pasteurization, in the correct labelling and storing of milk bottles with EBM and identify potential milk donors.
Cup Feeding in the Special Care Nursery

Although infants are discharged at weights of 1,600–1,800 g and a GA of 34 weeks, they will not yet have attained maximal oral feeding skills (35–37 weeks for most premature infants) [25]. As they are often unable to empty a breast and to obtain sufficient amounts of breast milk to meet their nutritional requirements, they need top-up feeds. Immediately after the breastfeed, the mother expresses milk from the partially emptied breast into a sterilized cup. This ensures that the breast is fully emptied to maintain a good milk supply and she can give her baby a top-up feed by cup.

Parenteral Nutrition

PN is usually not available for LBW infants treated in low-resource institutions due to the high costs and lack of medical and nursing expertise. It is reserved for the infant with enteral feeding intolerance, bowel obstruction, NEC, etc. An admixture unit in the hospital for daily mixing of tailor-made PN solutions is unaffordable. A commercially prepared 3-in-1 lipid-aminoacid-glucose preparation for LBW infants for short-term use (<3 weeks) is an affordable alternative.

Supplementation of the Infant in the Special Care Nursery

Electrolyte levels are only determined in these LBW infants when there is a clinical indication such as those with feeding intolerance, etc. A fortifier may be added to the EBM of the more immature LBW infants. Calcium and phosphate are not routinely supplemented. Enteral iron, at a dosage of 2 mg/kg per day, should be commenced at 2 weeks of age, in hospital for infants who have not been discharged and at clinics for those that have. A multivitamin supplement, containing at least 400 IU vitamin D, should be commenced once the infant is on full enteral feeding. Both are continued until 12 months of age.

Nutritional Management in the Postnatal Ward

Expressed Breast Milk and Breastfeeding

LBW infants ≥34 weeks’ gestation are managed with term babies in the PW. The latter are discharged early, i.e. between 6 and 24 h of age. Due to limited neona-
tal facilities in resource-constrained countries, LBW infants are usually discharged after 48 h. By the time they are discharged, feeding, be it breastfeeding or bottle feeding, must be established.

Establishing breastfeeding in LBW infants is a challenge due to their poor muscle strength, latching, suckling and swallowing. This may result in poor emptying of the breast, low milk intake, poor weight gain, dehydration, jaundice and lactation failure after discharge.

Breastfeeding support should be provided by skilled, sympathetic nursing staff. Initiating and establishing breast milk production when the mother is exhausted or ill or when infant and mother are separated is particularly challenging.

There are important differences in the principles for supporting breast milk feeding in these infants compared to those used in term infants [26].

Whereas term infants are encouraged to latch and suckle as frequently as possible in order to stimulate breast milk production and emptying of the breast, this may result in the opposite in these infants. This is due to the fact that the infant is weaker, latches poorly and slips off the nipple of the mother repeatedly, falls asleep easily and therefore is unable to generate suction pressure to remove milk from the breast. Waking the LBW infant frequently to feed is counterproductive as his/her limited energy stores are not replenished during the low milk volume intake of the first 48 h, and this approach may deplete his/her limited glycogen and fat stores even further and result in hypoglycemia. Instead, the mother should respond to feeding cues by allowing the baby to latch and suckle when he/she is awake. This should be approximately every 3 h. The infant should not be woken more frequently. If latching remains a problem, a nipple shield should be used as it will compensate for weak suction pressures [27]. Teach the mother the correct technique of manually expressing breast milk as this will stimulate breast milk production and help to empty the breast. Expressing breast milk should be done when the baby is asleep and directly after a feed in order to empty the breast. The mother should express 6–8 times/24 h until her breast milk production is established well enough to maintain breastfeeding.

If excessive weight loss, jaundice or hypoglycemia occurs, the doctor should be consulted to assess the infant.

The teenage mother, those with multiple births or where the introduction of breast milk feeding was delayed due to maternal illness will require longer hospitalization in order to establish breastfeeding.
Supplementation of the Infant in the Postnatal Ward

As these infants are discharged within the first week of life, multivitamin and iron supplementation at 2 mg/kg per day is provided at the clinic.

General Principles Applicable to Both Special Care Nursery and Postnatal Ward Infants

General Principles of Formula Feeding

Formula should be prescribed according to strict criteria which include:

- The mother has died or is too ill to breastfeed
- The HIV+ mother chooses not to breastfeed
- The HIV+ mother does not have facilities to pasteurize at home and changes to formula on discharge
- A mother has had twins or triplets and there is a need for supplementation with formula milk
- Supplemental feeding for the infant whose mother is experiencing ongoing low milk production, e.g. due to late initiation of breastfeeding
- As donor milk is not readily available for LBW infants >34 weeks in resource-constrained settings, breastfeeding may be supplemented by formula feeding by cup.

A standard infant formula should be prescribed. Mothers who will formula feed should be educated by the nursing staff in the hygienic and correct mixing of formula milk and of sterilizing bottles and teats [28].

General Principles of Predischarge Planning

Every infant must have a durable card containing all his neonatal and feeding information, supplementation and medication such as antiretrovirals, a summary of his neonatal management, etc. to present to the clinic at every visit.

The HIV+ mother who is breastfeeding should practice exclusive breastfeeding until she discontinues breastfeeding. She should be informed of the risks of supplementing breastfeeding with anything other than water [29].
General Principles of Discharge

Although there are guidelines for the early discharge of late preterm infants in a developed country [30], none exist for the LBW infant in a resource-constrained setting. Discharge principles are determined according to admission to the SCN or the PW.

Discharge from the Special Care Nursery

The decision to discharge a mother-infant dyad should be individualized. Infants are discharged home when they reach a GA of at least 34 weeks, a weight of 1,600–1,800 g, are gaining adequate weight, are fully breastfed or bottle fed and the mother is confident to care for her baby at home.

The timing of assessment at the community clinic is determined according to factors such as discharge weight or GA, teenage mother, etc.

Discharge from the Postnatal Ward

Discharge usually takes place after 48 h, often before the infant has regained his/her BW. Whether the mother-infant dyad is ready for discharge is determined on an individual basis. If the infant is discharged before day 3, i.e. while he/she is still losing weight, he/she should be assessed at the clinic within 24 h.

Nutritional Support at the Community Clinic

The clinics in the community function as an extension of the hospital management. The clinic nursing staff should also conduct home visits. The mother’s breasts should be examined for engorgement and her technique of breastfeeding observed. The baby should be assessed and weighed and the weight loss or gain should be interpreted according to the postnatal age. The infant should be referred to the hospital if there is excessive weight loss, lethargy, jaundice, poor feeding, etc.
Conclusion

Optimal nutrition can be provided to LBW infants in resource-constrained environments by maintaining the mother-infant dyad in hospital and providing skilled breastfeeding support. The clinics in the community must provide post-discharge nutritional support.

Disclosure Statement

There is no conflict of interest or sponsorship.

References

Abstract
Growth restriction among low-birthweight (LBW) infants occurs prenatally as well as postnataally. Regardless of when and how the growth restriction occurs, growth-restricted infants have the potential for catch-up growth. Catch-up growth has decidedly beneficial effects on later cognition. It also may have adverse effects on cardiovascular and metabolic health. Although the benefits for later cognition are well documented in a number of studies, growth-restricted LBW infants often do not experience catch-up growth and therefore do not enjoy its benefits. One reason is that for catch-up growth to occur, extraordinarily high protein intakes are required. Nutrient intakes have been estimated with the use of the factorial method based on the assumption that catch-up growth comprises essentially a restoration of lean body mass, with restoration of fat mass optional. The basic (no catch-up) nutritional needs of growth-restricted LBW infants are altered to a modest degree, with energy needs increased and protein needs decreased. With catch-up, however, protein needs are increased sharply. Since energy needs are only modestly increased, the protein/energy ratio of requirements is appreciably increased. The high protein needs are difficult to meet with the usual feedings for LBW infants unless special measures are taken to increase protein intakes and to increase the protein/energy ratio. Without the necessary protein intake, catch-up growth is not possible or will be delayed, which may compromise the realization of the long-term benefits on cognition.

The purpose of this review is twofold. First, to make the case that in growth-restricted low-birthweight (LBW) infants catch-up growth confers benefits for cognition later in life, regardless of whether catch-up occurs following intrauter-
ine growth restriction (IUGR) or postnatal growth restriction (PGR). And second, that the nutrient requirements for catch-up growth are high, meaning that catch-up growth and its benefits will only be realized if the high nutrient intakes are met. The similarities between pre- and postnatal growth restriction and the catch-up growth that can follow either have been recognized [1]. Since it is not widely appreciated that the nutrient needs for catch-up growth, especially the needs for protein, are very high and difficult to meet, the present discussion will provide estimates of nutrient intakes needed for the realization of catch-up growth.

It is generally recognized that infants who are classified at birth as small for gestational age (SGA) constitute a heterogeneous group. Some of these infants are intrinsically small and remain small. But the majority of SGA infants are small as a result of IUGR due to causes extrinsic to the infant. It is also widely appreciated that PGR occurs commonly in VLBW infants as a result of inadequate nutrient intakes. Common to all infants who have experienced growth restriction is the potential to return to their original size once the erstwhile obstacles have been overcome. Return to the original size is commonly known as catch-up growth and is the focus of the present discussion.

The undoing of the effects of growth restriction would seem to be unconditionally desirable were it not for the findings from long-term follow-up studies. Besides showing that catch-up growth improves cognition later in life, follow-up studies are also suggesting that catch-up growth has negative effects on later cardiovascular and metabolic health. This dichotomy of findings has led to a vigorous and ongoing debate about the merits of catch-up growth following growth restriction in LBW infants. Unfortunately, the debate has been focused predominantly on the negative effects of catch-up on later cardiovascular and metabolic health. To restore some kind of balance, this discussion will focus on the effects of catch-up on later cognition.

Catch-up growth is usually understood as growth that is returning toward the original size that existed before the onset of growth restriction, even though that size is not precisely known in the case of IUGR. Size is expressed in relative terms such as weight percentile or z score. The crucial deficit in growth restriction is a decreased lean body mass. Consequently, the most important aspect of catch-up growth is the restoration of lean body mass. Fat mass may also be diminished, at least in IUGR, but its restoration is of secondary in importance. Since the cause of IUGR differs from the cause of PGR, it is not too surprising that there are differences in body composition. A well-documented difference concerns body fat, which is diminished in IUGR but is often normal or increased in infants with PGR.
Catch-Up Growth and Later Cognition in Low-Birthweight Infants

Catch-Up after Intrauterine Growth Restriction

In infants born close to term, the adverse effects of IUGR on later cognition are well recognized [2, 3], as are the beneficial effects of catch-up growth [4]. In pre-term and LBW infants, the negative effects of IUGR on cognition are also well recognized [5, 6]. Less well recognized is the marked positive effect that catch-up growth has on later cognition in growth-restricted LBW infants. Brandt et al. [7] showed that VLBW SGA infants who did not experience head circumference catch-up had lower IQ scores as adults than SGA infants with head circumference catch-up or appropriate for gestational age (AGA) infants. Latal-Hajnal et al. [8] followed up VLBW SGA infants to age 2 years and found that those who caught up (weight or length >10th percentile at 2 years) scored significantly higher on the psychomotor development index (PDI) than those who did not catch up. More recently, Belfort et al. [9] examined the effect of catch-up growth in a large cohort of 613 premature infants who participated in a trial assessing the effect of omega-3 fatty acid supplementation on neurodevelopmental outcome. Among SGA infants, growth from one week to term was strongly positively associated with MDI and PDI scores at 18 months. The association was also significant among AGA infants, but it was less strong than in SGA infants. The importance of this study lies in the fact that it involved a very large number of infants.

Catch-Up after Postnatal Growth Failure

Most VLBW infants experience postnatal growth failure of some degree due to insufficient nutrient intakes. Their growth shares many characteristics with that of infants born SGA, as has previously been pointed out [1]. Although growth recovery often does not occur until after discharge from the hospital, it not infrequently occurs or begins before discharge. For example, in the study by Ehrenkranz et al. [10] the majority of infants were still showing growth failure at the time of discharge. But infants who were undergoing catch-up growth before discharge showed better neurocognitive outcomes on follow-up than infants who did not. Although it is likely that even infants with late catch-up would eventually recover from their growth deficit and derive benefits for cognition from it, with regard to neurocognitive outcome early recovery may be crucial. As in the study of Ehrenkranz et al. [10], it may be assumed that in all studies that examined the association between growth and neurocognitive outcome of
VLBW infants, the fastest growing infants (e.g. the top quartile in Ehrenkranz et al. [10]) were exceeding fetal growth rates and were thus showing catch-up growth.

A number of studies have examined the association of growth with developmental outcomes in VLBW infants. The age at which cognition was assessed ranged from 1 year [11] to 19 years [12]. As a result of changes in clinical practices, infants born after about 1995 have shown less postnatal growth failure than infants born before 1995. But even among infants born after 1995, follow-up studies have invariably found that cognitive development as measured between 2 and 5.5 years of age was strongly positively associated with growth before discharge [9, 13–15]. Because at least the fastest growing among the VLBW infants may be assumed to have been catching up, these findings constitute a large body of evidence documenting that catch-up after postnatal growth failure has positive effects on cognition.

**Estimation of Nutrient Needs**

In spite of its limitations, the factorial method has been useful in obtaining at least crude estimates of nutrient needs of LBW infants. Such estimates of the nutrient needs of premature infants [16] form the basis of recommendations by official bodies [17]. The factorial method has been used to obtain estimates of nutrient needs of extremely LBW SGA infants undergoing catch-up growth [18]. Using similar assumptions, it is used here to obtain estimates of the nutrient needs of LBW infants undergoing catch-up growth.

The nutrient needs of SGA infants differ from those of normally grown LBW infants because of (1) altered body composition and (2) catch-up growth. Catch-up is best understood as recovery of lean body mass. Full recovery would be a return of lean body mass to its original (pregrowth failure) channel. Nutrient needs are considered here for three scenarios: basic needs (no catch-up); half catch-up, defined as 50% of full recovery, and full catch-up defined as return to the original channel. Because nutrient needs are expressed per unit time, the assumption is made that catch-up occurs over a period of 4 weeks. Presented are estimates of nutrient needs for each of the three scenarios and, for purposes of comparison, needs of normally grown infants of similar size. Figure 1 shows two hypothetical SGA infants weighing 1,500 g at 34 weeks’ postmenstrual age. The infant growing parallel to the percentile line does not show catch-up growth, whereas the other infant shows full catch-up over a period of 4 weeks.
Body Composition of Growth-Restricted Infants

The hallmark of growth restriction is reduction of lean body mass relative to normally grown infants of the same age. In the case of IUGR, there is also a reduction of fat mass [19–21], whereas in infants with PGR fat mass is unchanged or often even increased [22]. This is explained by normal or increased energy intakes which typically accompany the insufficient protein intakes that are causing growth failure. In spite of its reduction in mass, the composition of lean body mass is commensurate with gestational age, meaning that its water content is lower, its protein content is higher and its resting energy expenditure higher than normally grown infants of the same size.

Basic Nutrient Needs

Because of the higher metabolic rate of the lean body mass, and also as a consequence of the reduced fat mass relative to lean mass, resting energy expenditure per unit of body mass is higher in growth-restricted infants than in normally grown infants, as has been documented in a number of studies [23–25]. Therefore, resting energy expenditure is increased and total energy needs are increased in SGA infants (table 1). Because the rate of growth per unit body weight is lower at 34 weeks’ postmenstrual age than at 30 weeks, protein needed for growth (accretion) is less per unit body mass in SGA without
catch-up than in AGA infants of similar weight. The net effect of these changes in basic needs in SGA infants is that the required protein/energy ratio is somewhat decreased.

**Nutrient Needs for Catch-Up**

Shown in table 1 are the nutrient needs of infants undergoing one-half catch-up and full catch-up within a period of 4 weeks. Compared to the modest impact on needs of just being SGA, the impact of catch-up growth is large, especially with regard to needs for protein as protein is needed for the restoration of lean body mass. As indicated in table 1, for full catch-up of lean mass within in 4 weeks, the protein requirement jumps to 5.1 g/kg per day, while for half catch-up it still is 4.2 g/kg per day. Restoration of energy stores (fat mass) is not essential in catch-up growth, and the increase in fat can therefore be variable. Energy intakes shown in table 1 are only modestly increased over basic needs, assuming that only a small fraction of the fat mass deficit is being restored. Greater energy intakes will of course permit more rapid restoration of fat mass. It is important
to distinguish between the essentiality of protein for the restoration of lean body mass and the optional nature of energy needed for restoration of fat mass. The disproportionately increased needs for protein due to catch-up necessitate substantial increases in the protein/energy ratio of feeds (table 1).

Comment on Nutrient Needs

The estimates of nutrient needs presented above cannot claim to be quantitatively accurate. For one thing, they depend on a number of assumptions that, if chosen differently, would alter the outcome. The use of a theoretical model has, of course, the advantage of allowing the examination of the effects of different assumptions. In spite of these limitations, the main conclusion derived from the model is robust enough to support recommendations for nutritional management of growth-retarded LBW infants. There can be no doubt that catch-up growth requires very high intakes of protein. If these protein needs are not met, catch-up will not occur. If they are met partially, catch-up will proceed at slower pace. Without the necessary protein, catch-up simply cannot take place. In practice, the high protein needs are probably seldom met, not least because the means for increasing the intake of protein are limited. Perhaps herein lies a reason why catch-up growth does not always occur, or proceeds more slowly than would seem desirable.

Nutritional Recommendations

The exorbitantly high amounts of protein necessary for catch-up growth are difficult to achieve. They can be achieved only with feedings with a suitably high protein/energy ratio. Such high ratios can be achieved only by selectively increasing the protein content of feedings. Whether the required protein intakes can be achieved with feedings with the usual protein/energy ratios is questionable as the required very high feeding volumes are probably beyond the ability of most LBW infants. One advantage of lower-protein feedings, if adequate protein intakes could be achieved, would be a more rapid restoration of fat mass. However, given the primacy of restoration of lean body mass, the use of high-protein feedings would still be preferred. Without high intakes of protein, catch-up growth is not possible and the infant’s ability to reap cognitive benefits is compromised. Although most growth-restricted infants may catch up eventually, the existing evidence suggests that delaying catch-up may compromise long-term cognitive benefits.
Disclosure Statement

The author reports no conflict of interest.

References

Human Milk Fortification in India
Neelam Kler · Anup Thakur · Manoj Modi · Avneet Kaur · Pankaj Garg · Arun Soni · Satish Saluja
Sir Ganga Ram Hospital, Old Rajinder Nagar, New Delhi, India

Abstract
Human milk fortification in preterm babies has become a standard of care in developed countries. Use of human milk fortifier (HMF) in very-low-birthweight infants is not a routine practice in India. There are concerns about high osmolality, feed intolerance, necrotizing enterocolitis, risk of contamination and added cost associated with use of HMF. There are limited data from India which address the issue of safety and short-term benefits of human milk fortification. This chapter highlights the issues related to human milk fortification in our country.

Introduction

The incidence of preterm birth is about 13% of all live births in India [1]. Major innovations in neonatology during the past few decades, such as mechanical ventilation, surfactant and antenatal steroids, have substantially improved survival rates of very preterm infants. Despite improved survival, growth failure continues to be a major problem in these infants [2–5].

Optimization of nutrition is a matter of debate in very preterm babies. Human milk (HM) usage has multiple beneficial effects like improved host defense, digestion of nutrients and better neurodevelopmental outcomes [6]. Despite these advantages, HM alone cannot meet the nutritional requirements of very-low-birthweight (VLBW) infants [7, 8]. Exclusive feeding of unfortified HM has been associated with poor growth and nutritional deficits during and beyond the period of hospitalization. A systematic review of 10 randomized controlled trials...
in infants with birthweight less than 1,850 g has shown that multicomponent fortification of HM was associated with small but statistically significant short-term improvements in weight gain, linear growth and head size as compared to the unfortified group [9]. In the current era, HM fortification has become a common practice in neonatal intensive care units. However, the issue of HM fortification in developing countries like India is far more complicated than anticipated.

Guidelines on feeding preterm babies by the World Health Organization and National Neonatology Forum (NNF), India, do not support the routine use of multicomponent fortification of the HM [10, 11]. The current recommendation in India is to reserve this option for preterm infants <32 weeks’ gestation or <1,500 g birthweight, who fail to gain weight despite full volumes of HM feeding [11].

**Issues in India**

*Risk of Contamination and Sepsis*

HM feeding for VLBW infants is advantageous in reducing infections when compared to preterm formula. HM has anti-infective properties due to the high content of IgA, lysozyme, lactoferrin, and interleukins. Fortification has been reported to be associated with alteration in quality of HM such as reduction in lysozyme and IgA levels [12]. In high-burden neonatal units, bacterial contamination and associated risk of sepsis remains a theoretical possibility during fortification. However, a recent study demonstrated that fortifying fresh HM does not affect bacterial growth during 6 h at room temperature [13]. Similarly, another study evaluated total bacterial colony counts (TBCC) in refrigerated fortified HM and found a decrease in TBCC in 0–72 h [14]. In clinical trials, including one conducted in India, risk of sepsis was not higher in babies who received fortified HM [15, 16].

*Osmolality, Feed Intolerance and Necrotizing Enterocolitis*

Another fear that looms in clinical practice in India is that fortification can result in increase in osmolality of HM. Agarwal et al. [17] showed that addition of fortifier (Lactodex-HMF; Raptakos, Brett and Co. Ltd.; 4 g/100 ml of milk) in expressed milk increased the osmolality up to 392 mosm/kg as compared to 302 mosm/kg in breast milk (per 100 ml). In an observational study, we measured
osmolality in random samples of HM fortified with same fortifier on the principle of freezing point depression osmometry, and found that the mean osmolality of FHM was 360.7 mosm/kg [unpubl. data].

Higher osmolality of FHM might lead to increased risk of feed intolerance and necrotizing enterocolitis (NEC) [18]. In fact, many trials that investigated HM fortification withdrew infants with feed intolerance and did not report results. Two randomized clinical trials from India on fortification of HM were published in the last decade. In one of the studies, there was no statistical difference between the episodes of possetting/day as well as the percentage of gastric aspirates of the total feeds/day between the fortified and the unfortified group [19]. In another study, the incidence of feed intolerance was higher in the unfortified group. The authors attributed it to the use of oral vitamins and minerals supplements in this group [16]. The Cochrane review of available studies comparing infants fed unfortified and fortified HM did not show increased risk of NEC in infants receiving FHM (RR 1.33, 95% CI 0.7–2.5) [9].

**Nutritional Adequacy**

Despite several nonnutritional benefits, infants fed with fortified HM show slower growth as compared to those receiving formula [20–22]. This raises concern about the nutritional adequacy of present HM fortifier (HMF). Empirical data show that weight gain comparable to in utero can be achieved with protein intake of approximately 3 g/kg per day, which increases linearly up to 4.5 g/kg per day [23–26].

The ESPGHAN Committee recommends protein intake 4.0–4.5 g/kg per day for infants up to 1,000 g, and 3.5–4.0 g for infants from 1,000 to 1,800 g [27]. Mukhopadhyay et al. [16] observed that fortification resulted in better growth until discharge or 2 kg weight in preterm VLBW babies as compared to the unfortified group. In India, the only HMF available has a protein content of 0.4 g/100 ml. Assuming the average protein content of HM to be 1.2 g/100 ml, FHM even at 200 ml/kg per day will provide an enteral protein intake of 3.2 g/kg per day, which is insufficient as per recent ESPGHAN guidelines. In a prospective observational study in India, routine fortification of HM with presently available fortifier showed a significant growth lag in VLBW infants during infancy [4, 5]. Miller et al. [28] in a randomized control trial in preterm infants less than 31 weeks’ gestation found that fortification of HM with higher protein content fortifier (1.4 g/100 ml vs. 1 g/100 ml) resulted in better weight gain and a significant reduction in the proportion of infants whose length was less than 10th percentile at 40 weeks or discharge. The for-
tification of HM with high versus low protein content has not been systematically evaluated in India. We are conducting a randomized control trial to study the impact of supplementation with HMF containing low protein (0.4 g/100 ml) versus high protein (0.8 g/100 ml) on growth and neurodevelopmental outcomes.

Apart from the effect of HMF on growth, biochemical parameters have also been studied. Two trials from India that evaluated the use of HMF and its impact on biochemical parameters found that the mean serum protein, calcium, phosphate, sodium and potassium were higher in the fortified group as compared to the unfortified group [16, 19].

Long-Term Benefits

There are insufficient data to evaluate the long-term neurodevelopmental and growth outcomes of HM fortification. Two trials investigating the long-term growth effects did not demonstrate any differences in weight, length or head circumference at 12 and 18 months of corrected age [29, 30]. One trial evaluated developmental performance at 18 months and did not find any significant difference in these outcomes [29]. There are no data on long-term effects of HMF on the Indian population.

Current Situation in India

We conducted an online survey in 2013 on the use of HMF in India. One hundred and four tertiary care neonatal units participated in the survey. Overall, 88% neonatologists were using HMF in the NICU, of which 11% used it routinely in babies with birthweight less than 1,800 g, 32% in all VLBW babies and 43% used HMF as per current NNF guidelines [11]. Amongst nonusers, 66% mentioned fear of contamination and sepsis as the reason for not using HMF. Other reasons cited were presumed high osmolality, fear of feed intolerance, NEC, and additional cost [unpubl. data].

Until recently, the only available HMF in India was Lactodex HMF (table 1). On fortification of HM with Lactodex HMF (assuming a feed intake of 180 ml/kg per day), the recommended intakes of protein, vitamin A, vitamin D and iron are not met. Another HMF named HIJAM (Endocura Pharma Pvt. Lmt.) has been recently introduced on the Indian market (table 1). Its nutrient composition in fortified HM at an intake of 180 ml/kg per day approximates the requirement recommended by ESPGHAN (table 2). It is being used already in some
parts of India – Goa and New Delhi [pers. commun.]. However, there are no published studies on its use, and the experience is limited. The short-term and long-term effects of this new fortifier need to be evaluated.

**Conclusions**

Fortification of expressed breast milk with HMF increases the nutrient content of the milk without compromising its nonnutritional beneficial effects. At present, WHO and Indian guidelines on feeding of preterm babies do not recom-

---

**Table 1. Composition of HM and Indian HM fortifiers**

<table>
<thead>
<tr>
<th>Components</th>
<th>Human milk per 100 ml</th>
<th>Lactodex HMF 2 sachets(^a)</th>
<th>HIJAM HMF 4 sachets(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Energy</td>
<td>67</td>
<td>15</td>
<td>14</td>
</tr>
<tr>
<td>Protein, g</td>
<td>1.1</td>
<td>0.4</td>
<td>1</td>
</tr>
<tr>
<td>Fat, g</td>
<td>3.5</td>
<td>0.2</td>
<td>1</td>
</tr>
<tr>
<td>Vitamin A, IU</td>
<td>48</td>
<td>240</td>
<td>620</td>
</tr>
<tr>
<td>Vitamin D, IU/day</td>
<td>8</td>
<td>76</td>
<td>400</td>
</tr>
<tr>
<td>Calcium, mg</td>
<td>25.3</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Phosphorus, mg</td>
<td>14.5</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>Iron, mg</td>
<td>0.09</td>
<td>–</td>
<td>1.44</td>
</tr>
</tbody>
</table>

\(^a\) Two sachets to be dissolved in 100 ml of expressed breast milk.

\(^b\) Four sachets to be dissolved in 100 ml of expressed breast milk.

---

**Table 2. 2010 ESPGHAN recommendation and nutrient value of EBM fortified with HMF available in India**

<table>
<thead>
<tr>
<th>Components</th>
<th>HM at 180 ml/kg</th>
<th>EBM + Lactodex at 180 ml/kg per day</th>
<th>EBM + HIJAM at 180 ml/kg per day</th>
<th>ESPGHAN per kg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Energy</td>
<td>120.6</td>
<td>147.6</td>
<td>145.8</td>
<td>110–135</td>
</tr>
<tr>
<td>Protein, g</td>
<td>1.98</td>
<td>2.7</td>
<td>3.78</td>
<td>3.5–4.5</td>
</tr>
<tr>
<td>Fat, g</td>
<td>6.3</td>
<td>6.5</td>
<td>8.1</td>
<td>4.8–6.6</td>
</tr>
<tr>
<td>Vitamin A, IU</td>
<td>86.4</td>
<td>518</td>
<td>1,202</td>
<td>1,320–3,300</td>
</tr>
<tr>
<td>Vitamin D, IU/day</td>
<td>14.4</td>
<td>151</td>
<td>734</td>
<td>800–1,000</td>
</tr>
<tr>
<td>Calcium, mg</td>
<td>45.5</td>
<td>225</td>
<td>225</td>
<td>120–140</td>
</tr>
<tr>
<td>Phosphorus, mg</td>
<td>26.1</td>
<td>115</td>
<td>116</td>
<td>60–90</td>
</tr>
<tr>
<td>Iron, mg</td>
<td>0.16</td>
<td>0.09</td>
<td>2.7</td>
<td>2–3</td>
</tr>
</tbody>
</table>

EBM = Expressed breast milk.
mend routine use of fortification; however, FHM improves short-term weight gain, linear and head growth without any adverse effect. There is paucity of data from India on long-term benefits of fortification on growth and development. There is a need for more research to identify ideal candidate and fortifier to achieve optimal short-term and long-term outcomes.

Disclosure Statement

All authors declare that no financial or other conflict of interest exist in relation to the content of this chapter.

References


Feeding Practices – Current and Improved?


Probiotic Supplementation for Preterm Neonates – What Lies Ahead?

Sanjay Patole

Department of Neonatal Paediatrics, KEM Hospital for Women, and Centre for Neonatal Research and Education, University of Western Australia, Perth, WA, Australia

Abstract

Systematic reviews of randomized controlled trials indicate that probiotic supplementation significantly reduces the risk of necrotizing enterocolitis (NEC) without adverse effects in preterm very-low-birthweight neonates. A change in practice in favor of probiotic supplementation is justified considering the health burden of NEC in this population. The reduction in the risk of NEC seems to occur even when the baseline incidence of the illness is as low as 5%. Facilitation of feed tolerance is a significant benefit of probiotics considering that optimizing enteral nutrition is a priority in extremely preterm neonates, including those with intrauterine growth restriction, who are at a higher risk for feed intolerance and NEC. The increasing number of reports on routine use of probiotics indicates that difficulty in accessing clinically proven and safe probiotic products is not a significant barrier towards a change in practice. Strategies to address important gaps in knowledge and the impact of routine use of probiotic supplementation are reviewed to prepare for what lies ahead in this field. © 2015 Nestec Ltd., Vevey/S. Karger AG, Basel

Necrotizing enterocolitis (NEC) is a potentially disastrous illness in preterm very-low-birthweight (VLBW) neonates with significant mortality and morbidity, including long-term neurodevelopmental impairment, especially in extremely low-birthweight neonates requiring surgical intervention for the illness [1]. The incidence, outcomes, and overall health burden of stage 2 NEC have not changed significantly despite the improvements in neonatal intensive care, and extensive research over decades. The poorly understood pathogenesis of the illness has been the main reason for the failure to develop strategies for primary
and early detection. Current evidence indicates that excessive intestinal inflammation due to an immature innate immune response, decreased stability, diversity and complexity of gut flora, and delayed colonization by beneficial microbes (‘dysbiosis’) play an important role in the pathogenesis of NEC [2]. Presence of substrate continues to be an important risk factor as an overwhelming majority (∼90%) of the cases occur in those who have been fed with milk.

Probiotics are defined as live microbial supplements which when administered in adequate amounts, colonize the gut and benefit the host [3]. Probiotics may prevent NEC by enhancing and protecting the gut mucosal barrier, promoting colonization of the gut with beneficial microbes, inhibiting colonization by pathogens, and modulating the immune system to the advantage of the host [4]. Probiotic-conditioned media have recently been shown to modulate enterocyte genes that regulate innate immune-mediated inflammation [5].

Systematic reviews of randomized controlled trials (RCTs) indicate that prophylactic probiotic supplementation significantly reduces the risk of NEC without adverse effects in preterm VLBW neonates [6]. Considering the health burden of NEC in this population, a change in practice in favor of probiotic supplementation is justified if safe and clinically proven products are available. The reduction in the risk of NEC seems to occur even when the baseline incidence of the illness is as low as 5% [7]. The increasing number of reports on routine use of probiotic supplementation indicates that many centers have recently adopted this strategy, and that accessing clinically proven and safe probiotic products is not difficult [8–11]. Currently, 15 tertiary neonatal intensive care units in Australia provide probiotic supplementation as a standard practice for preterm VLBW neonates. Considering the increasing acceptance of probiotic supplementation to prevent NEC in preterm neonates, a review of what lies ahead in this field is important.

**Extremely Preterm (Gestation <28 Weeks) Neonates**

Lack of adequate data specifically on extremely preterm neonates is often quoted as a problem with adopting probiotic supplementation in this population. A placebo-controlled probiotic trial with at least a few thousand extremely preterm neonates would be required to address this issue. Considering the increasing acceptance of probiotics for preterm neonates, feasibility of completing such a trial in a reasonable time frame is very much questionable, especially if the current evidence in totality is to be shared with honesty and transparency with the parents for an informed consent. Extremely preterm neonates are most deserving of probiotic supplementation as their burden of ≥stage 2 NEC is signifi-
Probiotics for Preterm Neonates

Significantly higher. Data on close to 800 extremely preterm neonates from RCTs and reports on routine use of probiotics are assuring with regard to the safety of probiotics in this population. Probiotic sepsis, even if it occurs, is easy to treat compared with sepsis due to other organisms. The efficacy of probiotics in extremely preterm neonates may be suboptimal considering the various factors adversely affecting the gut flora including frequent exposure to antibiotics, suboptimal enteral nutrition due to frequent stoppage of feeds, recurrent episodes of late-onset sepsis, and dependence on parenteral nutrition. Frequent exposure to antibiotics is a significant issue in extremely preterm neonates. Fouhy et al. [12] have reported that the combined use of ampicillin and gentamicin in early life had significant adverse effects on the evolution of the gut microbiota in infants. The gut microbiota of the antibiotic-treated infants had significantly higher proportions of Proteobacteria (p = 0.0049) and significantly lower proportions of Actinobacteria (p = 0.00001) and the associated genus *Bifidobacterium* (p = 0.0132) as well as genus *Lactobacillus* (p = 0.0182) than the untreated controls 4 weeks after stopping antibiotics. By week 8, the Proteobacteria levels remained significantly higher in the treated infants (p = 0.0049), but the Actinobacteria, *Bifidobacterium*, and *Lactobacillus* levels had recovered and were similar to those in the control samples [12]. Greenwood et al. [13] have recently reported that preterm neonates who received 5–7 days of empiric antimicrobials in the first week had significantly increased relative abundance of *Enterobacter* (p = 0.016) and lower bacterial diversity in the 2nd and 3rd weeks of life. The frequency of NEC, sepsis, and death was higher in those receiving early antibiotics compared with those not exposed to antibiotics [13]. Other investigators have also reported an association of prolonged exposure to antibiotics with NEC and death in preterm neonates [14]. The importance of early feeding with colostrum followed by breast milk, probiotic supplementation, antibiotic stewardship, and strategies for reducing the risk of late onset sepsis cannot be overemphasized in this context.

**Intrauterine Growth Restriction**

Preterm growth-restricted neonates are at high risk of feed intolerance, NEC, and postnatal growth failure [15]. Dorling et al. [15] have reported a meta-analysis of independent case series (n = 14) comparing NEC rates in neonates who had fetal absent/reversed end diastolic flow (AREDF) in the umbilical artery with a control group. Nine studies showed an excess of NEC in those with fetal AREDF. The overall odds ratio for developing NEC was 2.13 (95% CI: 1.49–3.03) compared with controls with forward fetal end diastolic flow [15]. Fre-
quent signs of feed intolerance (e.g. abdominal distension with visible ropy bowel loops, large/colored gastric residuals) and the fear of the higher risk of NEC means it often takes few weeks to get these neonates on enteral feeds of 120–150 ml/kg per day. Kempley et al. [16] have reported a post hoc analysis of data on neonates <29 weeks’ gestation from an RCT comparing benefits of ‘early’ (starting on day 2 after birth) with ‘late’ (starting on day 6) feeds in preterm neonates (gestation <35 weeks) with intrauterine growth restriction (IUGR). Subsequent feed advancement following a regimen should have achieved full feeds by day 16 in the early and day 20 in the late group. Neonates with gestation <29 weeks achieved full feeds significantly later compared with those ≥ 29 weeks; median (IQR) age: 28 (22–40) versus 19 (17–23) days (HR 0.35, 95% CI: 0.3–0.5). The incidence of NEC was higher in neonates with gestation <29 compared with ≥ 29 weeks: 32/83 (39%) versus 32/312 (10%), RR 3.7 (95% CI: 2.4–5.7) [16].

Several mechanisms may explain the higher risk of NEC and feed intolerance in preterm neonates with IUGR following fetal umbilical artery AREDF. These include fetal hypoxia, redistribution of the gastrointestinal blood flow to spare the brain of the adverse circulatory effects of AREDF, structural and functional changes in the intestine, and altered gut colonization [17–22]. Fetal hypoxia and increased mesenteric vascular resistance may cause prenatal hypoxic-ischemic injury of the intestine, affecting the development of intestinal motor, secretory, and mucosal function, and increasing its postnatal vulnerability to ileus, abnormal colonization, and bacterial invasion [17–22]. The postprandial rise in superior mesenteric artery (SMA) flow required for digestion is compromised in preterm IUGR neonates [23]. The recovery of the low-baseline SMA flow velocity is slow during the first week of life. On day 7, the values are similar to those in appropriately grown neonates not on feeds [23]. Pseudo-obstruction due to meconium plug is not uncommon, and the incidence of late-onset sepsis, which further compromises the gut, is higher in preterm IUGR neonates [24, 25]. D’Inca et al. [17] have reported that, at birth, intestinal weight and length, ileal and colonic weight per unit of length, and villous sizes were significantly lower in piglets with IUGR compared with same-age controls. These alterations persisted, although less marked at day 5. Counts of bacteria adherent to ileal and colonic mucosa were significantly greater in 2-day-old IUGR piglets compared with same-age controls. Study of the expression of genes involved in proliferation (proliferating cell nuclear antigen, PCNA) and apoptosis (BAX and CASP3) pathways indicated a significantly lower expression of PCNA at birth in IUGR piglets compared with controls, and at day 2 it tended to be significantly lower. BAX expression tended to be significantly greater at day 5 in piglets with IUGR compared with same-age controls. Apoptosis rates tended to be significantly greater in IUGR versus control piglets at birth but not at days 2 and 5 [17]. Fan-
ça-Berthon et al. [18] have studied the effect of IUGR on gut microbiota by comparing the composition and activity of cecocolonic microbiota from birth to adulthood in rats with and without IUGR. Bacterial density was increased at day 5 and decreased at day 12. In adulthood, rats with IUGR still differed from controls, containing fewer *Bifidobacterium* species at day 40 and more bacteria related to *Roseburia intestinalis* at day 100. In vivo, propionate concentration was decreased by IUGR before weaning, whereas the concentrations of other short chain fatty acids (SCFAs) were decreased at day 40, although the in vitro metabolic capability was unaffected overall. These results indicate that IUGR can cause both neonatal and long-term alterations of the intestinal microbiota [18]. Deficits in the bioavailability of butyrate could adversely affect the proliferation of colonocytes and the maintenance of colonic homeostasis by modulating the expression of intestinal transcripts involved in gut barrier function, and reducing mucin secretion [19, 20]. Faça-Berthon et al. (2009) have reported that IUGR impairs mucus barrier development and is associated with long-term alterations of mucin expression [21]. The lack of an efficient colonic barrier induced by IUGR may predispose to colonic injury not only in neonatal life but also in later life [21]. Wang et al. [22] have reported continuous impairment of intestinal development in neonatal piglets with IUGR using temporal proteomics analysis coupled with histological and biochemical studies.

Together, the consequences of pre- and postnatal disturbances of gut perfusion, altered intestinal structure and function, altered gut flora, and increased metabolic demands of enteral feeds may explain the increased risk of NEC and feed intolerance in preterm IUGR neonates. Studies specifically addressing the effects of probiotic supplementation in preterm IUGR neonates are required considering the significance of gut flora in IUGR.

**Focus on Facilitating Enteral Nutrition**

Optimizing enteral nutrition is a priority in extremely preterm neonates, including those with IUGR. Focusing on the benefits of probiotic supplementation on enteral nutrition is thus important. Probiotics may modulate gut motility by their secreted products or products of fermentation, influence on intestinal neuroendocrine factors, or by mediators secreted by the gut as an immune reaction to probiotics [26]. SCFAs are the main end products of colonic fermentation of dietary fiber by gut microbiota that play an important role in maintaining gut function and well-being. Colonic fermentation contributes to regulation of upper gastrointestinal motility, reduction in gastric emptying rate and lower inter-digestive acid output through the effects of SCFA [27]. Butyrate plays an impor-
tant role in gastrointestinal homeostasis [28]. Overall, these mechanisms of benefits of the gut flora support the findings from RCTs that probiotics significantly reduce the time to full enteral feeds (120–150 ml/kg per day) in preterm VLBW neonates. Strain selection is an important issue when targeting such specific beneficial effects of probiotic supplementation in preterm neonates. Lactobacillus reuteri DSM 17938 has been shown to improve gastric emptying (assessed by gastroelectrography and ultrasound) and feed tolerance in preterm neonates [29]. Awareness of factors affecting gastric motility and function (e.g. formula feeds, high osmotic load of milk due to medications and other additives, feeding position, sepsis, phototherapy) is important as they may reduce/negate the benefits of probiotic supplementation [30].

Advancing Knowledge in the Field

Rates of colonization of the gut depend on the probiotic strain properties, and host-related factors such as the gestational and postnatal age in neonates. Evidence indicates that colonization may not be necessary for the beneficial effects of probiotics. Adopting strategies to improve colonization is important if it is indeed required for optimal effects of probiotics. Yamasaki et al. [31] have reported that early administration of Bifidobacterium bifidum OLB6378 accelerated enteral feeds and optimized colonization. In their pilot study, 36 preterm VLBW neonates were randomly divided into either group E (B. bifidum supplementation started ≤ 48 h of birth) or group L, where it was started >48 h after birth. Group E reached 100 ml/kg per day feeds earlier than group L [median (interquartile): 10 (7–13) vs. 11 (10–15) days, respectively]. The daily weight gain was significantly higher in group E. Fecal Bifidobacterium levels were not significantly different between the groups (real-time polymerase chain reaction assay) at 1 and 4 weeks of age. However, the highest colonization rate of Bifidobacterium was observed when the supplementation was started between 24 and 48 h after birth [31]. These results need to be confirmed in larger studies, and with different strains.

Limited evidence indicates that the efficacy of multistrain probiotics may be greater than single strains, including strains that are components of the multistrain mixture themselves. It is not clear whether this benefit is due to the synergistic interactions between strains or a consequence of the higher probiotic dose used in such studies. Ishizeki et al. [32] administered a single-strain (Bifidobacterium breve M-16V, $5 \times 10^8$) or a multistrain probiotic (B. breve M-16V, Bifidobacterium longum subsp. infantis M-63 and B. longum subsp. longum BB536, $5 \times 10^8$ each strain) daily for 6 weeks in low-birthweight neonates. Detection rates and fecal counts of bifidobacteria increased significantly between weeks 1 and 6.
The proportion of bifidobacteria was significantly higher in the multistrain compared with the single-strain group at weeks 1 and 6. The proportion of infants with bifidobacteria-predominant microbiota was significantly higher in the multistrain than in the control group. The proportions of Enterobacteriaceae were significantly lower in the multistrain group at weeks 4 and 6. *B. breve* M-16V and *B. infantis* M-63 were detected in ≥85% of neonates during the administration period, while *B. longum* BB536 was detected in ≤40%. Administration of three strains of bifidobacteria was thus more beneficial [32]. Awaited results of the large multicenter probiotic trial from the UK will be important to judge whether the effects of single strain (*B. breve*, Yakult) are comparable to those reported in previous RCTs of single- or multistrain products in preterm VLBW neonates. Wu et al. [33] have reported that administration of a mixture of probiotic strains with *B. bifidum* and *B. longum* was most effective in preventing death and NEC in a rat model of NEC. Their observations are helpful in designing clinical trials comparing effects of single- versus multistrain probiotics.

Human milk oligosaccharides (HMO) are the third most abundant class of molecules in breast milk. As infants do not have the enzymes required for milk glycan digestion, HMOs pass undigested to the lower part of the gut, where they can be consumed as substrate by specific gut microbiota. Research on consumption of specific HMOs by different probiotic strains will help in developing optimal pre- and probiotic combinations (synbiotic) [34].

Further research assessing the effects of killed or inactivated versus live probiotic agents will be important considering the potential benefits with regard to probiotic sepsis, development of antibiotic resistance, and need for maintaining a cold chain which have implications for global utility of probiotics [35].

Development of new techniques (e.g. newer methods for encapsulation) for improving the tolerance of probiotic strains to bile, acid, and oxygen exposure is expected to enhance the benefits of probiotics.

In summary, current evidence from within and outside RCTs strongly supports the use of probiotic supplementation to reduce the risk of NEC in preterm VLBW neonates. Probiotic prophylaxis outside the rigid framework of RCTs is expected to provide data on real-life benefits, and importantly, the uncommon/rare adverse effects of this intervention in preterm neonates. Reporting outcomes and safety data following introduction of routine probiotic supplementation is thus important. Strain-specific population data will help in guiding clinical practice. As with any intervention, it is expected that the real-life benefits of probiotic supplementation may not be as dramatic as reported in RCTs. However, even a much smaller reduction in the risk of definite NEC (e.g. 20–25%) may be acceptable considering the overall health burden of the condition and the relatively very low cost of probiotics.
Probiotics will not be a panacea for NEC, which is known to present at different postnatal ages with different triggers and different mode of presentation. Strategies such as maximizing exposure to antenatal glucocorticoids, early feeding with maternal/donor breast milk, and an aggressive approach for prevention and treatment of late-onset sepsis are equally or perhaps more important if a ‘zero tolerance’ to NEC is required. Focusing on nutritional benefits of probiotics is important, especially when further reduction in the low baseline incidence of definite NEC is not a priority or possibility.

Finally, without easy access to safe and clinically proven probiotic products, it will be the case of ‘all dressed but nowhere to go’. Cooperation between various stakeholders including the regulatory authorities and the industry is urgently required to address the issue of quality control and, importantly, decide whether probiotics should be classified as drugs, food supplements, or biotherapeutic agents. Considering that different probiotic strains may benefit by different pathways, and in different ‘doses’, probiotics will not be available as a standardized packaged product like a conventional drug.

Disclosure Statement

The author declares that no financial or other conflict of interest exists in relation to the contents of the chapter.

References


Session 1 set the stage for understanding the global burden of low birthweight, preterm and small for gestational age by presenting the prevalence and the actual number of infants estimated to be born with these adverse outcomes in low- and middle-income countries each year. Neonatal and infant mortality given these adverse outcomes was presented as well as maternal risk factors and interventions that might reduce this burden.

Robert Black presented the small for gestational age estimate of 32.4 million (27% of 120.4 million live births in 2010) born in low- and middle-income countries, with 91% of these born at term. India was the country with the largest number of small for gestational age infants (12.8 million in 2010) and a prevalence of 42% of all live births. South Asia was the region of the world where small for gestational age was most prevalent.

James Tielsch described the prevalence, numbers and risk factors for preterm birth globally and by region of the world. A total of 15 million infants (12%) were born preterm in 2010. He also described some of the challenges of measuring gestational age, especially in resource-constrained settings. Evidence for maternal risk factors that can be intervened on to reduce preterm are less clear for preterm than for small for gestational age outcomes.

Joanne Katz presented the work of her doctoral student who unfortunately was taken ill and unable to present. This work described maternal nutritional and reproductive risk factors for preterm and small for gestational age. Maternal short stature, body mass index and weight gain in pregnancy were all strong predictors of small for gestational age and weak predictors of preterm birth. Nulliparous women, especially adolescents, were at higher risk for preterm and
small for gestational age, as were those with short birth intervals. Nutritional supplementation in pregnancy and family planning may be interventions that can reduce preterm and small for gestational age births.

Joanne Katz also presented the mortality associated with preterm and small for gestational age births. Preterm infants had higher mortality risk than those born small for gestational age. Infants born too soon and too small had the highest mortality risk. Early neonatal mortality of preterm infants was very high relative to term and appropriate for gestational age infants, with declining risk in the postneonatal period. Small for gestational age had lower mortality risk than preterm but persisted at this level throughout infancy. A total of 1.3 million (26%) of the 5 million infant deaths in 2011 were attributable to small for gestational age. Infants born term small for gestational age but not low birthweight were also at increased risk of mortality relative to term appropriate for gestational age infants.

The final presentation by Per Ashorn described the evidence for the impact of antibiotic treatment of maternal infections on reducing preterm and small for gestational age births. The evidence for an effect was strongest in Sub-Saharan Africa, and presumptive antimicrobial treatment that targeted reproductive tract, malaria, other parasitic diseases, skin infections, and periodontitis may improve fetal growth and reduce the incidence of preterm birth. One intervention not described that may be important is the role maternal HIV plays in these adverse birth outcomes and the extent to which treatment may reduce these.

There was lively discussion during the question and answer session that followed. The epidemiologic perspective was a contrast to the more clinical one of treatment and nutrition for infants born preterm and/or fetal growth restricted that followed in the next two sessions.

Session 2 aimed to develop the concepts and definitions provided by the epidemiological data presented in session 1, starting with the contentious topic of catch-up growth. Atul Singhal explained that this pattern is commonly seen in low-birthweight infants, but data over the last decade emphasized that whilst faster postnatal growth may have short-term advantages, several studies now show that it increases the risks of ageing, obesity and metabolic disease. In some resource-poor settings, and also in preterm infants, current consensus favors growth promotion because of the associated cognitive benefits, whilst in more affluent settings, and especially in in utero growth-restricted term infants, the current consensus favors slower postnatal growth and strongly supports the use of breast milk.

Nicholas Embleton developed these concepts focusing particularly on the role of growth promotion in infants born preterm. The human brain acquires around 90% of its final adult volume in the period between 24 weeks’ gestation and
2 years of age, with the peak brain growth spurt occurring in the few weeks before and after term age. Poor growth during this period is strongly associated with worse neurocognitive outcome, with evidence that growth in the postdischarge period (between term and 12 months corrected age) may provide a window of opportunity to improve outcomes. Nevertheless, there are data to show that faster growth during this period may be associated with metabolic risk in late adolescence and early adulthood, specifically insulin resistance.

Jatinder Bhatia emphasized the continuum of nutritional status, and how the mother’s own fetal growth and her diet and body composition, socioeconomic status, complications during pregnancy, infections and poverty all affect fetal growth and the incidence of low birthweight. Low birthweight itself is an important public health indicator since it encompasses maternal malnutrition, socioeconomic status, fetal and infant growth, mortality and morbidity. One of the major issues is that most of the nutrients considered ‘building blocks’ such as protein, calcium, phosphorus, iron and long-chain polyunsaturated fatty acids are supplied largely in the third trimester making the preterm infant especially vulnerable to deficiencies.

Ian Griffin presented the neuroendocrine model of catch-up growth with data from a number of animal models. During nutritional inadequacy, which invariably precedes catch-up growth, growth hormone levels increase under the influence of the oxygenic ‘hunger signal’ ghrelin. However, during malnutrition nutritionally responsive proteins block growth hormone signal transduction in the liver, thereby limiting IGF-1 production. The result is that growth hormone action is shifted from hepatic to effects in other tissues (for example muscle and adipose) and away from IGF-1-mediated effects.

Andrew Prendergast emphasized that children in developing countries are frequently stunted at birth and show a further decline in linear growth over the first 24 months of life. Children living in conditions of poor sanitation and hygiene are frequently exposed to pathogenic microbes and experience environmental enteric dysfunction which is characterized by disturbance in small intestinal structure and function. Reducing feco-oral microbial transmission by improving water, sanitation and hygiene may theoretically prevent or ameliorate environmental enteric dysfunction and improve linear growth; ongoing trials are exploring this hypothesis.

Session 3 reviewed the various interventions in the neonatal period that are designed to reduce the short-term risks and may improve long-term outcomes. Karen Simmer presented the theoretical underpinnings of human milk fortification and discussed the various approaches to fortification. Potential adverse effects of fortification, such as increased osmolality, were pointed out, as was the need for increased fortification when donor human milk is fed.
Gert Kirsten gave an account of how in a resource-poor setting the management of low-birthweight infants must focus on the avoidance of hypothermia and hypoglycemia while aiming to introduce enteral feeds in a timely fashion. Separation of the infant from the mother needs to be avoided or be kept to a minimum in order to facilitate early discharge from the hospital.

Ekhard Ziegler emphasized that catch-up growth enhances cognitive development whether it occurs after intrauterine or postnatal growth failure. But he emphasized that catch-up growth can only be realized if the extraordinarily high nutrient needs that it engenders are met.

Neelam Kler reported that India, in accordance with WHO recommendations, does not recommend the use of fortification routinely but reserves it for infants <32 weeks’ gestation who fail to gain weight while receiving full volumes of human milk. The concerns are contamination of human milk, high osmolality and feeding intolerance as well as risk of NEC. Nevertheless, a recent survey of tertiary care units indicated that a substantial number of units do use fortification routinely.

Finally, Sanjay Patole reviewed the evidence showing that probiotics reduce the risk of NEC and do so even in situations where the risk of NEC is already very low. Additional benefits include improved feed tolerance, which is often an issue in prenatally growth-restricted infants. Overall, the evidence supporting the routine use of probiotics is very strong and safety is not a concern.

The rising global incidence of low birthweight and the impact this has throughout the life course make these infants a high priority for public health. Low birthweight is the result of a complex interplay of factors involving the passage of risk across generations. Tackling the problem requires a multifaceted approach and an understanding of the factors that explain differences in epidemiology across the globe. Improving nutritional status in infancy requires actions to improve maternal health status, and an appreciation of the interaction between nutrient factors (e.g. use of breast milk, introduction of complementary foods, supplements and fortifiers, etc.) and local environmental factors such as healthcare organization, enteric (e.g. parasitic load) and nonenteric infections such as HIV. As chairs of the workshop, we hope this book provides a valuable insight into improving outcomes for all children ‘born too soon or too small’.

Nicholas D. Embleton
Joanne J. Katz
Ekhard E. Ziegler
Subject Index

Antibiotics, prevention of intrauterine growth restriction and preterm birth literature review 39, 40
mechanisms 47, 48
outcomes 40–46
overview 38, 39

BAX, expression in intrauterine growth restriction studies 156
BMI, see Body mass index
Body mass index (BMI), maternal risk factor for preterm birth 21, 22
Butyrate, gut homeostasis role 157, 158

Calcium
low birthweight nutrition recommendations 75–77
metabolism 75
Cardiovascular disease (CVD), growth acceleration effects and mechanisms 54–57
CASP3, expression in intrauterine growth restriction studies 156
Catch-up growth adolescence after preterm birth
cognitive outcomes 66, 67
mechanisms and lifestyle factors 69, 70
definition 53, 63
Developmental Origins of Health and Disease 62, 63
history of study 52, 53
low birthweight cognition outcomes
intrauterine growth restriction 137
postnatal growth failure 137, 138
intrauterine growth restriction overview 136
nutrient needs estimation 138–141
recommendations 141
models
epiphyseal growth plate hypothesis 89
neuroendocrine model 89–96
time tally model 88
Newcastle preterm birth growth study 67, 68
recommendations in low birthweight infants 57, 58
Cognition
catch-up growth outcomes
intrauterine growth restriction 137
postnatal growth failure 137, 138
preterm birth and adolescent outcomes 65–67
Copper, low birthweight nutrition recommendations 80
CVD, see Cardiovascular disease
Developmental Origins of Health and Disease, overview 62, 63
Diarrhea, stunting role 101
EED, see Environmental enteric dysfunction
Environmental enteric dysfunction (EED), stunting role 101, 102
Epigenetics, growth acceleration effects on long-term health 56, 57
Epiphyseal growth plate hypothesis, catch-up growth 89
EUGR, see Extrauterine growth retardation
Extrauterine growth retardation (EUGR) definition 112
human milk fortification studies 113, 119
long-term outcomes 112
FGF-21, see Fibroblast growth factor-21
Fibroblast growth factor-21 (FGF-21), hepatic growth hormone signaling and resistance 93
Gestational age, determination 10, 11
GH, see Growth hormone
Ghrelin, preterm infant levels 95
Growth acceleration definition 53, 64
history of study 52, 53
long-term health effects and mechanisms 54–57
recommendations in low birthweight infants 57, 58
Growth hormone (GH) catabolism 90, 91
catch-up growth 89–96
hepatic signaling and resistance fibroblast growth factor-21 93
JAK/STAT signaling 91, 92
SIRT1 92, 93
SOCS 92
hyperanabolism 91
inflammation and stunting 104
normal anabolism 89, 90
HMO, see Human milk oligosaccharides
Human milk fortification, see also specific nutrients benefits 114
donor human milk 118, 119
extrauterine growth retardation studies 113
fortifiers 116
India contamination and sepsis 146
feed intolerance and necrotizing enterocolitis 146, 147
fortifiers 148, 149
long-term benefits 148
nutritional adequacy 147, 148
overview 145, 146
prospects 149, 150
indications 115
protocols 117, 118
rationale 115
risks 114
timing 115
Human milk oligosaccharides (HMO), probiotic metabolism 159
Hygiene, see Water, sanitation, and hygiene
Hypertension, preterm birth and adolescent outcomes 66
IGF-1, see Insulin-like growth factor-1
Insulin-like growth factor-1 (IGF-1) catch-up growth 93–95
inflammation and stunting 104
preterm infant levels 95, 96
Insulin resistance, preterm birth and adolescent outcomes 66, 69
Intestinal barrier function, stunting studies 103–106
Intrauterine growth restriction (IUGR) antibiotic prevention in pregnancy literature review 39, 40
mechanisms 47, 48
outcomes 40–46
overview 38, 39
body composition 139
catch-up growth, see Catch-up growth
etiology 38
stunting risks 100
Iron, low birthweight nutrition recommendations 79, 80
### Subject Index

<table>
<thead>
<tr>
<th>Term</th>
<th>Page(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IUGR, see Intrauterine growth restriction</td>
<td>169</td>
</tr>
<tr>
<td>JAK/STAT signaling, hepatic growth hormone signaling and resistance</td>
<td>91, 92</td>
</tr>
<tr>
<td>Kangaroo mother care (KMC), low birthweight management in developing countries</td>
<td>124–126, 128</td>
</tr>
<tr>
<td>KMC, see Kangaroo mother care</td>
<td></td>
</tr>
<tr>
<td>Lactulose:mannitol ratio, environmental enteric dysfunction</td>
<td>102</td>
</tr>
<tr>
<td>LBW, see Low birthweight</td>
<td></td>
</tr>
<tr>
<td>Low birthweight (LBW) associations with small for gestational age and preterm birth</td>
<td>30, 31, 62</td>
</tr>
<tr>
<td>classification</td>
<td>2</td>
</tr>
<tr>
<td>definition</td>
<td>2, 17, 73, 124</td>
</tr>
<tr>
<td>geographic distribution</td>
<td>2, 5</td>
</tr>
<tr>
<td>growth patterns, see Catch-up growth; Growth acceleration</td>
<td></td>
</tr>
<tr>
<td>management in developing countries community clinic nutritional support</td>
<td>132</td>
</tr>
<tr>
<td>discharge</td>
<td></td>
</tr>
<tr>
<td>planning</td>
<td>131</td>
</tr>
<tr>
<td>postnatal ward</td>
<td>143</td>
</tr>
<tr>
<td>principles</td>
<td>132</td>
</tr>
<tr>
<td>special care nursery</td>
<td>132</td>
</tr>
<tr>
<td>formula feeding principles</td>
<td>131</td>
</tr>
<tr>
<td>kangaroo mother care</td>
<td>124–126, 128</td>
</tr>
<tr>
<td>labor ward</td>
<td></td>
</tr>
<tr>
<td>blood glucose monitoring</td>
<td>125</td>
</tr>
<tr>
<td>nutritional management</td>
<td>126</td>
</tr>
<tr>
<td>triage and transfer</td>
<td>124, 125</td>
</tr>
<tr>
<td>postnatal ward</td>
<td></td>
</tr>
<tr>
<td>expressed breast milk</td>
<td>129, 130</td>
</tr>
<tr>
<td>supplementation</td>
<td>131</td>
</tr>
<tr>
<td>special care nursery</td>
<td></td>
</tr>
<tr>
<td>colostrum</td>
<td>126</td>
</tr>
<tr>
<td>cup feeding</td>
<td>129</td>
</tr>
<tr>
<td>expressed breast milk</td>
<td>126–128</td>
</tr>
<tr>
<td>formula feeding</td>
<td>127</td>
</tr>
<tr>
<td>parenteral nutrition</td>
<td>129</td>
</tr>
<tr>
<td>pasteurized donor milk</td>
<td>127</td>
</tr>
<tr>
<td>supplements</td>
<td>129</td>
</tr>
<tr>
<td>mortality</td>
<td>29, 30</td>
</tr>
<tr>
<td>nutrient recommendations</td>
<td></td>
</tr>
<tr>
<td>calcium</td>
<td>75–77</td>
</tr>
<tr>
<td>copper</td>
<td>80</td>
</tr>
<tr>
<td>iron</td>
<td>79, 80</td>
</tr>
<tr>
<td>long-chain polyunsaturated fatty acids</td>
<td>81, 82</td>
</tr>
<tr>
<td>magnesium</td>
<td>78</td>
</tr>
<tr>
<td>overview</td>
<td>74, 75</td>
</tr>
<tr>
<td>phosphorous</td>
<td>76, 77</td>
</tr>
<tr>
<td>vitamin D</td>
<td>78, 79</td>
</tr>
<tr>
<td>zinc</td>
<td>81</td>
</tr>
<tr>
<td>prevalence</td>
<td>2, 3, 5, 6, 38</td>
</tr>
<tr>
<td>Magnesium, low birthweight nutrition recommendations</td>
<td>78</td>
</tr>
<tr>
<td>Menkes syndrome</td>
<td>80</td>
</tr>
<tr>
<td>NEC, see Necrotizing enterocolitis</td>
<td></td>
</tr>
<tr>
<td>Necrotizing enterocolitis (NEC) human milk fortification studies</td>
<td>114, 146, 147</td>
</tr>
<tr>
<td>probiotics in prevention</td>
<td>153–156, 159, 160, 166</td>
</tr>
<tr>
<td>PCNA, see Proliferating cell nuclear antigen</td>
<td></td>
</tr>
<tr>
<td>PGF, see Postnatal growth failure</td>
<td></td>
</tr>
<tr>
<td>Phosphorous, low birthweight nutrition recommendations</td>
<td>76, 77</td>
</tr>
<tr>
<td>Postnatal growth failure (PGF) cognition outcomes</td>
<td>137, 138</td>
</tr>
<tr>
<td>overview</td>
<td>136</td>
</tr>
<tr>
<td>Preterm birth (PTB) adolescent outcomes</td>
<td>65–67</td>
</tr>
<tr>
<td>antibiotic prevention in pregnancy literature review</td>
<td>39, 40</td>
</tr>
<tr>
<td>mechanisms</td>
<td>47, 48</td>
</tr>
<tr>
<td>outcomes</td>
<td>40–46</td>
</tr>
<tr>
<td>overview</td>
<td>38, 39</td>
</tr>
<tr>
<td>associations with small for gestational age and low birthweight</td>
<td>30, 31, 62</td>
</tr>
<tr>
<td>definition</td>
<td>11</td>
</tr>
<tr>
<td>growth patterns, see Catch-up growth; Growth acceleration</td>
<td></td>
</tr>
</tbody>
</table>

Subject Index 169
human milk fortification, see Human milk fortification incidence 12–14, 26, 62, 145 maternal risk factors age and parity 23, 24 birth interval 24–28 body mass index 21, 22 height 18–21 weight gain during pregnancy 22 mortality 111, 112 Newcastle preterm birth growth study 67, 68 probiotic supplementation, see Probiotics Probiotics enteral nutrition facilitation 157, 158 extreme preterm infant studies 154, 155 intrauterine growth restriction studies 155–157 necrotizing enterocolitis prevention 153–156, 159, 160, 166 Proliferating cell nuclear antigen (PCNA), expression in intrauterine growth restriction studies 156 PTB, see Preterm birth Sanitation, see Water, sanitation, and hygiene SGA, see Small for gestational age SIRT1, hepatic growth hormone signaling and resistance 92, 93 Small for gestational age (SGA) associations with preterm birth and low birthweight 30, 31 definition 3, 17, 124 epidemiology 4–6, 26 growth patterns, see Catch-up growth; Growth acceleration maternal risk factors age and parity 23, 24 birth interval 24–28 body mass index 21, 22 height 18–21 weight gain during pregnancy 22 mortality 30–34 Newcastle preterm birth growth study 67, 68 probiotic supplementation, see Probiotics Probiotics enteral nutrition facilitation 157, 158 extreme preterm infant studies 154, 155 intrauterine growth restriction studies 155–157 necrotizing enterocolitis prevention 153–156, 159, 160, 166 Proliferating cell nuclear antigen (PCNA), expression in intrauterine growth restriction studies 156 PTB, see Preterm birth Sanitation, see Water, sanitation, and hygiene SGA, see Small for gestational age SIRT1, hepatic growth hormone signaling and resistance 92, 93 Small for gestational age (SGA) associations with preterm birth and low birthweight 30, 31 definition 3, 17, 124 epidemiology 4–6, 26 growth patterns, see Catch-up growth; Growth acceleration maternal risk factors age and parity 23, 24 birth interval 24–28 body mass index 21, 22 height 18–21 weight gain during pregnancy 22 mortality 30–34 SOCS, hepatic growth hormone signaling and resistance 92 Stunting diet adequacy studies 100 enteric infection role 100, 101 environmental enteric dysfunction 101, 102 intestinal barrier function and chronic inflammation 103–106 intrauterine growth restriction risks 100 water, sanitation, and hygiene studies 106–108 Time tally model, catch-up growth 88 Vitamin D low birthweight nutrition recommendations 78, 79 metabolism 78 WASH, see Water, sanitation, and hygiene Water, sanitation, and hygiene (WASH), stunting studies 106–108 Zinc, low birthweight nutrition recommendations 81