Maternal nutrition and optimal infant feeding practices: executive summary[1–5]

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ABSTRACT

Much recent attention has been paid to the effect of the fetal environment on not only healthy birth outcomes but also long-term health outcomes, including a role as an antecedent to adult diseases. A major gap in our understanding of these relations, however, is the effect of maternal nutrition and nutrient transport on healthy fetal growth and development. In addition, this gap precludes evidence-based recommendations about how to best feed preterm infants. The biological role of the mother and the effect of her nutritional status on infant feeding extend to postnatal infant feeding practices. Currently, evidence is incomplete about not only the composition of human milk, but also the maternal nutritional needs to support extended lactation and the appropriate nutrient composition of foods that will be used to complement breastfeeding at least through the first year of life. Consequently, a conference, organized by the National Institute of Child Health and Human Development, the National Institutes of Health Office of Dietary Supplements, and the US Department of Agriculture Children's Nutrition Research Center was held to explore current knowledge and develop a research agenda to address maternal nutrition and infant feeding practices. These proceedings contain presentations about the effect of maternal nutrition and the placental environment on fetal growth and birth outcomes, as well as issues pertaining to feeding preterm and full-term infants. *Am J Clin Nutr* 2007;85(suppl):577S–83S.

KEY WORDS Maternal nutrition, infant feeding, NIH/USDA conference

INTRODUCTION

Much recent attention has been paid to the effect of the fetal environment on not only healthy birth outcomes but also long-term health outcomes, including a role as an antecedent to adult diseases (1). However, fundamentally, the ability to determine the actual effect of the fetal environment on these subsequent outcomes demands a better understanding of the specific elements of that environment. A major gap in that understanding is the intimate and inextricable role of maternal nutrition and nutrient transport in healthy fetal growth and development. Aside from an inability to pinpoint the mechanism or mechanisms by which the fetal environment might ultimately lead to long-term health consequences, this gap has resulted in an inability to make evidence-based recommendations about how best to feed infants whose access to that environment has been prematurely interrupted.

To develop an efficacious evidence-based approach to the care and feeding of preterm and low-birth-weight (LBW) infants, a need exists for a better appreciation of the source of nutrition that has been interrupted. This would dictate a better understanding of the nutritional needs of the mother and the process by which those needs are translated into healthy growth and development of the fetus. In addition to essential nutrients, the placenta supplies the fetus with hormones, growth factors, immunoglobulins, and other immunoactive factors. At present, we cannot deliver these components to preterm infants during the early postnatal age to optimize their growth and development. A need exists to ascertain how to substitute the third-trimester functions of the placenta postnatally, so that the growth and development of preterm infants is optimized.

The biological role of the mother and the effect of her nutritional status on the care and feeding of her infant obviously do not end with birth. With regard to the care and feeding of full-term infants, current World Health Organization policy for infant feeding endorses the use of exclusive breastfeeding as the preferred sole source of nutrition for the first 6 mo of life, with continued breastfeeding for up to 2 y (2). This policy assumes an evidence base with regard to the ability of human milk to meet infant needs for the first 6 mo, and an important role for complementary foods at 6 mo and beyond. Currently, in terms of the composition of human milk, the evidence is incomplete with regard to both maternal nutritional needs to support extended

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[2] From the conference "Maternal Nutrition and Optimal Infant Feeding Practices," held in Houston, TX, February 23–24, 2006.

[3] The conference was sponsored by the National Institute of Child Health and Human Development (NICHD), the Office of Dietary Supplements (ODS), NIH, US Department of Health and Human Services (DHHS) and the USDA/ARS Children's Nutrition Research Center at Baylor College of Medicine and was cosponsored by Ross Products. The publication of these proceedings was co-sponsored by the NICHD, ODS, NIH/DHHS, and USDA/ARS Children's Nutrition Research Center and Ross Products.

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lactation and the nutritional composition of foods that will be used to complement breastfeeding at least through the first year of life. Consequently, a need exists to assess our current knowledge about feeding of full-term infants during the first year of life.

To have a full appreciation of the evidence base, address critical needs and gaps in understanding about current strategies for feeding expectant and lactating mothers, preterm and LBW infants, and term infants through the first year of life, the National Institute of Child Health and Human Development (NICHD), the NIH Office of Dietary Supplements (ODS), and the US Department of Agriculture Agricultural Research Service (USDA/ARS) Children's Nutrition Research Center held a conference to address these core issues. The workshop was divided into 3 main topical sessions:

1) Effect of maternal nutrition and the placental environment on the periconceptional period (embryogenesis, implantation), fetal growth, and birth outcomes;
2) feeding preterm infants; and
3) feeding full-term infants.

The following is a summary of the articles presented and the deliberations of the workshop attendees.

SUMMARY

Session I: introduction and overview

The opening session provided an overview of the general issues contributing to LBW and preterm birth from a global perspective. Presenting from the perspective of a developed country, Robert Goldenberg of the University of Alabama at Birmingham observed that despite better perinatal outcomes compared with those in underdeveloped countries, adverse pregnancy outcomes, specifically in relation to preterm birth, are more common in the United States than in other developed countries (3). These result in both excessive medical costs in the perinatal period and increased risk of long-term neurological disability. Preterm births represent ≈12% of all births in the United States. Goldenberg observed that *1*) there are wide disparities in outcome among different populations, with poor and black women having twice the rate of preterm birth that other women do; *2*) maternal thinness, defined as low pre-pregnancy BMI, is a strong predictor of both preterm birth and fetal growth retardation; *3*) in the United States, several nutritional interventions including high-protein diets, calorie supplementation, and micronutrient supplements (eg, calcium and iron and various other vitamins and minerals) have not generally reduced preterm birth or growth retardation; *4*) bacterial uterine infections play an important role in the etiology of earliest preterm births; however, antibiotic treatment either before labor for risk factors such as bacterial vaginosis or during preterm labor, have not consistently reduced the preterm birth rate; *5*) progesterone treatment during the prenatal period is likely to be efficacious in reducing preterm birth, but only for a small group of at-risk women; and *6*) the substantial improvement in newborn survival in the United States over the past several decades is mostly due to better access to improved neonatal care. By contrast, in developing countries, the rates of chorioamnionitis, neonatal sepsis, pneumonia, and death are considerably higher than in underdeveloped countries.

Goldenberg concluded by observing that because there is little evidence that we can reduce preterm birth or LBW, we should focus our energies on providing the best possible obstetric care for the mother and neonatal care for the infant. He also suggested a greater use of available technologies to identify growth retardation and spontaneous preterm delivery. The development and validation of methods to assess body composition of neonates in developing countries will also be an important step as will the development of new biomarkers for the assessment of fetal growth.

Session II: effect of maternal nutrition and the placental environment on the periconceptional period (embryogenesis, implantation), fetal growth, and birth outcomes

The talks in session II were devoted to our current understanding of the role of maternal nutritional status to fetal health and the processes by which essential nutrients are transferred from mother to baby in utero. The session opened with a presentation by Fred Battaglia, from the University of Colorado Health Sciences Center, who reviewed new developments in the study of the role of the placenta in the delivery of fetal nutrition (4). He began by discussing factors influencing the placental permeability to nutrients including a variety of membrane-bound transporters and the development of placental surface area. Recent studies have shown that the transport of glucose and amino acids from the mother to the fetus is determined, in part, by their concentrations in maternal blood, by their metabolism in the fetal liver, and by subsequent competitive inhibitory effects. In relation to intrauterine growth retardation, it is now increasingly recognized that alterations in placental perfusion also affect fetal hepatic perfusion. Finally, the need to more fully explore the role of nonglucose carbohydrates in fetal and neonatal nutrition and metabolism was emphasized. In a comment about interpretation of data from both animal and human subjects, Battaglia raised the question whether the intergenerational effects of nutrient-environmental interactions are unique to rodents.

The role of nutrient delivery and fetal development was discussed as case studies: folic acid by Asok Antony (5) and calcium by Steven Abrams (6). Antony reviewed the important functions of folic acid for DNA synthesis and the role of folate receptors in the normal development of the central nervous system and of several neural-crest-derived tissues, as well as the consequences of folate deficiency. He presented an overview of studies documenting the role of a placental folate receptor in transplacental maternal-to-fetal folate transport. He also described studies that used knockout mice models lacking folate receptors to further elucidate the developmental consequences of impaired folate transport. Studies utilizing controlled dietary folate restrictions have also been used to demonstrate adverse effects on reproductive performance, implantation, fetal growth, and other more subtle effects. Long-term follow-up studies again in animal models have provided evidence that folate deficiency during gestation results in behavioral changes, including an anxiety phenotype in adulthood that could be interpreted as being analogous to "antisocial behavior" in humans. Antony summarized his presentation by pointing out that the persistent high incidence of neural tube defects among women in Northern India underscores the urgency for more sustainable ethnocentric strategies for ensuring adequate folate status in women, particularly those living in food insecure or resource-constrained settings.

Abrams followed with a description of calcium transport across the placenta via active transport. He observed that important details of this transport, including the roles of vitamin D receptor and of estrogens, remain to be elucidated. Epidemiologic studies in humans have shown that the whole-body bone mineral content in newborns is related to gestational age, mother's birth weight, and smoking habits. Studies in the United States and India suggest that very low maternal calcium intake is associated with lower bone mineral density in infants. Currently, no published data can be found regarding the relative effect of maternal phosphorus intake. Similarly, the role of maternal vitamin D status in these processes is also unclear. Abrams did note that some data exist to suggest that maternal vitamin D deficiency may limit fetal bone mineral accumulation. However, there is no definitive evidence that improving maternal calcium or vitamin D status can have a long-term positive effect on childhood bone mass.

In preterm infants with low bone mineral mass, in utero rates of calcium accretion cannot be achieved by parenteral nutrition, by routine preterm infant formula, or by unfortified human milk. Although continuation of a relatively high level of mineral intake after discharge from the hospital can enhance bone mineral acquisition, the optimal length of such supplement, as well as which infants will require such therapy, has not been determined. Future studies should focus on the role of maternal vitamin D supplementation on fetal and infant bone mass, the mineral needs of very-low-birth-weight (VLBW) infants, the optimal duration of mineral supplementation, and the long-term consequences of such interventions.

The discussion after the presentations in session II resulted in the delineation of several research priorities, including identification and characterization of the following:

- Potential mechanisms mediating the interaction between maternal phenotype at conception, fetal growth, and health and growth of infants across different racial/ethnic groups and the additional effect of environmental setting, ie, sociodemographics;
- The effect of maternal food patterns (eg, high or low protein, sources of carbohydrate and fat) on the risk of maternal metabolic complications and fetal growth;
- The relation between uterine blood flow and pregnancy outcome and fetal growth;
- The effect of intrauterine growth restriction on the frequency of spontaneous preterm birth;
- The role of polysaccharides and polyglycans in establishing the colonic flora in VLBW infants;
- Optimal bacterial flora of the colon in LBW infants as determined by using RNA sequence data and determination of the effect of nutrient composition on ecology of the gut;
- The role of placental folate receptor in mediating maternal-to-fetal folate transfer in vivo;
- The mechanism of how gestational folate deficiency might lead to affective disorders in offspring including anxiety disorder;
- Critical periods in folate requirements and possible timing of prophylaxis to protect or ameliorate neurological disorders in offspring;
- Epigenetic effects of dietary folate deficiency on placental and fetal development;
- The most efficient, sustainable methods for delivery of periconceptional folate to women in resource-constrained settings;
- The effect of vitamin D supplementation for mothers at risk of preterm or small-for-gestational-age delivery and its effects on fetal growth and bone mineralization;
- The nutritional needs of infants weighing <700 g as related to bone minerals;
- The optimal length of feeding high mineral supplements after discharge from the hospital; and
- Interactions of calcium with other bone-related minerals or other micronutrients, eg, zinc.

Session III: feeding premature infants

The overriding concern raised in this session was the dearth of evidence with regard to best approaches for the nutritional management of preterm and LBW infants. PJ Sauer, of Beatrix Children's Hospital and Groningen University Medical Centre, Groningen, Netherlands, opened the session by asking, "Can extrauterine growth approximate intrauterine growth, and should it? " (7). Sauer noted that although normal intrauterine fetal growth has been considered to be the gold standard for the extrauterine growth of preterm infants, there are several reasons this standard might not be optimal or even possible, considering the current state of knowledge and the practical limitations involved in meeting this goal.

Sauer described several limitations of the extant data that have presented obstacles to our understanding of what might constitute "normal" and "optimal" intrauterine growth. One concern is that current assumptions about intrauterine gains in length, weight, and head circumference are based on cross-sectional data from preterm infants but with a range of etiologies, any of which could adversely affect growth. Sauer noted that in situ–based body-composition and growth data are scant.

He emphasized relative differences between the extrauterine environment and the intrauterine environment that are manifested in terms of the ability of newborns to regulate key body functions. In addition, newborns need to contend with the effect of clinical disorders and medical treatments that also alter the actual contribution of the infant to this regulation. Furthermore, the source of nutrition for newborn preterm infants is provided primarily via the gastrointestinal tract or intravenously rather than via the placenta or umbilical cord. The biological significance of these differing feeding routes has not been fully explored.

Additional issues affecting the newborn's metabolism include continuous exposure to pathogens and external stimuli, as well as the variable but often rapid postnatal maturation of the skin, which produces considerably different amounts and patterns of epidermal water loss. All these factors have significant effects on energy and substrate metabolism and growth but remain insufficiently studied to determine their relative effect on nutrient requirements.

Sauer discussed the relative paucity of data to support either short-term (gain in weight or length or change in body composition) or long-term (psychomotor development, or perhaps even development of biomarkers of risk for adult disease) outcomes of infant feeding practices. Clearly, growth and body composition in early age are influenced by the nutrition given in that period. It is possible to mimic intrauterine weight gain as well as the assumed intrauterine change in body composition by changes in

the composition of formulas and supplements added to the milk given to preterm infants. However, Sauer emphasized that although total body fat might increase in a manner consistent with intrauterine accretion, the distribution of body fat in preterm infants at term is different from that of newborn term infants. He concluded by stressing the need for further research in this area because current studies are too few, of varied scientific design and quality, and show highly disparate outcomes without obvious rationale.

Michael Georgieff, University of Minnesota, followed with an overview of nutrition and the brain, nutrient priorities, and measurements (8). He noted that nutrients and growth factors regulate brain development during fetal and postnatal life and emphasized both the vulnerability and the potential plasticity of the developing brain. He reviewed extant data on several essential nutrients that have been most often associated with brain development, including protein, energy, certain fats, iron, zinc, iodine, selenium, vitamin A, and folate. He noted that the effect of any nutrient deficiency or overabundance on brain development will be governed by the principle of "timing, dose, and duration" of the abnormal malnutrition and provided evidence to support each of these principles. In the context of timing, he stressed the importance of knowing which brain areas are developing in a particular period and whether they have a high requirement for a given nutrient during that critical period of development. The ability to detect the specific effects of nutrient deficiencies is dependent on this knowledge and having neurological assessments that tap into the functions of those specific areas. He offered several examples of the effects of specific nutrient problems on specific brain areas and functions and tests that could confirm such effects.

Georgieff observed that almost all insults during the mid-to-late gestational period alter frontal lobe development, resulting in poorer executive function, planning, and spatial memory in preterm infants, and are more severe in preterm infants with intrauterine growth retardation than in preterm infants with normal intrauterine growth. Overall, circuit-specific behavioral and neuroimaging tests are being developed for use in progressively younger infants to more accurately assess the effect of nutrient deficits while the subject is deficient and after recovery from the deficiency.

Georgieff offered a brief list of research priorities:

- Identification of critical periods of brain sensitivity to suboptimal nutrient intake;
- Determination of the ideal timing of interventions intended to "repair" deficiencies in brain growth and development and even from brain injuries (stroke, hypoxic-ischemic encephalopathy, hypoglycemia); and
- Development of more sensitive and specific tests for assessment of developmental outcome (ie, beyond the Bayley scales).

Scott Denne, from Indiana University, followed with a presentation on the regulation of proteolysis and optimal protein accretion in extremely preterm newborns (9). Denne reviewed the extant literature documenting that current practices regarding protein accretion and growth are suboptimal for extremely low-birth-weight (ELBW) infants. He offered possible approaches to modulating this nearly universal deficit in protein growth, including inhibiting proteolysis to preserve existing protein stores and affect protein accretion. He noted that proteolysis is not reduced in preterm infants by physiologic increases in insulin concentration produced by glucose infusion. However, delivery of pharmacologic concentrations of insulin can effectively suppress proteolysis in ELBW infants, although it may be accompanied by significant lactic acidosis. Whereas they can produce meaningful increases in protein synthesis, perhaps even approaching normal in utero growth rates when given in sufficient quantities, intravenous amino acids have not been shown to consistently reduce proteolysis in preterm infants. Some evidence does exist to indicate that altering the amino acid composition of parenteral nutrition may more effectively reduce proteolysis in preterm infants.

Delivery of calorically sufficient parenteral nutrition solutions produces only minor decreases in proteolysis in ELBW infants, albeit substantially less than the reductions achieved in term infants. Some preliminary data also suggest that combining enteral and parenteral nutrition may more effectively reduce proteolysis in preterm infants. Moreover, current enteral preterm formulas do not appear to provide protein in sufficient quantities for optimal protein accretion and growth. However, recent evidence suggests that formula with a higher protein content can result in improved protein accretion and growth in preterm infants.

On the basis of this review, Denne outlined several suggestions for research beginning with studies to identify those factors that provide the best opportunity for promoting protein accretion, ie, is it just the level of nonprotein calorie intake that is most important in promoting net protein balance, or is there evidence that would favor carbohydrate versus fat? An additional need is for evidence to support a better understanding of the interaction between energy and protein intake and their relative effect on protein balance. A related question would be whether a scaled approach to protein intake should be developed that reflects protein requirements that are dependent on fractional protein synthesis and growth rates. For example, should nutrient regimens provide more protein at 24–26 wk ($4\ g \cdot kg^{-1} \cdot d^{-1}$), less at 32 wk ($2–3\ g \cdot kg^{-1} \cdot d^{-1}$), and even less at term ($2\ g \cdot kg^{-1} \cdot d^{-1}$)? Or, echoing themes raised by Sauer, is it the case that despite best efforts to provide optimal protein and energy intakes early after birth to match estimated gestational requirements, medical complications limit nutrient intake and, therefore, produce a deficit in nutrient supply and body protein and energy balance that requires continued efforts to achieve higher nutrient intakes and catch-up growth to meet gestational-age-specific growth rates and body compositions? Other suggestions included

- Conduct of large clinical trials to test the efficacy and safety, including long-term developmental outcomes as well as growth in length, height, and body composition, of higher-protein formulas;
- Testing of different combinations of parenteral plus enteral nutritional strategies;
- Basic clinical research to determine the role of enteral nutrition in preventing proteolysis and enhancing protein accretion;
- Basic clinical research to determine the effects of altering the amino acid composition of existing intravenous amino acid solutions; and
- Evaluation of higher protein contents of milk fortifiers and development of a more optimal form of protein supplement for milk and formula supplementation.

The role of human milk in feeding LBW and preterm infants was reviewed by Richard Schanler of North Shore University Hospital (10). Schanler noted that the beneficial effects of human milk extend to the feeding of preterm infants, because their nutritional support must be designed to compensate for metabolic and gastrointestinal immaturity, immunologic compromise, and maternal psychosocial conditions. Significant effects, such as reduction in sepsis and necrotizing enterocolitis (NEC), have been reported for preterm infants fed their mothers' milk. However, nutritional concerns arise because the quantity of nutrients in preterm human milk may not meet the greater nutrient needs of infants born weighing <1500 g. Human milk supplements, or fortifiers, are available to augment the nutrient content of mother's milk. Host defense benefits also are observed in preterm infants receiving fortified human milk.

Availability of milk is an issue for mothers delivering prematurely. Donor pasteurized human milk has been suggested as a proxy for mother's own milk, but pasteurization appears to limit some of the potential benefits.

In conclusion, Schanler offered several questions and areas for future research. Among these were the need to identify the limits of the protective effects of human milk in preterm infants, eg, is there a dose-response relation? How should milk be processed, if pasteurized, to preserve host defense protein and factors? Another priority would be the determination of those nutritional regimens that are optimal for hospitalized preterm infants weighing 1500–2000 g. Additional topics included

- The optimal nutritional regimen for breastfed preterm infants during the postdischarge period;
- Whether mineral and protein supplements should be provided to breastfed preterm infants; and
- How can maternal lactation performance be improved for the mothers of preterm infants?

Josef Neu, from the University of Florida, concluded this session with a presentation on gastrointestinal development in preterm infants and its effect on meeting the nutritional needs of preterm infants (11). Neu noted that the fear of NEC and feeding intolerance are major factors that inhibit the use of the enteral route to feed preterm infants. Although parenteral nutrition may help to meet many of the nutritional needs of these infants, exclusive intravenous feeding has significant detrimental side effects that include intestinal atrophy, sepsis, and increased susceptibility to inflammatory stimuli and systemic inflammatory responses.

Neu suggested that the use of minimal enteral nutrition or trophic feedings may partially alleviate these problems. However, other factors need to be taken into account. These include the macronutrient composition of the minimal enteral or trophic feedings and the microecology of the intestinal lumen.

In addressing the need for further research, Neu itemized several priority areas:

- An understanding of the microecology of the developing gastrointestinal tract;
- Increased efforts to understand the normal role of the preterm gut microflora and the potential of probiotics (safety, efficacy, mechanisms of action, testing paradigms, etc);
- Elucidation of the short- and long-term effects of loss of the normal microflora in preterm infants, eg, after use of broad-spectrum antibiotics;
- How to feed the developing gastrointestinal tract in sick preterm infants in the first days to weeks of life;
- A better understanding of how to best use the gastrointestinal tract in VLBW sick infants in the first weeks postnatally to minimize the use of total parenteral nutrition and its attendant complications;
- Exploration of the possibility of developing an enteral formulation that specially promotes intestinal growth and development, prevents systemic inflammatory response syndrome, and improves motility: and
- Studies to determine the efficacy and safety of new formula compositions that might selectively promote gut growth and development, including formulas with a higher protein content overall as well as with the addition of selective amino acids, fatty acids, and trophic stimulators such as glucagon-like peptide 2 and epidermal growth factor.

In the summary panel discussion, there was general consensus about the critical need for new research, both basic and clinical-translational, to develop more fundamental information about the optimal growth rate and change in body composition of preterm infants. Despite the growing success in terms of survival, preterm infant growth remains suboptimal. However, there was less unanimity of opinion about what this growth should consist of, how to determine what is optimal, or how to promote it. Higher protein intakes, both intravenously and in formulas and milk, were considered essential and studied utilizing large, randomized clinical trials as well as smaller developmental studies to test new protein supplements were recommended. Furthermore, it was suggested that such studies include evaluations of the role of rapid weight gain (overall and of body fat specifically) in producing obesity and its many complications throughout the life cycle.

Because most preterm infants have suboptimal brain growth and neurodevelopment, the role of macro- and micronutrient deficits in this pathology requires expanded attention. In this regard, because human milk appears to produce developmental advantages, despite limitations on body growth when not supplemented with more protein and calories, more research is needed to determine which components of milk are most advantageous and whether they can be isolated and added to formulas. Although caution was expressed about the use of donor human milk, the need for further research to promote lactation in the mothers of preterm infants was emphasized.

For both human milk and formula, more research is needed to determine optimal enteral feeding, in terms of nutrient mixtures and specific supplements that promote gut growth and development. An additional area of interest would be the development of methods to promote gut motility and gut blood flow. Supplements to be studied should include those that affect the microecology of the gastrointestinal tract as well as its growth and function.

The participants acknowledged that although many advances in intravenous and enteral nutrition of preterm infants have been developed recently, the increasing survival at lower birth weights, the degree of immaturity of the surviving infants, and the increasing dependence on extrauterine nutrition of these vulnerable infants dictate a renewed interest in the absolute importance of postnatal nutrition. The diminishing frequency and severity of other disorders in these infants means that the many adverse long-term outcomes experienced by preterm infants can

no longer be attributed solely, or even primarily, to the consequences of other morbidities. Growth and development of sensitive organs, particularly the brain, clearly are dependent on unique, although variable, mixes of specific nutrients, provided at optimal rates and by safe and efficacious routes. There also is abundant evidence from animal experiments and human observational studies that prolonged undernutrition during critical periods of development (particularly but not exclusively between 22 and 40 wk postconceptional age) adversely affects long-term growth and neurodevelopmental and cognitive outcomes.

Despite advances in the nutritional care of preterm infants, the need to more fully define the specific needs of these infants must assume a higher priority for clinicians and researchers alike. The participants agreed that the community of caregivers and researchers is at a new threshold of refining the clinical armamentarium to include more specific evidence-based recommendations about what nutrients should be provided, at what rates, in what mixtures, and by what means to optimize the growth and development of these infants.

Session IV: feeding full-term infants

Session IV focused on issues pertaining to the postnatal nutritional needs of mothers and of infants born at term and through the first year of life. The issues surrounding the debate with regard to the optimal duration of exclusive breastfeeding were discussed by Ronald Kleinman, of Massachusetts General Hospital and Harvard Medical School (12). Kleinman presented an overview of the key issues and the extant literature on exclusive breastfeeding including a critical review of the evidence-based review that led to the current global policy on exclusive breastfeeding. He offered several factors that could militate against a definitive line of 6 mo as the optimal duration for exclusive breastfeeding. These factors are as follows: *1*) the proportion of infants throughout the world who do not consume adequate volumes of breast milk between 4 and 6 mo, when known, is significant; *2*) healthy full-term infants can digest and absorb the nutrients in foods commonly consumed as part of complementary feeding by 3–4 mo of age; *3*) the optimal period during which infant feeding influences later health is as yet unknown; *4*) the period during which complementary foods can begin to have an important influence on the development of taste, chewing, swallowing, and food preferences also remains to be established; *5*) human developmental milestones occur at a range of ages, rather than a specific time point for all individuals; *6*) the concentration of nutrients in breast milk, such as iron and zinc, that are critical for growth, immune competence, and cognitive and neuromotor development become limiting between 4 and 6 mo of age; and *7*) the age of introduction of complementary foods to confer protection against allergic disease in infants from families that are not at high risk of allergy (>90% of the population) is largely speculative.

On the basis of his review, Kleinman concluded that limited evidence exists to support a change in current recommendations for developed nations. Specifically, he noted that on the basis of the extant data there is no evidence of significant harm for 4 mo introduction and no significant benefit from exclusive breastfeeding for 6 mo in any of the health outcomes measured to date. Moreover, he noted that there has been no examination of risks for 6 mo of exclusive breastfeeding to the substantial portion of the population who are low-breast-milk consumers.

He emphasized the need for more randomized clinical trials and well-designed observational studies with a particular focus on subgroups (eg, low breast milk consumers, LBW infants) who may need earlier (ie, <6 mo) supplemental feeding. There is a paucity of evidence from either observational studies or randomized clinical trials to support excluding complementary foods before 6 mo of age; ie, there is limited evidence to support current recommendations for exclusive breastfeeding for 6 mo, particularly in the developed world. Little theoretical or empirical evidence exists to support the notion that healthy breastfed infants require complementary foods before 4 mo of age. Kleinman concluded that a need exists for well-designed randomized trials to address outstanding issues and to provide more definitive evidence to support recommendations for the optimal duration of exclusive breastfeeding.

Nancy Krebs, from the University of Colorado Health Sciences Center, concluded this session with a review of key issues associated with the timing and composition of complementary feeding (13). After outlining maternal (maternal nutritional status and milk composition) and infant-related factors influencing infant nutritional requirements during the first year of life (eg, birth weight and maturity, rate of postnatal growth, and infectious illness), Krebs highlighted several critical factors that might dictate the decision to introduce supplemental foods to breastfed infants. Prominently, by ≈6 mo, the amount of iron and zinc in human milk is unlikely to meet infant requirements without contributions from complementary foods. In describing potential sources of complementary nutrition, Krebs noted that plant-based foods, if not fortified, are low in both iron and zinc. According to available data, older infants in both the United States and in developing countries have total intakes of zinc that are well below estimated requirements. Although animal-based foods have been recommended as a good source of complementary nutrition for infants after 4–6 mo of age, such recommendations have not been commonly implemented in the United States or in international settings. Iron deficiency remains common in older infants and toddlers, and available evidence suggests that zinc deficiency is also common. Krebs concluded that the effect on growth, nutritional status, and functional outcomes of earlier and consistent intake of animal-based foods by breastfed infants after 6 mo should be systematically evaluated.

In the discussion of the presentation in session IV, several key research priorities emerged. These included

- The need for well-designed randomized clinical trials to assess the effect of differing durations of exclusive breastfeeding on critical short- and long-term health outcomes;
- Studies to assess the needs of subgroups of infants, eg low consumers and LBW and preterm infants, in the context of supplementary feeding and the timing and duration of exclusive breastfeeding;
- Studies of the effect of severe maternal undernutrition on health, lactation performance, and milk composition;
- Studies to identify strategies to improve maternal nutrition, particularly of those nutrients that might be limited in human milk as a consequence of poor maternal intake; and
- Studies to develop culturally acceptable highly nutritious complementary foods, particularly animal-based foods.

CONCLUSIONS

This workshop provided a sobering assessment of our current understanding of the critically important interface between maternal nutrition and infant health and feeding practices. We currently have very little useful information about how to feed preterm infants. The reason for that is that we do not have a clear appreciation of the role of maternal nutritional and health status on meeting needs for normal fetal growth and development. We similarly have little knowledge about the mechanisms by which that status affects the fetal environment. In light of all that we are learning about the potential role of the fetal environment in infant and child health and risk of subsequent development of chronic diseases, a concerted effort is needed to examine the mechanisms by which maternal health, ie, nutritional status, body composition, infection, etc, affects the fetal environment and possible risk of the myriad noncommunicable diseases. Perhaps more importantly, a better understanding of these issues would have immediate potential for refining our clinical acumen with regard to the feeding of LBW and preterm infants. An additional benefit would be seen in terms of translational activities such as the development of evidence-based messages with regard to the effect of maternal health on birth outcomes and our ability to meet public health goals for infant feeding. Finally, such an initiative would also have significant global interest and consequence.

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