86th Nestlé Nutrition Institute Workshop

Protein in Neonatal and Infant Nutrition: Recent Updates

24-27 May 2015 | Beijing, China
Introduction

The quality and quantity of proteins introduced to infants can have a major impact on long-term health. The 86th Nestlé Nutrition Institute Workshop was held in Beijing, China between 24 and 27 May 2015. The workshop gathered key stakeholders from across the globe to discuss and evaluate current evidence and emerging data on protein in neonatal and infant nutrition. This workshop was chaired by three distinguished experts in the field of neonatal health and nutrition: Professor Jatinder Bhatia, from the Georgia Health Sciences University in the United States; Professor Raanan Shamir, the University of Tel Aviv in Israel; and Professor Yvan Vandenplas from the Universitair Ziekenhuis Brussels in Belgium.

The workshop began with a keynote address by Kunling Shen (Chairman of Pediatrics from the Chinese Medical Association). China has a population of 1.4 billion people of which 17% are between the ages of 0 and 14 years. Professor Shen highlighted that China reduced its under-five mortality rate by 66.8% from 2000 to 2012. Chinese paediatricians played key roles in capacity building, continuing medical education and training, immunisation, and creating a public medical insurance system for children. In rural areas, the priorities were to reduce maternal and neonatal mortality and improve nutrition. Although Chinese nutritional studies have shown significant improvements in the children's nutritional status, some disparities remain. For instance, underweight, stunting, and anaemia are still common in rural areas. Professor Shen also explained that there was a lack of priority in addressing malnutrition for those between the ages of 6 and 36 months. To address these issues, an infant complementary food supplement that met 50–60% of the daily nutrient requirements of infants and young children was developed and implemented. The fortification of inadequate homemade complementary food in low-income areas in China has significantly improved the nutritional status of infants, decreased the incidence of anaemia, increased height and weight, and improved cognition and development.

Despite these achievements, China continues to face a challenge of high caesarean delivery rates. Further, a decrease in exclusive breastfeeding rates (Figure 1), and increases in the rate of preterm birth, the prevalence of overweight or obesity (for children younger than 5 years), and the prevalence of asthma have an impact on long-term outcomes in Chinese children.

Figure 1. Decrease in the rate of exclusive breastfeeding of children under 6 months of age in China.

Despite the achievements in infant and childhood nutrition in China, economic, geographical and age-related disparities exist.”

– Kunling Shen

This presentation sets the stage for the meeting as it highlights the key issues pertinent to those involved in the care of infants and children. The agenda of this 86th Nestlé Nutrition Institute Workshop was designed to share the latest findings and stimulate discussion among key stakeholders involved in early infant nutrition. The three sessions – Hydrolysed Protein in Infant Feeding, Protein in Feeding of Term Infants and Protein in Feeding of Preterm Infants – place the focus of discussions at this meeting firmly on the role of protein in neonatal and infant nutrition.
Hydrolysed protein in infant feeding

Chairperson: Yvan Vandenplas
Co-chairperson: Junshi Chen

Presentations in this first session focused on the role of hydrolysed proteins in preterm infants, and term infants with various conditions, including allergies and intestinal disorders.

Sophie Nutten (Nestlé Research Centre, Switzerland) started the session with a presentation that examined the role of proteins and amino acids in infant feeding. As proteins are the main building blocks of the body, a high rate of protein synthesis is crucial for rapid growth during the infant’s first year. Breast milk is the gold standard. In breast milk, both total protein content and concentrations of individual proteins change throughout the first year of lactation to cater to the needs of the growing infant. When breastfeeding is not possible, infant formula should ideally be similar to breast milk in its composition and functional outcomes to achieve appropriate growth, optimal development, maturation of the immune system, and programming of the metabolic system. There have been many innovative changes and great progress in the manufacturing of infant formula. In particular, the protein in selected infant formulas is now closer to breast milk than ever before. Human and cow’s milk have different protein fractions. With cow’s milk, it is near impossible to obtain a similar protein profile to breast milk without modifications to protein structures. One application of protein modifications is in formula for infants with allergies. It is known that cow’s milk protein allergies are associated with specific protein components. The allergenicity of cow’s milk proteins can be reduced by modifying the conformation and/or structure of the protein associated with allergy. Typically, this is done by ‘cutting’ the protein into peptides. Depending on the level of hydrolysis, protein acquires different properties. A partially hydrolysed cow’s milk protein formula has reduced allergenicity and at the same time contains specific immunomodulatory peptides which can induce oral tolerance. An extensively hydrolysed formulas (eHFs) have very short peptides and amino acids, with almost no allergenic properties.

The specific quality, quantity and conformation of proteins are essential for safe growth and development.

– Sophie Nutten

Silvia Salvatore (Pediatria, Ospedale, Italy) built on these concepts with her presentation on hydrolysed protein in allergy. Hydrolysed proteins are commonly used in the therapeutic management of infants with allergic manifestations. They have long been proposed as a dietetic measure to prevent allergy in at risk infants. The generally accepted distinction between partially (pHF) and extensively hydrolysed (eHF) formulas is by molecular weight and percentage of peptide fragments. A pHF contains peptides with a molecular weight below 6 kilodaltons (kDa), typically ranging from 3–10 kDa. An eHF usually has more than 90% peptides below 3 kDa, with 1–5% of peptides above 3.5 kDa. Based on evidence from a meta-analysis, a whey pHF offers a valid option for primary allergy prevention. This pHF can be used for the prevention of atopic dermatitis in high-risk infants who are not exclusively breastfed. eHF based on cow’s milk protein is the preferred treatment option for infants with cow’s milk allergy who are not breastfeeding. The exceptions are infants who refuse, or do not tolerate eHF. In the most severe allergic cases, amino acid formula could be a solution. Importantly, protein molecular weight profile only differentiates protein characteristics but does not determine the allergenic properties of formulas.

The choice of the hydrolysed infant formula for allergy prevention or management should be based on scientific evidence of efficacy.

– Silvia Salvatore

Yvan Vandenplas (Universitair Ziekenhuis Brussel, Belgium) focused on the role of pHFs in the management of gastrointestinal (GI) disorders including constipation, colic and infantile regurgitation. Fifty percent of infants present with one or more symptoms of a functional GI disorder in the first year of life. pHFs result in more frequent, and softer stools. pHF, fortified with prebiotics and/or probiotics, appears to be a good option for the management of functional constipation in infancy. However, there are no studies evaluating the efficacy of pHF as a single intervention in constipated infants. Data suggest that pHFs may reduce infant colic, but dietary changes often include lactose reduction, supplementation with prebiotic oligosaccharides, inclusion of structured lipids, and decreasing the formation of calcium soaps. There have been no randomised clinical trials demonstrating the efficacy of pHF in infantile colic. Nevertheless, experience with pHF indicates that it can be a useful option if cow’s milk protein allergy is not a potential cause of colic. A prospective double-blind, randomised cross-over trial showed a statistically significant decrease in the mean number and volume of regurgitation. Although there were no associated serious adverse events, published long-term safety data are non-existent.

Based on limited available literature, pHF tend to have some beneficial effects on functional GI manifestation, such as regurgitation and constipation, although the evidence is insufficient to formulate a recommendation.

– Yvan Vandenplas
In this second session, presentations examined the composition of breast milk as the gold standard in early nutrition for term infants. The benefits of breastfeeding and concepts around metabolic programming were also explored.

Thibault Senterre (University of Liège, Belgium) presented data on protein hydrolysates in preterm infants. The few studies evaluating the use of protein hydrolysates in preterm infants used varying sources of protein, degrees of hydrolysis, and nutrient content. These studies demonstrated that an adequate source of protein is required in preterm formulas. Protein hydrolysates have been proposed in preterm infants to improve feeding tolerance. Several studies have shown that protein hydrolysates may accelerate gastric emptying and transit time in both term and preterm infants but the clinical benefit for preterm infants is unclear. Further data are required in this setting. There is some evidence supporting the use of protein hydrolysates in preterm neonates to prevent future development of atopic diseases. However, preterm infants are not at an increased risk of atopic disease later on in life. Further, most studies did not show a reduction in cow's milk protein sensitisation or allergic manifestations in these infants.

David Fleischer (Children's Hospital Colorado, United States of America) concluded the session with a review of the data on whether hydrolysed formulas are suitable for all infants. Hydrolysed formulas are increasingly being used worldwide primarily in infants of parents who cannot or choose not to exclusively breastfeed. There is a paucity of long-term data suggesting similar growth in infants fed HF and standard infant formula. Based on limited available literature, pHFs have some beneficial effect on functional GI disorders, such as regurgitation and constipation. A meta-analysis of formula consumption and the risk of atopic dermatitis (AD) found that infants fed pHF had a 65% lower risk of AD than those fed cow's milk formula. Other studies have identified differences between feeding with pHFs and eHFs. Feeding with partially hydrolysed whey formula (pHF-W) and extensively hydrolysed casein formula (eHF-C) had a preventative effect on the cumulative incidence of AD in high-risk children, lasting up until age 10 years (Figure 2), but there were no effects on asthma, allergic rhinitis, or specific sensitisation. pHF given to every formula-fed infant is a cost-effective intervention for the prevention of atopic disorders, such as AD but these effects cannot be extended to the prevention of other allergic diseases in the atopic march.

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**We use hydrolysed preterm infant formula in our clinical practice with good result, but more scientific evidence is needed for a formal recommendations** – Thibault Senterre

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**Current data support the use of hydrolysed formula for the prevention of AD in high-risk infants who are not exclusively breastfed** – David Fleischer

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**Figure 2. Preventive effect against atopic dermatitis up to age 10 years in high-risk children fed with pHF-W and eHF-C formulas in the first 4 months of life**

CMF: cow's milk formula; eHF: extensively hydrolysed formula; eHF-W, extensively hydrolysed whey formula; pHF-W: partially hydrolysed whey formula; eHF-C: extensively hydrolysed casein formula

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**Session 2**

**Protein in feeding of term infants**

Chairperson: Raanan Shamir
Co-chairperson: Weiping Wang

In this second session, presentations examined the composition of breast milk as the gold standard in early nutrition for term infants. The benefits of breastfeeding and concepts around metabolic programming were also explored.

Raanan Shamir (Tel-Aviv University, Israel) began the session with an overview of the benefits of breastfeeding. Breastfeeding offers extensive benefits encompassing nutritional, environmental, socioeconomic, psychological, as well as genetic interactions for both the breastfed infant and the breastfeeding mother. Therefore, exclusive breastfeeding is recommended for about 6 months, continuing for as long as mutually desired by mother and child. It should be noted that the extensive evidence on the effects of breastfeeding on health outcomes are based on

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<table>
<thead>
<tr>
<th>Infant health outcomes</th>
<th>Strong or casual evidence</th>
<th>Evidence in development</th>
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<tbody>
<tr>
<td></td>
<td>Gastrointestinal tract infection</td>
<td>Cognitive development</td>
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<td>Upper and lower tract respiratory infection</td>
<td>Atopic diseases</td>
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<td></td>
<td>Otitis media</td>
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<td></td>
<td>All</td>
<td>Obesity</td>
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<td></td>
<td>Sudden infant death syndrome</td>
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Table 1. Strength of evidence for improvement of infant health outcomes
breastfeeding had no effect on the prevalence of coeliac disease, even when gluten was introduced while breastfeeding.

Breast milk is the natural food for infants and is the optimal exclusive food for infants up to the age of 6 months. However, demonstrating specific benefits other than infectious complications is difficult.

Le Ye Lee (National University of Singapore, Singapore) and Sagar Thakkar (Nestlé Research Centre, Switzerland) shared consolidated data on the evolution of protein in breast milk during the first year of lactation and presented the results of their collaborative study on protein content in breast milk. The protein content of breast milk is higher in the early stages of lactation and decreases in later stages. In an observational, longitudinal trial conducted in the National University of Singapore, breast milk from 50 mothers (singleton-deliveries of 25 male and 25 female infants) was collected at 30, 60 and 120 days postpartum. Results show that protein content decreased over time. Conversely, lipid and carbohydrate content increased. The gender of the offspring may play a role in the nutrient content. The study has shown that although the protein and energy content in the breast milk of mothers with female infants are lower than those who were nursing male infants, both male and female infants had appropriate growth (Figure 3). Further studies are needed to confirm these differences, to investigate the changes in the other macronutrients and micronutrients, and to assess the impact of maternal diet on breast milk.

Breast milk adapts to the changing needs of growing infants

Ferdinand Haschke (Landeskrankenhaus Salzburg-Universitätsklinikum der PMU, Austria) continued the theme of this session with a presentation on the effects of early nutrition on growth, metabolism and body composition. Early nutrition and in particular the consumption of protein affects the growth of children; and accelerated weight gain during infancy and early childhood is a strong predictor of childhood and adult obesity. Breastfeeding, especially exclusive breastfeeding during the first 4–6 months and continuation of breastfeeding during the second half of infancy, appears to protect against childhood and adulthood obesity. Children fed high protein infant and follow-up formulas (protein concentrations >2.25 g/100 kcal) during the first year of life grew at a faster rate than the WHO standards. High protein intake stimulates the insulin-like growth factor (IGF) axis and insulin release, which is associated with a higher weight-for-length and body mass index at the age of 2 years. High protein intake also lowers the beta-oxidation of fatty acids, which is linked to higher early weight gain and increased body fat deposition. Infants on low protein formulas with modified protein (1.6-1.8 g/100kcal) between 3 and 12 months of age have slower weight gain than infants fed high protein formulas. Infants given modified whey base formula with 1.8 g protein per 100 kcal during the first 4 months have similar growth patterns as breastfed infants.

If the breastfeeding period is too short, term infants older than 3 months can be given clinically-tested low protein content infant formulas.

Bo Lonnerdal (University of California, United States of America) wrapped up this session with a presentation on the bioactive proteins and functional properties of breast milk. Bioactive proteins in breast milk confer both short- and long-term health outcomes. In the GI tract, milk proteins are involved in the enhancement of nutrient absorption, inhibition of enzymes, enzyme activation, growth stimulation, modulation of the immune system, and defence against pathogens. Some proteins in breast milk are comparatively resistant towards digestion, exerting their functions in the GI tract in intact form or as larger fragments. Examples of proteins that are found intact in the stool of breastfed infants are lactoferrin, lysozyme and secretory immunoglobulin A (IgA). These proteins are resistant to proteolytic degradation in the gut, and offer protection against infection. They also support the immune function in the immature infant. Other milk proteins may be partially digested in the upper small intestine,
with the resulting peptides exerting functions in the lower small intestine. Alpha-lactalbumin, beta-casein, kappa-casein and osteopontin are examples of proteins that are partially digested and the resulting peptides are active in the gut, with functions that include stimulation of immune function, mineral and trace element absorption, and defence against infection.

// Bioactive protein in breast milk are likely to contribute to the advantages of breast-feeding // – Bo Lonnerdal

Session 3
Protein in Feeding of Preterm Infants
Chairperson: Jatinder Bhatia
Co-chairperson: Jianxing Zhu

The role of protein in preterm infant nutrition was the focus of this third and final session of the workshop. In this session, presentations explored breast milk fortification to meet the nutrient needs of preterm infants, and the role of parenteral nutrition for extremely low birth weight infants.

Jatinder Bhatia (Georgia Regents University, United States of America) kicked off the session with an overview of breastfeeding and breast milk fortification for preterm infants. Breast milk reduces the incidence of necrotising enterocolitis and sepsis in preterm infants. There is also evidence showing long-term benefits in neurocognitive development. Insufficient milk supply, the variability of nutrient composition of human milk and the limitation of human milk itself makes adequate nutrition a challenge for low birth weight infants. The nutritional requirements of preterm infants are higher than that of term infants. Protein content of mature milk is usually insufficient to meet the nutritional demands of a rapidly growing infant. Mature milk also does not have adequate quantities of calcium, phosphorus and vitamin D to support bone health. Energy density of human milk declines over time. Donor milk, which is recommended in situations where maternal milk is not available, has low protein and energy content. This is because most donor mothers have also been breastfeeding for months. Donor milk also typically contains low levels of vitamins and bioactives due to pasteurisation. Therefore, fortification and appropriate fortification methods are important to meet nutrient requirements of preterm infants, while protecting the beneficial effects of human milk itself. Figure 4 illustrates the different stages in addressing the nutritional requirements of preterm and low birth weight infants.

Ekhard Ziegler (University of Iowa, United States of America) continued the session by outlining the challenges in meeting the protein needs of preterm infants. As preterm infants have a high rate of growth, they also have high nutritional requirements. These requirements have been estimated by the factorial method based on the body composition of the foetus. An example of the estimated protein and energy needs for growth of the preterm infant is shown in Table 2. Although infant formulas can provide the nutritional requirements of preterm infants, breast milk remains the preferred choice for preterm infants. However, breast milk must be fortified. There is also the problem of variability of the composition of expressed milk. High intakes of protein may be dangerous for premature babies. For this reason, protein content of fortifiers should be kept low when the

Table 2. Requirements for protein and energy

<table>
<thead>
<tr>
<th>Body weight (g)</th>
<th>600-700</th>
<th>700-900</th>
<th>900-1200</th>
<th>1200-1500</th>
<th>1500-1800</th>
<th>1800-2200</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight gain (g/d)</td>
<td>13</td>
<td>16</td>
<td>20</td>
<td>24</td>
<td>26</td>
<td>29</td>
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<tr>
<td>(g/kg/d)</td>
<td>21</td>
<td>20</td>
<td>19</td>
<td>18</td>
<td>16</td>
<td>14</td>
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</table>

Protein requirement (g/kg/d)

- Parenteral: 3.5, 3.5, 3.5, 3.4, 3.2, 3.0
- Enteral: 4.0, 4.0, 4.0, 3.9, 3.6, 3.4

Energy requirement (kcal/kg/d)

- Parenteral: 89, 92, 101, 108, 109, 111

Protein/Energy (g/100 kcal): 3.8, 3.7, 3.4, 2.8, 2.6, 2.6

// One of the key elements in meeting the nutritional requirements of preterm infants is reducing the time to regain birth weight // – Jatinder Bhatia
protein content of expressed milk is high. Consequently, preterm infants typically have very low protein intake. Other reasons for inadequate protein intake in this population include slow feeding advancement and low feeding volumes, as well as the lack of feedback to the caretaker on whether their preterm infants are growing adequately. Growth is considered to be inadequate when there is evidence of neurodevelopmental impairment.

// We need to know what the growth of premature infant is like when neurocognition is no longer likely to be impaired //

– Ekhard Ziegler

Atul Singhal (University College of London, United Kingdom) then presented on protein intake and long-term health in the preterm infant. Studies since the early 1980s have supported the notion that preterm infants need high protein intake to achieve a post-natal growth rate close to the intra-uterine rate of growth of a normal foetus of the same gestational age. Growth faltering and poor growth in head circumference are signs of suboptimal nutrition. Extensive observational evidence has shown that suboptimal nutrition in the early post-natal period, as well as inadequate protein intake, are linked to impaired long-term neurocognitive development. Nevertheless, the effects of high protein supplementation in improving cognitive function in preterm infants have yet to be established. Accelerated post-natal weight gain has been linked to cardiometabolic diseases in adulthood. This has been proven in both randomised and observational studies. The current nutritional policy for preterm infants is based on the widely accepted consensus that supporting optimal neurodevelopment is the neonatologist's highest priority. Therefore, on balance, this policy favours early high protein intake in order to improve cognitive function. This is irrespective of any increase in cardiovascular risk. However, this consensus is largely based on evidence from infants <31 weeks’ gestation. It is not known if the risk-benefit of this accelerated weight gain differs for larger, more mature, healthy preterm infants than those with extreme prematurity. Furthermore, the critical window for these effects is unknown. The jury is still out on whether the same nutritional policy should apply after discharge.

// There is a need to investigate the optimal target of postnatal weight gain in terms of the cognitive and cardiovascular outcomes in later life //

– Atul Singhal

Chris van den Akker (Erasmus MC – Sophia, The Netherlands) reviewed the evidence around foetal nutrition and protein metabolism. Although postnatal nutrition and other forms of neonatal care have improved, stunted growth and suboptimal outcomes are still common. Inadequate nutrition plays a role in this. Therefore, amino acids should be administered early and in large amounts starting from birth. Over the last few decades, several studies have investigated amino acid metabolism in premature neonates. The studies typically compared different nutritional regimens in terms of protein content. However, protein metabolism is influenced by many other factors. For example, the quality (individual amino acid composition) of the intravenous solution or enteral formula or concomitant energy intake may influence the efficacy of protein handling and, therefore, will ultimately have an impact on overall requirements. Amino acid requirements of preterm infants through the different postnatal stages need to be determined. Non-nutritional factors influence the requirements for, and tolerability of, amino acids, but these are hardly ever studied. The effects of intra-uterine growth restriction, and nutritional needs during and following additional critical illnesses (besides prematurity itself) should also be studied. Our knowledge of foetal and neonatal physiology helps us understand the amino acid requirements of stable preterm infants. However, little is currently known about the requirements for specific subgroups such as small for gestational age or stressed infants with multiple concomitant diseases.

// Knowledge on foetal nutrition gives us an insight into the capabilities of metabolism and growth and could help improve neonatal nutrition strategies //

– Chris van den Akker

Virgilio Carnielli (Polytechnic University of Marche, Italy) gave the last presentation at this conference. He spoke about amino acid intake in parenteral nutrition. Many extremely low birth weight infants require parenteral nutrition for different lengths of time, but the indication to provide parenteral nutrition has changed throughout the years and varies from centre to centre. Amino acids are the key ingredient of parenteral nutrition. These nutrients promote anabolism and optimal cellular development, with the final goal of reducing postnatal growth restriction. It is widely known that postnatal growth restriction is associated with neurodevelopmental delays. It is therefore important to provide amino acids as soon as practicable, even on the first postnatal day. A minimum of 1.5 g/kg/day is needed to achieve an anabolic state. To promote growth, 2.5 g/kg/day of amino acid intake is required. The benefits of an amino acid intake above 2.5 g/kg/day remain undetermined. There have been two randomised controlled trials of parenteral nutrition with high dose amino acid. These studies did not show short-term growth benefits, nor any improvements in neurodevelopment at two years. Studies with an amino acid intake above 2.5 g/kg/day with added energy have shown that preterm infants have some improvements in short-term growth. Further research is required to confirm the effect. Although the early introduction of amino acids for these infants may be beneficial, the long-term effects are still unknown. Current data on parenteral nutrition in this setting are mainly derived from retrospective and cohort studies.

// The amount and composition of the nutrients in parenteral nutrition, the increasing use and the variable amount of minimal enteral feeding and the progression to enteral feeding are some of the factors that affect the outcomes of parenteral feeding //

– Virgilio Carnielli
Conclusions
The 86th Nestlé Nutrition Institute Workshop themed Protein in Neonatal and Infant Nutrition: Recent Updates focused on hydrolysed protein as well as the use and importance of protein in term and preterm infants. Breast milk is the best food for infants. In situations when breastfeeding is no longer possible, infant formulas containing partially hydrolysed whey proteins are recommended for infants at risk for allergy, as a scientifically proven and cost-efficient way of preventing atopic dermatitis. An extensively hydrolysed infant formula with proven efficacy can be used in infants with allergy to cow’s milk protein. The other benefits of the hydrolysed cow’s milk protein can be considered for preterm infants or full-term infants with functional GI symptoms. The content and composition of breast milk change over time depending on the stages of lactation to cater to the specific nutritional and growth needs of the infant. When breastfeeding duration is short, low protein formulas can help maintain an appropriate growth rate similar to breastfed babies. Low protein formulas are therefore more appropriate than high protein formulas as the former may reduce the risk of cardiometabolic syndrome later on in life. In preterm infants, breast milk alone cannot meet high nutritional requirement therefore appropriate nutrition strategies including human milk fortifications are required. A balanced approach to feeding in preterm infants is called for. This is because sufficient protein is required to avoid the risk of infection and impairment in neurocognitive development. However, too much protein has also been proven to increase the risk of cardiometabolic syndrome in adulthood.

“Consider the whole spectrum of benefits of breastfeeding, recognise the limitations of research on breastfeeding and continue to protect, promote and support breastfeeding”

– Raanan Shamir