81st Nestlé Nutrition Institute Workshop
Low Birth Weight Baby:
Born Too Soon or Too Small
30 March – 2 April 2014
Magaliesburg, South Africa
Introduction

The 81st Nestlé Nutrition Institute Workshop, titled ‘Low Birth Weight Baby: Born Too Soon or Too Small’ was held in Magaliesburg, South Africa from 30 March to 2 April 2014. This workshop was chaired by three distinguished experts in the field of neonatal health and nutrition: Prof Joanne Katz, from the Johns Hopkins Bloomberg School of Public Health; Dr Nicholas Embleton from Newcastle University in the United Kingdom and Prof Ekhard Ziegler from the University of Iowa.

In his opening address, Prof Ferdinand Haschke (Head of Nestlé Nutrition Institute, Switzerland) highlighted the importance of nutrition from conception to the second year of life – the ‘first 1000 days’. Nevertheless, Prof Haschke emphasized that emerging evidence from the field of adolescent health suggests that this window of opportunity should, in fact, encompass nutrition in adolescence. The latest data from low-income countries show that infants born appropriate for gestational age do grow according to the World Health Organization (WHO)’s growth curves.

However, small for gestational age (SGA) babies in developing countries fall behind in terms of growth, with little chance of catching up. This underscores the importance of maternal nutrition upfront.

It is well documented that 80–85% of all low birth weight (LBW) infants are born in developing countries. LBW is an important public health indicator since it encompasses maternal malnutrition, socioeconomic status, foetal and infant growth as well as mortality and morbidity. In resource-poor environments, quality of medical services comes with a price. Therefore, the affordability of any nutritional intervention and recommendation is a key determinant of success.

The agenda of this 81st Nestlé Nutrition Institute Workshop was designed to share the latest findings and provoke discussion about key stakeholders involved in early infant nutrition. The three sessions – Global Epidemiology, Catch up Growth and Feeding Practices – place the spotlight firmly on LBW and SGA infants.
Session 1

Global epidemiology
Chairperson: Joanne Katz

Presentations in this first session formed a scientific base for this workshop on low birth weight babies. Speakers presented data on global prevalence and burden, risk factors as well as the prevention of SGA and preterm births.

Robert Black (Johns Hopkins Bloomberg School of Public Health, USA) kicked off the workshop by presenting the global prevalence of foetal growth restriction and SGA births. It is estimated that approximately 15% of newborns globally weigh less than 2,500 g. It is known that foetal growth restriction has significant consequences on subsequent survival, health, growth and development. Foetal growth restriction is usually assessed by comparing the weight of the newborn with the expected weight for the child’s gestational age. SGA refers to children weighing less than the 10th centile of a reference population for foetal growth. In this presentation, Black explained the methods used to estimate the global prevalence of SGA. Further, he emphasized that the prevalence of SGA is much higher than that of preterm births. In 2010 alone, it is estimated that 32.4 million babies were born SGA in low- and middle-income countries. This constitutes almost one-in-three of all live births. Given the consequences of being born SGA, data on gestational age should be used to assess risks and guide clinical care both in the pre- and postnatal settings.

//There are substantial consequences of being SGA, and it is particularly important to remember that the data shows that this is a very real problem, particularly in low- and middle-income countries. //

– Robert Black

James Tielsch (George Washington University, USA) followed with data on the global burden of preterm birth. Defined as a live born infant delivered prior to 37 weeks gestation, preterm birth is associated with significant morbidity and mortality. It is, in fact, the leading cause of neonatal mortality in the world. In preterm babies who survive, many continue to have lifelong disabilities. There are a variety of measurements to determine gestational age. While calculation based on the last menstrual period is the most common, foetal anthropometry within the first trimester through an ultrasound examination provides the most accurate estimates. Globally, the incidence of preterm births is about 11% of all live births in 2010. This translates into almost 15 million preterm births annually. There is significant variation in rates by country and region, ranging from 5% in northern Europe, to 18% in Malawi. Time trends suggest that the incidence of preterm birth is increasing.

This is probably a reflection of changes in global delivery practices. It is not known whether there are major changes in spontaneous preterm births. Tielsch also presented a new paradigm for defining and classifying preterm births proposed by the Global Alliance for the Prevention of Preterm and Stillbirths (GAPPS) working group. It is anticipated that multiple-intervention approaches are required to significantly decrease the rates of preterm births.

// In many countries, gestational age and pregnancy outcomes data are not routinely collected. Therein lies the difficulty in making global estimates of the consequences of preterm births. //

– James Tielsch

On behalf of Naoko Kozuki (Johns Hopkins Bloomberg School of Public Health, USA), Joanne Katz discussed the risk factors of SGA and preterm births, focusing specifically on nutritional and reproductive risk factors. Katz also explained proposed mechanisms associated with risk factors which may contribute to SGA and preterm births. Data included in this presentation were primarily from work done by the Child Health Epidemiology Reference Group (CHERG). The risk factors highlighted in this presentation were height, body mass index (BMI) and weight gain during pregnancy, maternal age and parity as well as time between births. It is known that maternal short stature (presumably a cause of limited uterine volume for foetal growth) is strongly associated with both preterm and SGA births. The main exposures that determine linear growth occur during the foetal period and the first two years of life. Nevertheless, interventions during childhood and adolescence may promote catch-up growth. In this presentation, Katz also presented data from systematic reviews that show statistically significant associations between low BMI/low weight gain and foetal growth restriction. Data from CHERG showed that women below 18 years of age and nulliparous had the highest risk of SGA and preterm births compared with women aged 18–35 years old who had given birth only once or twice. Older women who were parity 3 or more had an increased risk of preterm births. CHERG data showed an increased risk of both SGA and preterm births in mothers with short birth intervals (<18 months between births). Several interventions (i.e., breastfeeding, contraception and education) addressing these risk factors were also discussed.

// Both nutritional and reproductive health-related exposures contribute to SGA and preterm outcomes. Interventions are not straightforward. Chronic malnutrition may require intergenerational intervention, and interventions for acute malnutrition need to take into consideration the potential consequences of increased foetal size among stunted mothers. //

– Joanne Katz

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Joanne Katz (Johns Hopkins Bloomberg School of Public Health, USA) then presented CHERG data on the mortality risk of being born preterm or SGA. In total, 26% of the five million infant deaths in low- and middle-income countries in 2011 were attributable to SGA. SGA infants born preterm are at higher mortality risk than term SGA infants. But, the majority of SGA infants born in low- and middle-income countries in 2010 were born at term. For those who were preterm but not SGA, mortality risk was observed to decline from the early-to-late through post-neonatal periods. SGA is a significant underlying cause of neonatal and infant mortality. These data suggest that interventions to prevent SGA could have a major impact on neonatal and infant survival in resource limited settings. The WHO's fourth Millennium Development Goal is to reduce child mortality. Concerted efforts to reduce preterm and SGA births will significantly contribute to progress in this area.

If interventions could effectively eliminate term SGA births, approximately 1 million infant deaths could be averted annually. – Joanne Katz

Per Ashorn (University of Tampere, Finland) turned the spotlight on prevention of SGA and preterm births. In particular, data on antibiotic use during pregnancy were presented. Maternal infections are frequently associated with intrauterine growth restriction and preterm births. For this reason, the efficacy of presumptive or targeted treatment of pregnant women with antibiotics can promote foetal growth and prevent preterm births. In his presentation, Ashorn presented the Lungwena Antenatal Intervention Study (LAIS). Conducted in Malawi, the study investigated the reduction of preterm births by treating pregnant women with antimalarial medications. The study found that in rural Malawi, intermittent preventive treatment of malaria in pregnant mothers reduced the incidence of preterm delivery and LBW. Further, Ashorn also highlighted data from a systematic literature review to identify predictors of its efficacy in preventing SGA and preterm births. The review found that presumptive antimicrobial treatment of pregnant women may improve birth outcomes in some, but not all, contexts. An effect is more likely if the intervention targets maternal infections in general, not only those of the reproductive tract. Nevertheless, further data, particularly regarding resistance and the effect of antibiotics on microbiota, are warranted.

Maternal infections are important causes of intrauterine growth restriction and preterm births. Use of antibiotics can improve birth outcomes in some contexts and sustained benefits are likely. However, more data is required to determine its efficacy and safety in target populations. – Per Ashorn

Atul Singhal (UCL Institute of Child Health, UK) started this session with a discussion on catch up growth, or growth acceleration, in LBW infants. Patterns of growth in early life may influence long-term health. The short-term advantages of postnatal catch up growth, or growth acceleration, in LBW infants. Patterns of growth in early life may influence long-term health. The short-term advantages of postnatal catch up growth in LBW infants are well documented. These include a decreased risk of hospitalization. However, the long-term impact of this pattern of growth is increasingly recognized. Accelerated postnatal growth has been shown to be associated with an increased risk of obesity, diabetes and cardiovascular disease in adult life. This effect has been observed irrespective of confounding factors (ie, preterm, SGA, or in developing countries). Data from studies that investigate the impact of accelerated postnatal growth were also presented.

The optimal pattern of postnatal growth is likely to differ in different populations. There is, therefore, a trade-off in order to optimize growth trajectories between short-term gains and long-term costs. – Atul Singhal
Nicholas Embleton (Newcastle Neonatal Service, UK) followed with a presentation about catch up growth and its association with metabolic and cognitive outcomes in adolescents who were born preterm. Poor cognitive function is the major adverse outcome of preterm birth. While growth failure is common in preterm infants, it is poor nutrition that is associated with poor cognitive outcomes long-term. Embleton examined the literature on early nutrition and its effects on adult health through programming – what is known as the Developmental Origins of Adult Disease Hypothesis. Prospective data suggest that slow growth in-utero may not result in later metabolic harm unless a period of accelerated postnatal growth followed. Even though growth is dependent on many factors, there is strong evidence that nutrient intakes determine patterns of growth. While growth may be an important indicator of later outcomes, growth *per se* is not the mechanism linking early nutrition and later metabolic or cognitive outcomes. A more rapid linear growth may be associated with a decreased risk of low IQ, but a higher risk of overweight and obesity. Further, he also described the findings of the Newcastle Preterm Birth Growth study which involved 247 preterm infants, as well as a follow up study (n=153) with the same cohort conducted when the subjects were aged 8–12 years. Finally, Embleton shared some personal practice points when faced with infants born preterm.

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Jatinder Bhatia (Children’s Hospital of Georgia, USA) spoke about the role of specific nutrients that are important for the growth and development of LBW infants. Most of the nutrients considered to be ‘building blocks’ (e.g., protein, calcium, iron, long chain polyunsaturated fatty acids) are supplied largely in the third trimester. Infants born premature are especially vulnerable to deficiencies of these nutrients. The importance of adequate nutrition and nutrients to support appropriate growth in preterm babies is paramount to breaking the vicious and potentially intergenerational cycle of growth failure. Calcium, phosphorus and magnesium play prominent roles in a host of biochemical reactions. Specifically, calcium and phosphorus are principal components of the skeleton while magnesium is a co-factor in a wide variety of enzymatic reactions. Premature and LBW infants likely have inadequate levels of calcium and phosphorus. As breast milk may not adequately meet the calcium requirements of these infants, fortification may be required. In his presentation, Bhatia also discussed the roles of other nutrients (including vitamin D, iron, copper, zinc and polyunsaturated fatty acids) for growth and normal development.

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Ian Griffin (UC Davis Medical Center, USA) explained the basic mechanisms of catch up growth. Catch up growth follows a variety of nutritional or non-nutritional insults that slow the normal rate of growth, and is characterized by faster than expected growth once the insult is over. There are three basic models that explain how catch up growth can occur: Tanner’s Time Tally Model, The Growth Plate Hypothesis and the Neuroendocrine Hypothesis. Griffin’s presentation focused on the Neuroendocrine Hypothesis as it is most extensively studied and has gained wide acceptance. The mechanisms of hepatic growth hormone resistance were also explained in this presentation. Growth arrest in malnutrition is a highly regulated response. It is not simply a response to substrate inadequacy. In fact, it is likely to be a combination of increased ghrelin and growth hormone coupled with increased deacetylase sirtuin-1 (SIRT1) and fibroblast growth factor 21 (FGF21). The ghrelin and growth hormone model appears to be consistent with existing animal and human data on catch up growth. Nevertheless, there is still no clear understanding on how to manipulate the system to minimize growth failure and catch up growth while minimizing long-term metabolic risks.

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Andrew Prendergast (Centre for Paediatrics, Blizard Institute, Queen Mary University of London, UK and Zvitambo Institute for Maternal & Child Health Research, Zimbabwe) then discussed the phenomenon where stunting occurs despite optimal feeding. The length-for-age in children in developing countries is generally below the WHO’s standard at birth. These children then show a further decline in linear growth within the 1000-day window, with little or no recovery thereafter. It is highly likely that stunting does occur due to inadequate diets, as nutrition programs have had an impact on growth. Nevertheless, this effect is only modest at best. In this presentation, Prendergast explained how recurrent infections may be implicated in the aetiology of stunting. In particular, there is now data showing that diarrhoea has a significant impact on height. Children living in environments of poor sanitation and hygiene are exposed to pathogenic microbes. This continuous environmental insult can result in chronic changes to intestinal structure and function.

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We need to balance the risk of under- and overfeeding, particularly for LBW infants who are SGA. Rightly or wrongly so, the accepted goal for premature infants is to achieve postnatal growth similar to that of a normal foetus born at term.

– Jatinder Bhatia

When you are malnourished, you don’t grow. Fundamentally, it is important to remember that this is a highly regulated response, rather than simply due to inadequate nutrients.

– Ian Griffin
Intestinal damage is inversely associated with linear growth. Prendergast proposed that episodes of diarrhoea may represent only the tip of the ‘enteric disease iceberg’. In fact, these children may have a substantial underlying burden of chronic, subclinical enteropathy. Further, there are multiple overlapping and interacting causes of enteropathy in children living in developing countries. Improvements in water, sanitation and hygiene may well address this environmental enteric dysfunction which leads to increased linear growth. There is now increasing interest in combining interventions during the first 1000-day window to address stunting. SHINE and WASH Benefits are two ongoing cluster-randomized trials aiming to evaluate the independent and combined effects of sanitization and feeding interventions on stunting.

Karen Simmer (Centre for Neonatal Research and Education, University of Western Australia, Australia) spoke about human milk fortification – a serious problem for very preterm infants. Ex-utero growth retardation is a serous problem for very preterm infants and associated with long-term low growth and cognitive impairment. Human milk is the feed of choice. For preterm infants, it should be fortified to achieve recommended dietary intakes (RDI) so that they are able to achieve growth rates similar to those in-utero. However, the evidence now clearly shows that it is not beneficial for preterm infants to grow along foetal growth charts. Rapid catch up growth in the early years of life has been shown to have deleterious health consequences in adult life. The optimal rate of growth should be determined for preterm infants. In this presentation, Simmer outlined the benefits, risks and limitations of human milk fortification. Further, she also provided information on the potential impact of water sanitation and hygiene.

Karen Simmer (Centre for Neonatal Research and Education, University of Western Australia, Australia) spoke about human milk fortification – what it is, what nutrients are required, as well as a glimpse of current practices at the bedside. There was also a short discussion on the future role probiotics may play in our population of interest.

Gert Kirsten (University of Stellenbosch, South Africa) then discussed feeding LBW infants in resource-poor environments. This is important because there are significantly more LBW infants born in developing than first-world countries. Further, LBW infants are often born to women with serious antenatal risk factors and are delivered at hospitals with inadequate facilities. Due to limited neonatal intensive care facilities, these infants are predominantly managed in the special care nursery (SCN) and postnatal ward (PW). In this presentation, Kirsten described a triage system in the labour ward by midwives in Tygerberg Hospital in Cape Town (Figure). Associated feeding interventions for LBW infants in each group were also described. The challenges of feeding a larger LBW infant in a resource-poor setting were also discussed. The role of community clinics as an extension of the hospital management was emphasized.

Feedings practices were the focus of the third, and final, session of this workshop. In this session, presentations explored human milk fortification – what it is, what nutrients are required, as well as a glimpse of current practices at the bedside. There was also a short discussion on the future role probiotics may play in our population of interest.

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The aim of human milk fortification is to prevent ex-utero growth retardation. Fundamentally, what we need to work out is how to create a balance between the benefits and risks of catch up growth.

– Karen Simmer

No nutrition program or intervention trial has ever normalized linear growth among children in developing countries. Perhaps enteropathy is the primary driver of stunting and we have been massively undervaluing the potential impact of water sanitation and hygiene.

– Andrew Prendergast

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.

– Gert Kirsten
Ekhard Ziegler (University of Iowa, USA) explained the nutrient needs of SGA infants. In utero or postnatal growth restriction both lead to a deficit in lean body mass. Postnatal growth restriction is very common in LBW infants. Catch up growth is important as it is associated with long-term neurocognitive benefits, but is also associated with long-term adverse effects on cardiovascular and metabolic health. It is well known that an increase in protein intake is required for catch up growth. This must occur in a timely fashion for long-term benefits to accrue. The needs for protein are very high when catch up is to be achieved in a timely fashion. These high protein needs are difficult to meet with the usual feedings for LBW infants. Special measures are required to increase protein intake. In this presentation, Ziegler showed differences between the basic nutritional needs of undergrown infants with those of normally grown infants. Without adequate protein intake, catch up growth is not possible, or will be delayed. Delayed or partial catch up growth will likely compromise any long-term cognitive benefits that can result from catch up growth.

// Both intrauterine and postnatal growth restrictions have adverse effects on long-term cognition, unless it is followed by catch up growth. //

– Ekhard Ziegler

Neelam Kler (Sir Ganga Ram Hospital, India) shared perspectives on human milk fortification in India. Survival rates of preterm infants have improved dramatically due to improvements in neonatal medicine. Nevertheless, growth failure remains a major clinical hurdle in those who are LBW and SGA. There is evidence that human milk alone cannot meet the nutritional demands for catch up growth. Growth failure is associated with long-term consequences, particularly on cognition. For this reason, human milk fortification has become standard clinical care for LBW, especially SGA infants, in many developed countries. However, this is not part of routine care in India. In part, this is because the WHO and Indian guidelines on feeding preterm infants do not recommend the routine use of fortification. In this presentation, Kler explored the barriers to clinician acceptability of human milk fortifiers in India. The data on the advantages of human milk and importance of fortification for this population were also presented.

// More research is required to identify the ideal candidates and milk fortifiers to achieve optimal short- and long-term outcomes. //

– Neelam Kler

Sanjay Patole (King Edward Memorial Hospital for Women, Australia) provided a glimpse into the future of probiotic supplementation in preterm neonates. Necrotizing enterocolitis (NEC) in preterm, very low birth weight infants is associated with devastating consequences. In particular, infants with NEC may suffer long-term neurodevelopmental impairments. Pre- and postnatal disturbances of gut perfusion, altered intestinal structure and function, altered gut flora and increased metabolic demands of enteral feeds, all contribute to an increased risk of NEC and feed intolerance in preterm neonates with intrauterine growth restriction. In this presentation, Patole reviewed the evidence for prophylactic probiotics in the prevention of NEC. Real-life data on the benefits of probiotic prophylaxis in this population are required. Stakeholder collaborations, particularly between regulatory authorities and industry, are required to ensure safe and effective probiotic options for clinical use.

// It is important to appreciate that probiotics are not the panacea for NEC, which is known to present at different postnatal ages with different triggers, and different modes of presentation. //

– Sanjay Patole

Panel discussion

LBW and SGA are often the ‘forgotten’ group in early childhood nutrition. Public debates and health policies often concentrate on maternal nutrition as well as nutrition of healthy, term babies. As a result, nutritional recommendations for LBW and SGA babies are often omitted from national and international guidelines.

Currently, LBW and SGA infants do not receive milk fortifiers in many low- and middle-income countries simply because of a lack of guidelines in this regard. As the majority of LBW and SGA births occur in low- and middle-income countries, guideline recommendations are important to lobby policy change.

The fora of pertinent stakeholders present at this 81st Nestlé Nutrition Institute Workshop provided an opportune time to debate and discuss the issues at hand. Following presentations in Sessions 2 and 3 of the workshop, participants were given the opportunity to engage in a discussion with the experts. The title of the first panel discussion was Catch up or Not to Catch up, and the subsequent panel discussion focused on Feeding Practices.

There is strong evidence showing that any growth failure impacts long-term neurocognitive development. Data show that growth faltering is linked to delayed maturation and subsequently delayed puberty. For this reason, it is important to provide nutritional support so that infants born LBW and SGA do not experience growth failure.

Nevertheless, the strongest evidence show that accelerated growth is associated with a long-term risk of cardiometabolic disease. For SGA babies, extra protein supplementation (possibly in the form of human milk fortification) is required until they are within the 25th to 50th centile. Beyond this, exclusive breastfeeding would

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be sufficient to prevent growth faltering. It was also acknowledged that there is a paucity of robust evidence regarding catch up growth. In particular, there is no consensus on feeding for larger preterm infants.

It is known that preterm babies require an increased amount of protein in their milk to meet growth requirements. Unfortunately, depending on the degree of prematurity, breast milk may not contain adequate protein to meet these requirements. For this reason, milk fortifiers may be required.

While fortification itself does not cause NEC, it does slow down gastric emptying. Generally, milk fortification can commence once babies are able to tolerate at least 100 mL/kg/day of milk. However, if growth is not optimal, there is no reason to withhold or delay fortification. Clinicians were cautioned against waiting until the infant has growth failure to start milk fortification. It is important to preempt and prevent growth failure. Urinary, blood and other markers are not reliable clinical indicators for milk fortification. The baby’s growth is the best indicator of how much to fortify.

Over the course of this workshop, many aspects of nutrition for LBW infants were discussed. It is evident that there is no consensus regarding the right way, and no recommendations regarding the extent of human milk fortification. It may be years before conclusive evidence is available to inform guidelines or consensus on these matters. In the meantime, clinicians continue to strive for improvement by the bedside to prevent growth failure, and to give LBW and SGA babies a chance to catch up. Until data from randomized clinical trials emerge, important information may be derived from observational studies.

In developing countries, there is a paucity of nutrition research in LBW and SGA babies. This is primarily due to a lack of experience and expertise in setting up nutrition trials. Further, there is also inadequate funding in the resource-poor environments which could be allocated to these kinds of studies. There is a call for increased collaborative projects between developing and developed countries. Further, collaborations between pertinent stakeholders, including governments, clinicians and industry, can hasten policy change to improve care for LBW and SGA infants.