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Executive Summary of the Workshop "Nutritional Challenges in the High Risk Infant"

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Abstract

In 2009, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) invited an expert panel to a workshop to address the current knowledge gaps and lack of evidence-based guidelines that preclude optimal nutritional care for infants in neonatal intensive care units. Since much research needs to be done in this complex area of science, the group was requested to propose new research to rectify current deficiencies in this field. This paper provides a summary of the workshop presentations and discussions.

Keywords

prematurity; preterm infants; intensive care; infant; nutrition

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Introduction

Pediatricians caring for preterm infants at the beginning of the 20th century faced the daunting challenge of providing nutritional support for their patients, who were surviving at increasing numbers due to the introduction of neonatal incubators. Over the course of a few decades, several key innovations followed. These included, but were not limited to, the invention of tube feeding, development of human milk banking systems, manufacturing of infant formulas, and, in the late 1970s through the 1980s, the introduction of continuous intravenous nutritional feeding.

Neonatal experts at the beginning of the 21st century are facing challenges identical to those faced by their professional colleagues a century ago. Recent advances in perinatal and neonatal care have dramatically increased survival rates of even the smallest and earliest born infants since the early 1980's.[1] Over the past 10-15 years, improvement in neonatal morbidity and mortality has plateaued.[2,3] A major concern, and part of the impetus for the Workshop on "Nutritional Challenges in the High Risk Infant", is that this flattening in neonatal morbidity and mortality might be due to inadequate or suboptimal (or both) nutrition of these extremely low birth weight (ELBW), extremely preterm and immature infants. Furthermore, newborn infants surviving from a variety of critical care conditions appear to require focused attention to optimize nutritional support.

There is growing evidence, for example, that the "routine" intravenous nutritional mixtures, human milk, or currently available infant formulas (even those designed for preterm infants) may not be appropriate for infants recovering from major surgical conditions, especially those involving the gastrointestinal system. Similarly, late preterm, low birth weight (LBW) newborn infants and those with congenital anomalies may need different nutritional requirements than growing healthy term infants. Thus, the healthcare team is challenged to develop focused strategies to meet high-risk infants' demands based on stage of development, prior and current growth disorders, and underlying disease process, as well as stages of recovery from serious medical and surgical conditions.

Given that more than 90% of preterm infants survive through their first birthday, there is an ever increasing fraction of the population of preterm infants that will survive to adulthood. It is now clearly appreciated that abnormal perinatal nutritional conditions link directly to and may actually cause adult-onset illnesses.[4-6] There also is a growing realization that technical advances in providing intensive care have outpaced advances in perinatal nutritional research. Thus, there is a considerable urgency to refocus attention on much needed research in the field of neonatal nutritional support

Now more than ever, we are facing new challenges for providing optimal nutritional support to the sickest and the smallest of newborn infants in our neonatal intensive care units (NICUs). The challenges are no longer limited to offering calories and proteins to promote weight gain. The challenges are more fundamental. There is new need to define what constitutes optimal postnatal growth; to find means of optimizing not only growth but also maturation (e.g., the immune system; the brain; the skeletal muscle system; and bone); and

need to provide improved and firmer foundations for nutrition of the sick newborn infant that will better promote growth as healthy children and adults.

To address these wide-ranging issues, one needs to explore knowledge gaps, and refocus a perinatal nutritional research agenda. Therefore, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) held a workshop in 2009 to explore knowledge gaps and refocus interest on a perinatal nutritional research agenda. This review provides a brief summary of the discussions held at this Workshop and is designed for researchers who deal with neonatal nutrition to consider for development of future investigations.

Fetal Nutrition and Long-term Implications

Healthy embryonic development is a prerequisite for healthy fetal growth and development. A variety of maternal and fetal conditions and genetic and environmental factors have been shown to influence embryonic and fetal development. It also is known that normal fetal growth is affected by maternal diet and nutrition. The specific components of maternal nutrition and intrauterine nutritional milieu that are needed to promote healthy fetal growth still need to be delineated.

Most studies related to fetal nutrition have assessed changes in fetal growth rates. While there are postnatal growth curves specific for African-American and Caucasian ethnic groups and for male and female infants, such standards are not widely used in clinical settings and do not reflect current demographic distributions. Moreover, the fetal growth curves currently in use have not been updated to reflect the contemporary population of pregnant women that has a higher proportion of those who are overweight or obese.

Meticulous assessment of fetal growth and growth rates can provide insights into fetal nutritional status. Normal growth curves have been developed for the fetus.[7] In a prenatal ultrasound study, Doubilet et al[8] reported that singleton fetuses subsequently born preterm were, as fetuses, smaller and grew at slower rates than their gestational age-matched controls who went on to be born at term gestation, even in the absence of identifiable causes for growth restriction. This lag in fetal growth in those who are born preterm occurs a few weeks prior to their birth. This may indicate that decline in fetal growth rate might be a signal of fetal malnutrition or illness, leading to preterm birth.

Normal fetal growth also requires adequate amounts of amniotic fluid and fetal swallowing activities. Although amniotic fluid composition, nutrients, and turnover rates vary across the range of gestational age and adequate placental health is critical for the volume and composition of the amniotic fluid, the exact nutritional value of the amniotic fluid for the fetus has not been well investigated. Birth before 29 weeks' gestation hinders the development of intestinal secretory functions, absorptive characteristics and motility. Amniotic fluid has growth factors, hormones, cytokines and nutrients that bathe the gastrointestinal tract and results in better performance when an infant reaches term gestation.[9] Fetal swallowing beyond 29 weeks of gestation is important in this process. Preterm birth and upper gastrointestinal anomalies disrupt this phenomenon. This critical

fetal mechanism for intestinal maturation and its contribution to nutrition of the fetus during the 3rd trimester requires additional investigation.

Some questions concerning fetal and preterm infant growth and growth rates for future researchers to consider are listed below.

1. What are the optimal growth rates for the fetus and preterm infants? The impact of maternal overweight and underweight status as well as obesity on growth rates is not well described. Gender-, race-, and ethnicity-specific growth rates are needed to define normal as well as abnormal fetal and neonatal growth.
2. The role of oxygen as a nutrient deserves further exploration. The impact of oxygen delivery on embryonic development, cell differentiation, growth, and development is not well understood.
3. Intrauterine growth restriction (IUGR) can be due to a single cause or multifactorial causes. Disorders in the uterus, placenta, and fetus all can be contributing factors. Advanced maternal diabetes with vascular disease and hypertension also results in IUGR. The role of each of these contributing factors in producing IUGR needs further investigation.
4. The impact of changes in gestational age-specific growth rates and body composition at critical periods of development are not well described. Fetal programming as a result of such changes in growth rate and body composition likely play a major role in future development of health and disease and need further investigation.
5. Ideal growth of the brain needs to be considered when studying somatic growth of the fetus. A healthy balance needs to be struck between optimal somatic growth while promoting normal fetal brain development and growth. Specific tools to assess fetal brain growth and determine its optimal development are needed.
6. Genetic determinants of normal and abnormal growth with a variety of additional factors including race, ethnicity, and gender need further investigation.
7. Pregnancy complications can significantly impact fetal growth and timing of these complications is likely to be gestational age specific with respect to the outcomes for the fetus. The rate of fetal growth and conditions such as fetal growth “insufficiency” are likely to be gender and gestational age-dependent and are in need of investigation.

There are critical periods when specific insults uniquely affect fetal development. Improvements in growth or insults to growth also depend on the duration of these events. Gestational age is shorter when the pregnant mother is under nourished, leading to important research raising the question of whether optimal nutrition of the pregnant mother could prevent prematurity? Related research should focus on the particular nutritional factors, including macronutrients and micronutrients, which contribute to optimal pregnancy outcome; these require coordinated studies in both mother and fetus, with emphasis on the role of the placenta in transferring nutrients to the fetus when changes in the diet of the pregnant mother are made. Such studies should include research on macronutrients as well

as micronutrients, with more attention to the interaction of these major classes of nutrients. With respect to abnormal fetal growth, life cycle studies should be developed to address longitudinal growth over time and generations. Development of model systems is desirable to study perturbations in growth, particularly with attention to gestational age.

Current Nutritional Practices: The Preterm Infant

Growth following birth can be investigated in several areas There are short term growth outcomes immediately following birth, matched versus mismatched growth between *in utero* and *ex utero* periods for preterm infants, and the impact of exogenous nutrition (enteral and parenteral) on physiological function.

Just after birth, there is an early window of nutritional management for which observational and interventional studies could potentially provide important information. Protein, fat, and carbohydrate intake and metabolism, energy expenditure, and temperature balance are all elements of an optimal nutritional environment. Practice strategies for parenteral nutrition are in flux, with increasing use of higher amino acid infusion rates earlier after birth, but there is no long term assessment of the value of this change in practice and no uniformity of practice according to known short and long term outcomes. Assessment of safety, efficacy, and appropriateness of both enteral and parenteral nutrition are needed to direct evidenced based practice.

Gut microbiota and gut development are integral to developing strategies for optimizing both enteral and parenteral nutrition. Gut development and the impact of feeding are likely gestational age and postnatal age dependent, both of these factors should be considered in study designs of optimizing nutrition after birth of preterm infants.

Further studies are needed to assess the long-term effects on growth, development, and particularly cognitive outcomes of the timing of initiation, initial volume, and rate of advancing feedings in the preterm infant. Nutritional management is likely to depend on prior fetal growth, gestational age at birth, and postnatal age. Total parenteral nutrition (TPN) has been lifesaving, but comes at a cost to infants that include delayed gut growth and major changes in the gut microbiota, as well as the known metabolic complications. Early provision of amino acids has been associated with improved growth at hospital discharge and less suboptimal head growth at 18 months of age.[10] Modification of TPN to minimize or eliminate hepatic toxicities deserves further investigation, as cholestasis remains a major problem in infants on long-term TPN.

There also are many unanswered questions related to the use of human milk in preterm infants, including the timing of colostrum administration, volume of feedings, and supplements added to human milk. While many have noted that human milk feedings are considered the best type of nutrition for all infants, including those born preterm, many problems remain with its use in these infants, not the least of which is the need to optimize supplements

Human milk is now known to contain probiotic bacteria in addition to lactoferrin, oligosaccharides, and lactose that promote their growth.[11-15] There is evidence that

lactobacilli upregulate the epidermal growth factor [EGF] receptor, thus increasing the effectiveness of human milk EGF in promoting intestinal growth and maturation. Dvorak [16,17] and other investigators[18-19] have shown the mitigating effects of feeding EGF on necrotizing enterocolitis in the neonatal rat model. Lactoferrin administration has been studied in the laboratory and is in need of clinical research.[20-22] One recent lactoferrin study shows promise for prevention of late onset sepsis.[23]

Several studies have been conducted to assess the impact of probiotic agents on necrotizing enterocolitis, sepsis and death.[24-28] A recent meta analysis from Australia concluded that probiotic supplements have significant benefits in reducing death and disease.[29] The meta analysis concludes that additional trials are unnecessary if a suitable product is available.[29] An accompanying commentary[30] to the meta analysis points out that no product has appropriate regulatory mechanism in place for assurance of quality in the United States.

Feeding strategies during the transition from parenteral to enteral intake are understudied. Supplementation of milk during the transition from hospital discharge to home and continued nutritional management during infancy need rigorous exploration, particularly in light of recent evidence demonstrating potential impact of changes in growth rate and body composition during this critical period on later development of problems of overweight, obesity,[31] insulin resistance, and diabetes.

Poorly studied potential long-term effects of suboptimal nutrition include alternations of the renal, cardiovascular, metabolic and neurological systems. Rapid catch up growth, though positive in the short term with respect to weight gain may have many long term ramifications. Is a moderate growth rate better? Does this help provide the required balance between regulated somatic growth without compromise to cognition? Prevention of growth failure in preterm infants may be better than trying to treat it after a period of growth failure is established. Thus, long term investigations assessing the association between aberrant fetal and postnatal growth and later glucose intolerance, hypertension, and renal abnormalities are essential

Brain maturation, growth, development, and function are important outcome measurements for assessing the nutrition of preterm infants. Such studies also should include the effect of the NICU environment and procedures, as well as the impact of somatic growth and movement on long term neurodevelopmental outcomes.[32] Nutritional strategies following brain injury may be important determinants of long-term outcomes including cognitive development, sensory outcomes, and motor outcomes. This may be particularly important in population subgroups of infants with bronchopulmonary dysplasia, gastrointestinal disease, and cardiac disease. Bone growth, composition, and health also are understudied. While most preterm infants regain bone mineralization later in infancy, the impact of the period of poor bone mineralization during the hospitalization of preterm infants remains uncertain and under studied.

Specific questions for current nutritional practice and intervention include the following highlighted areas for investigation:

1. Extremely low birth weight (ELBW), preterm infants face significant challenges including optimizing parenteral nutrition; initiation, advancement and method of feeding; fortification and supplementation of feedings; and use of banked human milk when mother's milk is not available.

2. Research barriers in this area include equipoise with current practices that are considered routine clinical practice in individual nurseries. Feeding practices, once established, may be very difficult to change or alter in such settings.

3. The research agenda for nutrition in the preterm infant includes standardization of nutrition practices that optimize outcomes in these infants. Examples would include various aspects of intravenous nutrition including protein, glucose/carbohydrates, and fats as well as additional nutrients which are essential for growth. The level of parenteral intake of amino acids suggested for extremely preterm infants is approximately 3.0 to 4.0 g/kg/day. Concern remains for azotemia and metabolic acidosis with higher amino acid intakes during parenteral nutrition.[33] The side effects of high amino acid intake are needed. Evidence indicates concern for protein load and higher blood urea nitrogen levels in the first week of life.[34] Proinflammatory effects and toxicity of parenteral nutrition components with respect to hepatic injury is an area for investigation of mechanisms causing injury, healing and repair, as well as prevention of toxicity. Failure of infants to feed or to be able to increase their feeding volume is an area that is markedly understudied.

4. The goals for nutrition should be optimum growth and development. A large majority of infants leaving the NICU following preterm birth have postnatal growth failure.[35] Post natal growth failure urgently needs research to define preventive strategies or interventions for optimizing outcomes in these infants. Optimal health includes the programming effects of early nutrition on short-and long-term health problems--late onset sepsis, NEC, rehospitalizations after NICU stay, and early origins of adult-onset diseases

5. The true requirements of vitamins, trace elements and minerals for optimal growth and development of preterm infants are unknown.

Human Milk feeding for Preterm Infants

Human milk functions as a source of nutrition and as a protective agent for the human newborn. The protective properties, which include immunomodulatory, anti-inflammatory, anti-oxidant, intestinal growth-promoting and epigenetic functions, have been shown to reduce the risk of short-and long-term morbidities in extremely preterm infants.[36]

Human milk confers long term benefit for infants in a dose-response relationship, with higher lifetime doses of human milk reducing the risk of atopy and increasing cognitive function. This same dose-response relationship was demonstrated in extremely preterm infants, with higher doses of human milk reducing the rates of rehospitalization and increasing Bayley scores at 18 and 30 months of age, corrected for prematurity.[37,38] Special populations including infants with surgical disease as well as neurologically impaired infants

may also benefit from human milk. Te benefits of donor milk may not be the same as the benefits of the mother's own milk.

Human milk varies widely within and between mothers with respect to volume, composition, and caloric density. Colostrum, the milk that flows in the first days after birth, contains high concentrations of high-molecular weight protective proteins that cross into the milk via the open paracellular pathways that close with the onset of lactogenesis II. Animal studies suggest that colostrum has its greatest impact on protection, growth and maturation of the gastrointestinal tract when received by the infant as "first feedings". Subsequently, mature human milk varies markedly in calories, primarily as a function of variability in the lipid content. Human milk lipid is not homogenized, and clings to collection, storage and feeding containers, further reducing the content that is delivered to the extremely preterm infant when these devices are needed.

Donor human milk has been used for preterm infants when mother's milk is not available in sufficient quantity. Donor human milk is available from commercial human milk banks, where it has collected from screened donors, pooled and pasteurized. Some, but not all human milk banks perform compositional analyses and provide this information on the individual milk containers. As a result of pasteurization, many protective components are either destroyed or their bioavailability is markedly reduced. However, donor human milk does not contain bovine protein, a fact that may be important for extremely preterm infants and those with surgical conditions.

For human milk feedings to be successful, evidence-based education that is specific to the NICU infant and family should be provided to the entire NICU team, including physicians, nurses and dietitians. This well-informed team should be encouraged to provide consistent counseling about optimizing lactation to provide as much human milk as feasible for preterm infants. The team should be knowledgeable about lactation technologies that optimize human milk feedings for NICU infants and families, including the creamatocrit and other milk analysis techniques, test-weights to measure milk intake and the use of evidence-based breast pump technology.

Specific areas for consideration of research include the following:

1. Standardize definitions for human milk feeding including colostrum, human milk, foremilk, hind milk, and mature milk and for the amount of human milk (e.g., dose) that is fed during the NICU hospitalization. .
2. Large randomized studies comparing donor human milk versus formula for preterm infants to determine if banked human milk offers advantage over commercially available formula. Studies regarding nutritional supplements of human milk for preterm infants are needed.
3. Mechanisms of human milk protection, specifically with respect to neonatal immunity for preterm infants
4. Optimum promotion of breast feeding and human milk use.

5. Standardization of commercial and private milk donors should be done to assure safety first in the use of donor milk. There is need for standardization of the milk testing to inform care providers about the composition (e.g., macro and micro nutrients

Neonatal Nutrition Niche Areas

There are many areas of neonatal nutrition in need of additional investigation. These include:

1. Amniotic fluid and growth factors – There is a growth promoting effect of amniotic fluid. Further investigation regarding potential use of amniotic fluid for postnatal growth may provide increased knowledge for clinical application.
2. Probiotics have been studied in over 2000 infants.[24-28] Meta analysis confirms beneficial effects of probiotics, but points out the need for a product with well-documented and reliable composition and with established safety.[29] Studies reported to date, have not demonstrated bacteremia with lactobacilli or bifidobacteria. Oxygenation of the blood may kill anaerobic bacteria translocated from the intestine. Questions remain as to the optimal probiotic(s), consistency of product, ideal target population, and timing of initiation and duration of treatment. The need for a product that has appropriate regulatory mechanisms in place to insure quality of the product has been identified as a major gap.[30] The importance of feeding probiotic bacteria goes beyond the concept of preventing necrotizing enterocolitis. Probiotic bacteria may enhance growth in prematurely-born infants, but more research is needed because controversy exists regarding their effectiveness.[39,40]
3. Prebiotics are gaining attention to promote optimal nutrition. The exact role(s) of prebiotics in the neonatal population needs further investigation.
4. Dietary supplements, including trace elements and vitamins, may hold promise for neonatal nutrition.
5. Transitional nutrition after birth to determine the optimal method, initiation, timing, quality, and quantity of feeding are important areas of study, particularly for the preterm infant. This needs to be tailored to the gestational age and medical status of the infant.
6. Nutritional monitoring of high risk infants to optimize outcomes including growth and neurodevelopment is needed.

In summary, nutritional management is a major challenge for the developing fetus and newborn. Very preterm and ill infants, in particular face many nutritional challenges. Optimal nutrition for growth and development to obtain the best outcomes for infants are desired. Neonatal nutrition and its impact on overall health throughout the life course must be examined to make progress in this area of medicine.

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