Nutrition and Health
Series Editor: Adrianne Bendich

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Sherma Zibadi *Editors*

Nutrition in Infancy

Volume 1

Humana Press

Nutrition and Health Series

Adrianne Bendich, PhD, FASN, FACN, Series Editor

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ISBN 978-1-62703-223-0 ISBN 978-1-62703-224-7 (eBook)
DOI 10.1007/978-1-62703-224-7
Springer New York Heidelberg Dordrecht London

Library of Congress Control Number: 2012952097

Printed on acid-free paper

Humana Press is a brand of Springer
Springer is part of Springer Science+Business Media (www.springer.com)

Preface

For millennia the importance is known to mothers and critical for child growth and survival. With the expansion of biomedical research in the late twentieth century fine details and specific solutions to prevention and treatment of childhood growth, diseases, and health can be defined. The editors have decades of research and interest in nutrition and health including editing a previous version of Nutrition and Infancy a dozen years ago. With many advances in studies on the role of foods and nutrients in childhood necessitated an updated version with expanded authors and topics in seven major areas as part of a *two volume set*.

Volume 1

Overview: global perspectives. This section begins with discussions of infant nutrition and lifelong health including adverse effects on infants in the Middle East and aboriginals in Canada. Developing problems for infants are reviewed on the role of fatty acids on neurological development and obesity.

Premature infant feeding. This section has six sections focusing on nutrition and premature infant health. These range from protein supplementation, colostrums, and total parenteral nutrition. Importantly these therapies effects on growth as well as defining knowledge and research gaps are discussed.

Breast feeding: growth and health. This historical and traditional method of infant feeding makes up one of two major sections of the book with nine diverse reviews. Breast milk has major roles in growth, development, obesity, and body composition. The causes and solutions to early breast milk feeding cessation. Thus the need to store breast milk and maintain their functions is critical to many mothers. Breast feeding in special populations including the Indian subcontinent vary. A variety of factors affect breast milk including maternal dietary salt, diet, milk oligosaccharides, and tobacco smoking are discussed to thereby modifying infant health. The question of breast milk and risk of subsequent breast cancer is reviewed. Importantly methods to improve use of breast feeding and its duration on infant growth and health are defined.

Micronutrients and healthy infant nutritional status. Clearly maternal supplement has been used to have effects on infants and benefits/risks are reviewed along with food fortification. Importantly the role of nutritional support of children with inborn errors of metabolism will be very helpful to physicians. Finally major vitamins are reviewed including vitamin A status assessment and role in health, vitamin K deficiency, and micronutrient deficiencies in infant skin problems. Magnesium is developing as a new mineral to use in infant health as described in its chapter.

Volume 2

Nutrition and neonatal/infant disease. Nutrition in infant diets plays key role in treatment of various challenging diseases and form the second major section with eight reviews. For examples, the reviews of intractable epileptic, chronic diseases, liver disease, short bowel syndromes, and Crohn's disease show important roles of diet to manage and treat them. Nutrition and diet supplement are reviewed as modulators of undernutrition-induced hearing loss, diabetes, and HIV-induced malnutrition. Hormones as therapy affect beneficially infants with kidney disease. Glangliosides are modified by diet affecting neurological development. The role of dietary supplementation in developmental or genetic disease like celiac disease, acute gastroenteritis, and intestinal failure are reviewed. Surgery is sometimes needed to correct birth issues and an example is reviewed, percutaneous endoscopic gastrostomy designed for children. In support of surgeries in infants the role of nutrition for those undergoing it is defined. Many diseases of infants have a nutritional component or therapy.

GI tract considerations. Parental nutrition can play important roles in the growth and development of the gastrointestinal tract of infants that need supplementation. This can include home parenteral nutrition in developing countries or low-income families. Colonic flora respond to diets and supplements and affect the infants' growth and development. Thus pro and probiotics are reviewed as potential over-the-counter prevention and therapies to treat disease and promote growth.

Formulas in health and disease of infants. Historically formulas with food and nutrition components have been used as therapies by physicians. Home and hospital parenteral nutrition are reviewed in two chapters. Two other chapters review parenteral nutrition in premature infants and promotion of safety in disease prevention. Parenteral nutrition is the major focus of this section. Probiotics and probiotics are novel and developing for disease therapy and promotion of infant growth. Protein nutrition is key for helping undernourished preterm infants.

Hormones and lipids: growth and development of infants. Hormones and lipids are becoming applied in diets, therapies, and from mother's milk to affect infants. Diet's role in managing hypercholesterolemia is defined. The role of infant adipose tissues and its hormones in changing infant development are carefully and completely reviewed. Maternal behavior and diet affect the infant as defined by clinicians in a review. Finally hormone therapy is described as it improves growth in infants with chronic kidney disease.

Summary. A wide range of nutritional and food-related therapies to prevent or ameliorate disease, growth retardation, and promote health are outlined by 113 experts in 59 chapters. This book becomes a definitive source for much of the methods and approaches to use nutrition to promote well-being in infants.

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Series Editor

The great success of the Nutrition and Health Series is the result of the consistent overriding mission of providing health professionals with texts that are essential because each includes: 1) a synthesis of the state of the science, 2) timely, in-depth reviews by the leading researchers in their respective fields, 3) extensive, up-to-date fully annotated reference lists, 4) a detailed index, 5) relevant tables and figures, 6) identification of paradigm shifts and the consequences, 7) virtually no overlap of information between chapters, but targeted, inter-chapter referrals, 8) suggestions of areas for future research and 9) balanced, data-driven answers to patient as well as health professionals questions which are based upon the totality of evidence rather than the findings of any single study.

The Series volumes are not the outcome of a symposium. Rather, each editor has the potential to examine a chosen area with a broad perspective, both in subject matter as well as in the choice of chapter authors. The editor(s), whose training(s) is (are) both research and practice oriented, have the opportunity to develop a primary objective for their book, define the scope and focus, and then invite the leading authorities to be part of their initiative. The authors are encouraged to provide an overview of the field, discuss their own research and relate the research findings to potential human health consequences. Because each book is developed de novo, the chapters are coordinated so that the resulting volume imparts greater knowledge than the sum of the information contained in the individual chapters.

"Nutrition in Infancy", edited by Professor Ronald Ross Watson, PhD, Professor George Grimble, PhD, Professor Victor R. Preedy, PhD, DSc, FRIPH, FRSH, FIBiol, FRCPath and Dr. Sherma Zibadi, MD, PhD clearly exemplifies the goals of the Nutrition and Health Series. The major objective of this comprehensive two volume text is to review the growing evidence that nutrition provided in utero and during infancy directly affects the entire lifetime health of the individual. This volume includes 60 up-to-date informative reviews of the current major dietary issues. Practicing health professionals, researchers and academicians can rely on the chapters in this volume for objective data-driven sources about essential vitamins and minerals, proteins, fats, and carbohydrates. This new comprehensive review of the science behind the nutritional strategies to assure the health of the neonate is of great importance to the nutrition community as well as for health professionals who have to answer patient, client or graduate student questions about the newest clinical research in nutrition and infancy.

"Nutrition in Infancy" represents the most comprehensive compilation of the recent data on the actions of specific essential nutrients and bioactive dietary components on fetal development and growth of the preterm and term infant. It is to the credit of Drs. Watson, Grimble, Preedy and Zibadi that they have organized this volume so that it provides an in-depth overview of the critical issues involved in the determination of the best nutrition for infants including those born preterm, those with medical conditions that require specific dietary interventions, those born in developing nations or in developed nations, those with special GI tract requirements and those with genetic factors that affect the metabolism of certain foods and/or nutrients.

Each of the two volumes contains about 30 comprehensive chapters. The first volume contains four related sections. The first section, an overview of global perspectives on infant feeding practices, contains seven chapters that include reviews of the history of breast feeding from the beginning of time up until present times; there are several unique chapters that describe the discovery of the infant requirements for vitamins and government projects to assure the nutritional adequacy of infant feeding programs. This is especially important when populations may be far from medical resources such as described in the chapters discussing infant nutrition issues in Aboriginal children living in remote regions such as in Northern Canada; infants from India, Pakistan, and Bangladesh; Middle East and North Africa. Infants can triple their birth weight during the first year of life and the quantity as well as the nutritional quality of the diet can affect the growth rate dramatically. The introduction of complementary foods during infancy in developing countries is usually dependent upon cultural norms and these are outlined for a number of African and East Asian nations in the next chapter. The final chapter in this section includes a synthesis of studies examining the potential for development of food allergies in children from developed countries. The chapter provides valuable discussions and tabulates the data on the importance of timing of introduction of specific foods to infants and subsequent development of asthma and/or allergies.

The second section contains six chapters on premature infant feeding. The chapter authors remind us that fetuses increase their weight 10 fold in the second and third trimester with concomitant gains in height and head circumference. Preterm birth may therefore result in stunted growth due to a variety of medical conditions. There is an important discussion of accurately determining whether a preterm neonate is small for its gestational age or growth retarded. If the birth weight is less than the 10th percentile-for-gestational age, this is defined as small-for-gestational age (SGA). Growth restriction and constitutional slow growth represent two distinct processes independent of SGA and are associated with different potential adverse outcomes. Potential maternal factors linked to preterm birth are reviewed in several chapters. These include smoking, gestational diabetes, infections, malnutrition, preeclampsia and most recently, excessive maternal weight as well as excessive maternal weight gain during pregnancy.

Preterm infants usually lose more weight after birth than term infants. Preterm infants require greater protein and lipid administration following birth and increased vitamin, mineral and caloric supplementation throughout the first year of life. The absorption and bioavailability of nutrients by the premature gut differs from that of the fetus that obtains nutrients across the placenta. The significant medical morbidities seen in preterm infants especially lung disease that requires ventilation and/or serious infections that require targeted nutritional interventions, add to the nutritional stresses seen in the preterm infant. The development of the microbiome also differs in preterm infants compared to term infants due to gut immaturity and medical conditions as mentioned above. Even when preterm infants reach term equivalent, their pattern of growth continues to differ from infants born at term. Thus, these chapters provide detailed information on methods used to evaluate growth and nutritional status in preterm infants.

One of the major considerations of preterm morbidity is that preterm infants exhibit intestinal wall immaturity which is measured as increased intestinal permeability. The importance of human breast milk and other sources of nutrients for the premature infant are discussed in a single detailed chapter. The authors discuss the fact that the gastrointestinal (GI) system doubles in length from 25 to 40 weeks' gestation. Preterm birth significantly increases the risk of necrotizing enterocolitis, an inflammatory cascade that leads to ischemia/necrosis of the intestines. This disease is found in 7-10% of very low birth weight infants who are usually born before the 25th week of gestation and is associated with 33% mortality and 33% long-term GI and/or neurodevelopmental morbidity. Several chapters review the data concerning the importance of glutamine and arginine in reducing gut permeability. Related to GI tract maturation is the availability of maternal colostrum. The chapter on colostrum reviews the immunological as well as nutritional importance of this first milk especially to very low birth weight preterm infants. Another important nutrient for the preterm infant is protein. Unlike term

infants who have a recommended daily protein intake of 1.5 g/kg/day for the first 6 months of life, the smallest preterm infant can have an increased protein need of about 4 g/kg/day and preterm infants >750-1500 grams require at least 3-3.5 g/kg/ day depending upon their medical conditions.

The preterm infant's protein requirements from parenteral and enteral sources are discussed in detail in the next two chapters. The chapters review the importance of parenteral nutrition (PN) for preterm infants. The provision of nutrients intravenously is complicated in adults, and it is extremely complicated in the smallest, least developed preterm infants. Not only are the procedures complex, but the administration of the correct balance of nutrients, fluids and maintenance of non-infective complications is of paramount importance. The determination of standards of growth for the preterm infant given parenteral nutrition is ongoing and several important studies are reviewed and extensively tabulated for the reader. These detailed chapters provide practice-based suggestions concerning the most critical aspects of assuring the health of the preterm receiving PN during the first days of life.

Nine chapters examine the role of breastfeeding in the growth and health of the term infant. The third section includes reviews of the nutritional value of human breast milk and the consequences of maternal smoking on these nutrients. There are also unique chapters on methods to improve the initiation and success of breastfeeding, another on potential reasons why infants stop breastfeeding and potential ways to restart breastfeeding; a chapter that reviews the totality of the evidence concerning the association of breastfeeding and cancer risks in the breastfed child, and a chapter on storage of breast milk with protocols tabulated for the reader. The section begins with a chapter on human milk oligosaccharides (HMO), complex carbohydrates abundant in human milk. Recent data show that HMO might protect very-low-birth-weight preterm infants from necrotizing enterocolitis. HMO help establish and maintain a healthy colonic microbiome. The authors remind us that currently there are no human clinical research studies with HMO.

The next chapter updates information concerning the role of breastfeeding duration and lowered risk of childhood and adult obesity. The authors objectively review the recent meta-analyses and also examine the data from studies with formula-fed infants. Maternal dietary factors that can affect breastfeeding duration are discussed in the chapter that describes the role of maternal dietary salt intake. Factors including maternal diabetes, obesity and undernutrition are examined in detail. Maternal smoking and/or fetal exposure to environmental tobacco smoke and its effects on the neonatal immune and respiratory systems is reviewed in the next chapter. There is a strong association between smoking exposure and increased risk of asthma and allergies in the neonate and the child of smoking parents. Moreover, maternal smoking is associated with reductions in oxytocin that is required for release of milk from the breast.

The fourth section, entitled "Micronutrients and Healthy Infant Nutritional Status", contains nine chapters that include examination of foods as well as individual nutrients. The prevalence of micronutrient deficiencies in infancy and in the second and third years of life are reviewed in the first chapter. Reference values from the World Health Organization are tabulated. Provision of supplements to expectant mothers is one strategy proposed to reduce infant nutritional deficiencies especially in developing countries. Supplemental iron, folic acid, calcium, zinc, vitamin D, vitamin A and other essential nutrients are discussed. Another strategy is food fortification that has the benefit of not having to change dietary habits. Successful fortification programs including iodization of salt, addition of iron and folic acid to staple foods and addition of vitamin A to rice are reviewed in detail.

The importance of examining the amino acid and protein sources and content of infant formulas is reviewed in the next chapter that reminds the reader that cow's milk and human milk differ significantly in their major proteins as well as the protein's amino acid concentrations. The potential consequences of these differences are discussed in light of the differences in compositions between currently available formulas. Taurine is considered a non-essential amino acid in adults, but may be essential to the developing embryo, fetus and neonate. The value of taurine for optimal development of the cardiovascular system is discussed in a separate, well-illustrated chapter. There is an additional chapter that reviews the importance of gangliosides in neuronal development and the value of

placental transfer and human breast milk as sources of gangliosides for the developing fetal and infant brain and nervous systems.

Determination of micronutrient deficiencies in infants, especially in developing countries where medical facilities may not be nearby, is of great importance as these are often multi-micronutrient deficiencies that can result in serious adverse effects. The chapter describing the cutaneous and mucous membrane manifestations of nutritional deficiencies reviews the symptoms that can be seen during the early stages as well as later deficiency diseases. In addition, treatment modalities for the most commonly seen vitamin and mineral deficiencies are described. One of the micronutrient deficiencies that may be overlooked is magnesium deficiency. The chapter on magnesium tabulates the requirements for this mineral in infants and young children, manifestations of low as well as high magnesium status and the consequences of these conditions in infants. Vitamin K is another essential micronutrient that may be low in the term infant and is often in very low concentrations in the blood of preterm infants. Vitamin K is essential for the synthesis of certain coagulation factors. If the neonate's plasma concentration of vitamin K is low, they may suffer from vitamin K deficiency bleeding, previously called hemorrhagic disease of the newborn. In the developed nations, neonates are supplemented with vitamin K immediately after birth. As described in the next chapter, neonates, and particularly those who are breastfed, benefit from prophylactic vitamin K but cost implications may be prohibitive in some regions of the world. The final chapter in this section reviews the importance of optimal vitamin A status in the mother and infant as a key determinant in maintaining the infant's natural immunity. Also included in the chapter is a discussion of the weaning transition time and diet as weaning is a risk factor for vitamin A deficiency. One strategy may be to improve maternal vitamin A status and her breast milk vitamin A levels so that the infant can build sufficient body reserves of vitamin A prior to the transition. Improving vitamin A content in weaning foods is also important.

The second volume of "Nutrition in Infancy" emphasizes clinical conditions found in infancy. Half of the second volume is devoted to reviews of the clinical significance of nutritional factors in infants with diseases and/or conditions that are either inherited or develop postnatally. Section E contains 17 chapters devoted to these critical practice- related topics. The first chapter in this section describes two examples of altered body composition in children; those with cerebral palsy and Down syndrome, both prevalent disorders with differing etiologies, but significant and opposite impacts on growth, body composition and nutritional status. These differences require separate approaches for accurate nutrition-related clinical assessment and management that are described in detail. The second chapter provides an extensive overview of the major nutritional consequences and treatments of inborn errors of metabolism. Conditions reviewed include amino acid genetic errors such as phenylketonuria, errors in carbohydrate metabolism resulting in glycogen storage diseases and errors in fat metabolism. The third chapter on epilepsy in infancy reviews the importance of the ketogenic diet which is a high fat, low carbohydrate diet with an adequate amount of protein that mimics the metabolic state of fasting during an anabolic situation. This special dietary regime is used in conjunction with anti-epileptic drugs and also when the drugs do not provide benefit to the infant or young child. The chapter includes detailed appendices and tables.

Seven of the 17 chapters examine serious acute as well as chronic gastrointestinal (GI) diseases. There is a unique chapter that describes the effects of inherited malformations in the cranium and/or oral cavity on the nutritional status of the infant and growing child. Also included in this chapter are discussions of maintenance of the early teeth and avoidance of caries. Even when cranio-facial development is normal, feeding difficulties can arise in the neonatal period due to biological, developmental or behavioral issues. Reduced efficiency in feeding often occurs when there is oral motor dysfunction, which is common in children with developmental disabilities. With regard to acute gastroenteritis, this is the commonest indication seen in children in emergency rooms in the US. Diarrhea, usually caused by viral infection, is reviewed in detail and provides current treatment methods depending upon laboratory findings, diagnosis and current nutritional status of the child. The detailed description of the physiology of the gastrointestinal tract provides excellent background information for

understanding the effects of pathological conditions discussed in subsequent chapters. Over 20 pathogenic conditions are described in detail including viral, bacterial and parasitic infections.

As described in the chapter on short bowel syndrome, intestinal failure is defined as the critical reduction of functional gut mass below the amount that is minimally necessary for adequate digestion and absorption to satisfy nutrient and fluid requirements for growth in children. Therefore the use of parenteral nutrition (PN) is required. Intestinal failure may result from intestinal obstruction, dysmotility, surgical resection, congenital defects, or disease-associated loss of absorption. Intestinal failure may be caused by short bowel syndrome (SBS), mucosal enteropathy, or dysmotility syndromes. SBS is a subcategory of intestinal failure, which may result from surgical resection, congenital defect or disease-associated loss of absorption. This condition is characterized by the inability to maintain protein-energy, fluid, electrolyte or micronutrient balances when on a conventionally accepted, normal diet. One of the mechanisms used to provide nutrition to the infant with serious gastrointestinal issues is the use of a gastric feeding tube (gastrostomy). The next chapter describes this procedure, its benefits and risks. The commonest reason for gastrostomy placement in children is neurological disability, either congenital or acquired brain injury; other causes include congenital heart disease, chronic lung disease, cystic fibrosis, congenital malformations that prevent swallowing and malignancy.

The chapters that review Crohn's disease, celiac disease, intestinal failure, acute and chronic gastroenteritis and liver diseases also contain clinically relevant discussions of signs and symptoms and current therapies including considerations of use of enteral as well as PN where warranted. The chapters include excellent tables and figures as well as guidelines for patient evaluations of macro and micronutrient levels that are often affected by these chronic disease states that often develop in infancy, during the transition to semi-solid foods from breast feeding, and/or in early childhood. Relevant data on occurrences in developed and developing nations are included. As there are many commonalities between the symptoms seen in these chronic conditions, including failure to thrive, diarrhea and stunting, each chapter author provides specific mechanisms available to determine the exact causes of the gastric distress.

The final five chapters in this section examine the nutritional effects of kidney disease, HIV infection and diabetes. The chapters on the effects of undernutrition on hearing capacity, and the ability to fight infections that may be associated with surgery in infancy complete this section. The common thread of potentially severe malnutrition associated with these conditions is reviewed with emphasis on clinically validated methods to overcome growth retardation and improve GI functions. Specifically, in the chapter on HIV infection, the WHO guidelines are included as well as tabulation of the clinical studies in HIV-infected mothers and multifactorial effects of breastfeeding. Another unique chapter describes the fetal development of hearing and reviews the anatomy and physiology of the auditory processes. The chapter examines the micronutrients most commonly associated directly or indirectly with hearing impairment including iodine, iron, zinc and vitamins A, B12 and D. The chapter on Type I and Type II diabetes reminds us that this is the most common metabolic disease in infants and children. Nutritional management during early childhood is described in detail. The final chapter in this clinically-focused section examines the effects of severe stresses on the infant that include events such as cardiac surgery and burns. Young children, due to their low protein reserves, are particularly vulnerable to the adverse nutritional effects of stress. The chapter reviews the role of nutrition support in helping to preserve skeletal muscle and support organ and immune function. The optimal levels of macronutrients, micronutrients, energy and nutrition support in critically ill children are unknown. Predictive equations may not adequately predict energy needs during critical illness. As all of the authors acknowledge, more research in the area of nutrition support for the acute and/or chronically ill child is urgently needed.

The sixth section contains five chapters that examine PN in detail as well as the importance of the microbiome in the infant, toddler and growing child. The two comprehensive chapters that describe PN in the hospital and home settings provide important clinical data. PN is the technique of artificial nutrition that provides the patient with fluids, energy and nutrients that are delivered directly to the

circulatory system through the venous network. This non-physiological path of nutrient provision results in a dramatically different gastrointestinal response than that with enteral nutrition as PN provides no trophic effect on intestinal mucosa. Descriptions of protocols for determining constituents of PN for infants in hospitals and home settings are included.

Three chapters examine the role of the microbiome in the health of healthy as well as infants with serious GI-related diseases. As described by the authors, at birth, the intestine is sterile and colonic function of the human infant is immature. The development of the infant's microbiome is described in detail. The development of the colonic functions, including water absorption and carbohydrate fermentation, is related in part to the intestinal microbiota. These bacteria have well-established metabolic functions and perform important inmunoregulatory roles. Data from the human microbiome project has begun to identify and characterize the microorganisms found in both healthy and diseased individuals. The chapters objectively describe the functions of beneficial microorganisms that are consumed, and are referred to as probiotics, and nutritional sources for the probiotics, that are referred to as prebiotics. The microbiome contributes to the nutritional welfare of the infant through its metabolism of complex carbohydrates, generation of short-chain fatty-acids as an energy substrate for colonic epithelia, and production of folate and other B vitamins. Prebiotics have been found to selectively stimulate favorable growth and/or activity of selected probiotic bacteria in the colon. Probiotics have been shown to be beneficial in the treatment of acute infectious diarrhea as these reduce duration and stool frequency. We are reminded that optimal prebiotic usage as well as probiotic strains and dosages for preterm as well as full term infant patients still remain to be determined.

The final section of the second volume examines the newest research on the importance of long chain lipids in the growth of infants and also reviews the data linking early nutritional exposure to the risk of developing hypercholesterolemia, premature cardiovascular disease and obesity. The first chapter reviews in detail the value of lipid emulsions for the preterm and very preterm infant provided as either PN or enteral nutrition. The chapter includes a valuable discussion of the sources of oils used in available emulsions and provides recommendations based upon efficacy and safety data. Another chapter extensively reviews the roles of long chain omega-3 and omega-6 fatty acids in the neurological development and growth of the fetus and neonate with emphasis on the increased requirements in the preterm infant. The development of the brain and retina, visual and cognitive functions are reviewed and relevant epidemiological and intervention studies are tabulated. Recommendations for maternal intakes of long chain polyunsaturated fatty acids during pregnancy are included.

The balance between infant energy and growth requirements and increased risk of higher than normal serum lipids is compounded by genetic factors that predispose certain infants to premature cardiovascular disease. Relevant treatments, patient evaluation and review of the literature are provided in the next chapter. The mechanisms of action of adipose tissue cells, adipocytes, in regulating hunger, satiety and weight in utero as well as in infancy are examined in a separate chapter. Details concerning the effects of preterm birth followed by rapid weight gain and significantly increased risk of cardiovascular disease in adulthood are described. The receptors on adipocytes, hormones synthesized by adipocytes and their actions are reviewed.

The reader is reminded that currently there is no national or international agreed upon diagnostic cut off or definition of obesity in infants and young children. Strategies, from individual recommendations to public health measures are discussed and provide options for health providers. An overriding issue remains that there is no agreed-upon recommendation concerning when to begin screening for potential weight problems in infants, toddlers and young children. The two main hypotheses to explain the observed inverse association between small size at birth and adult disease are fetal programming i.e. the thrifty phenotype hypothesis and genetic susceptibility hypothesis. These, as well as future research areas and implications, are reviewed in detail in the following chapter. The book's final chapter examines the interactions between maternal behaviors and infant's weight gains. This unique chapter reviews the data that suggest that a mother can overfeed by virtue of failing to heed her infant's satiety signals, with a resultant heavier infant. The historic overview of studies on infant

feeding practices in this chapter suggests that clinicians can help guide mothers to better read their infants' hunger and satiety cues to avoid overfeeding.

The logical sequence of the Sections as well as the chapters within each Section enhance the understanding of the latest information on the current standards of practice in infant feeding for clinicians, related health professionals including the dietician, nurse, pharmacist, physical therapist, behaviorist, psychologist and others involved in the team effort required for successful treatment of infants with relevant diseases and conditions that adversely affect normal metabolic processes. This comprehensive two volume resource also has great value for academicians involved in the education of graduate students and post-doctoral fellows, medical students and allied health professionals who plan to interact with parents of infants with disorders that may be beneficially affected by nutritional supports including enteral and parenteral nutritional modalities.

Cutting edge discussions of the roles of signaling molecules, growth factors, hormones, cellular and nuclear receptors and all of the cells and tissues directly involved or affected by the nutrients provided to infants, both term and preterm are included in well-organized chapters that put the molecular aspects into clinical perspective. Of great importance, the editors have provided chapters that balance the most technical information with discussions of its importance for clients and parents of patients as well as graduate and medical students, health professionals and academicians.

The volume contains over 200 detailed tables and figures that assist the reader in comprehending the complexities of breast milk, breastfeeding, other sources of infant nutrition as well as the biological significance of critical nutrients and the microbiome in maintaining infant growth and health. The over-riding goal of this volume is to provide the health professional with balanced documentation and awareness of the newest research and therapeutic approaches including an appreciation of the complexity of the interactions between genetics, intrauterine growth, maternal health, and term compared to preterm birth issues in this relatively new field of investigation. Hallmarks of the 60 chapters include key words and bulleted key points at the beginning of each chapter, complete definitions of terms with the abbreviations fully defined for the reader and consistent use of terms between chapters. There are over 4000 up-to-date references; all chapters include a conclusion to highlight major findings. The volume also contains a highly annotated index.

This unique text provides practical, data-driven resources based upon the totality of the evidence to help the reader understand the basics, treatments and preventive strategies that are involved in the understanding the role dietary components may play in the early development of healthy infants as well as those with gastrointestinal diseases, genetic defects, metabolic or other complications and/or neurological impairments. Of equal importance, critical issues that involve parental concerns, such as food preferences in children, potential effects on weight gain or growth, breastfeeding versus formula feeding and differences in critical issues such as HIV infections in developing and developed nations are included in well-referenced, informative chapters. The overarching goal of the editors is to provide fully referenced information to health professionals so they may have a balanced perspective on the value of various preventive and treatment options that are available today as well as in the foreseeable future.

In conclusion, "Nutrition in Infancy", edited by Professor Ronald Ross Watson, PhD, Professor George Grimble, PhD, Professor Victor R. Preedy, PhD, DSc, FRIPH, FRSH, FIBiol, FRCPath and Dr. Sherma Zibadi, MD, PhD provides health professionals in many areas of research and practice with the most up-to-date, well referenced and comprehensive volume on the current state of the science and medical practice guidelines with regard to maintaining the optimal nutritional status of the infant. This volume will serve the reader as the most authoritative resource in the field to date and is a very welcome addition to the Nutrition and Health Series.

Adrianne Bendich, Ph.D., F.A.C.N., F.A.S.N.

Series Editor Bios

Dr. Adrianne Bendich has recently retired as Director of Medical Affairs at GlaxoSmithKline (GSK) Consumer Healthcare where she was responsible for leading the innovation and medical programs in support of many well-known brands including TUMS and Os-Cal. Dr. Bendich had primary responsibility for GSK's support for the Women's Health Initiative (WHI) intervention study. Prior to joining GSK, Dr. Bendich was at Roche Vitamins Inc. and was involved with the groundbreaking clinical studies showing that folic acid containing multivitamins significantly reduced major classes of birth defects. Dr. Bendich has coauthored over 100 major clinical research studies in the area of preventive nutrition. Dr. Bendich is recognized as a leading authority on antioxidants, nutrition and immunity and pregnancy outcomes, vitamin safety, and the cost-effectiveness of vitamin/mineral supplementation.

Dr. Bendich, who is now President of Consultants in Consumer Healthcare LLC, is the editor of ten books including "Preventive Nutrition: The Comprehensive Guide For Health Professionals," fourth edition coedited with Dr. Richard Deckelbaum, and is the Series Editor of "Nutrition and Health" for Springer/Humana Press (www.springer.com/series/7659). The Series contains 50 published volumes—major new editions in 2010–2011 include "Vitamin D," second edition edited by Dr. Michael Holick; "Dietary Components and Immune Function" edited by Dr. Ronald Ross Watson, Dr. Sherma Zibadi, and Dr. Victor R. Preedy; "Bioactive Compounds and Cancer" edited by Dr. John

A. Milner and Dr. Donato F. Romagnolo; "Modern Dietary Fat Intakes in Disease Promotion" edited by Dr. Fabien DeMeester, Dr. Sherma Zibadi, and Dr. Ronald Ross Watson; "Iron Deficiency and Overload" edited by Dr. Shlomo Yehuda and Dr. David Mostofsky; "Nutrition Guide for Physicians" edited by Dr. Edward Wilson, Dr. George A. Bray, Dr. Norman Temple, and Dr. Mary Struble; "Nutrition and Metabolism" edited by Dr. Christos Mantzoros, and "Fluid and Electrolytes in Pediatrics" edited by Leonard Feld and Dr. Frederick Kaskel. Recent volumes include "Handbook of Drug-Nutrient Interactions" edited by Dr. Joseph Boullata and Dr. Vincent Armenti; "Probiotics in Pediatric Medicine" edited by Dr. Sonia Michail and Dr. Philip Sherman; "Handbook of Nutrition and Pregnancy" edited by Dr. Carol Lammi-Keefe, Dr. Sarah Couch, and Dr. Elliot Philipson; "Nutrition and Rheumatic Disease" edited by Dr. Laura Coleman; "Nutrition and Kidney Disease" edited by Dr. Laura Byham-Grey, Dr. Jerrilynn Burrowes, and Dr. Glenn Chertow; "Nutrition and Health in Developing Countries" edited by Dr. Richard Semba and Dr. Martin Bloem; "Calcium in Human Health" edited by Dr. Robert Heaney and Dr. Connie Weaver, and "Nutrition and Bone Health" edited by Dr. Michael Holick and Dr. Bess Dawson-Hughes.

Dr. Bendich serves on the Editorial Boards of the Journal of Nutrition in Gerontology and Geriatrics, and the e-journal, Antioxidants and has served as Associate Editor for "Nutrition" the International Journal; served on the Editorial Board of the *Journal of Women's Health and Gender-Based Medicine*, and was a member of the Board of Directors of the American College of Nutrition.

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pages). For 30 years he was funded by Wallace Research Foundation to study dietary supplements in health promotion. Dr. Watson has edited more than 100 books on nutrition, dietary supplements and over-the-counter agents, and drugs of abuse as scientific reference books. He has published more than 500 research and review articles.

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Acknowledgments

The work of editorial assistant, Bethany L. Stevens, and Daniel Dominguez of Humana Press in communicating with authors, working with the manuscripts and the publisher was critical to the successful completion of the book and is much appreciated. Their daily responses to queries and collection of manuscripts and documents were extremely helpful. Support for Ms Stevens' work was graciously provided by the National Health Research Institute as part of its mission to communicate to scientists about bioactive foods and dietary supplements was vital (http://www.naturalhealthresearch.org). This was part of their efforts to educate scientists and the lay public on the health and economic benefits of nutrients in the diet as well as supplements. Mari Stoddard of the Arizona Health Sciences library was instrumental in finding the authors and their addresses in the early stages of the book's preparation. The support of Humana Press staff as well as the input by the series editor, Adrianne Bendich is greatly appreciated for the improved organization of this book.

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Part I
Overview: Global Perspectives

Chapter 1
Infant Nutrition and Lifelong Health

Siân Robinson and Caroline Fall

Key Points

- A lifecourse approach is needed to understand the aetiology of adult disease—there is now significant evidence that links patterns of infant feeding to adult health outcomes.
- Characterisation of infant feeding is challenging and the evidence base is reliant on studies that provide data of sufficient quality to prevent misclassification of individuals.
- Findings from high-income countries could be confounded by social background—further data are needed from populations where the determinants of infant feeding practice differ.
- Breastfeeding is associated with a range of health benefits, and breast milk remains the ideal food for young infants.

Keywords Infant nutrition • Breastfeeding • Weaning • Nutritional programming

Early Nutrition and Lifelong Health

The pioneering work of McCance and Widdowson carried out 50 years ago showed that manipulation of nutrition in foetal and early postnatal life can cause permanent changes in the offspring [1, 2]. For example, altering litter size of rats at birth results in overfeeding or underfeeding during the period of lactation. Rat pups raised in small litters gain weight more rapidly and achieve a greater adult size; we now know that they can also go on to develop hyperphagia and greater adiposity in adult life [3]. An important finding from the original studies was that although altering the plane of nutrition after the period of lactation affected the rate of weight gain of the rat pups, these effects were not permanent [1, 2], suggesting that there is a critical period within which variations in postnatal nutrition impact on growth and body composition.

The link between early experience and physiological function in later life was described by Lucas in 1991 as 'programming' [4]—defined as a process whereby a stimulus or insult acting at a critical phase of development results in long-term changes in the structure or function of the organism. It appears to be particularly important during phases of rapid growth and differentiation, when the

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R.R. Watson et al. (eds.), *Nutrition in Infancy: Volume 1*, Nutrition and Health,
DOI 10.1007/978-1-62703-224-7_1,

organism may be more vulnerable to the effects of external influences. From epidemiological evidence collected in the decades since McCance and Widdowson's experimental studies, it is clear that programmed effects, arising from events in prenatal and early postnatal life, are also important influences on human health. A key observation, from follow-up of historical cohorts, was that there is an inverse association between weight at birth and a number of adult degenerative conditions that include cardiovascular disease and type 2 diabetes [5, 6]. The greater risk observed in individuals of lower birth weight is a reproducible finding, seen in different populations across the world [6, 7]—and is not explained by shorter length of gestation or differences in adult lifestyle [7, 8]. Since much of the observed variance in birth weight results from variations in the intrauterine environment [9], this highlights the importance of maternal nutrition, to enable foetal nutrient needs to be met to support intrauterine growth.

Rapid growth continues in the early postnatal period, and the type of feeding in infancy is known to influence both the rate of weight gain and the type of tissue deposited [10], infancy may also be a critical period when nutritional programming occurs. This chapter reviews the evidence that links variations in early postnatal nutrition to function in later life—and the importance of appropriate nutrition for lifelong health.

Infant Nutrition

Our understanding of the long-term consequences of variation in early nutrition has come mainly from historical studies, in which individuals' details of infant feeding were documented. The quality and type of infant feeding data available from these cohorts differ and are often based on recalled information. Contemporary prospective studies in which infant feeding is described in detail therefore provide important data—although they rely on markers of long-term health or disease risk as outcomes measured in childhood or early adult life. Most of the existing evidence is observational, although there are two experimental trials that have contributed important evidence. In the first of these, preterm infants were randomised to receive preterm infant formula or breast milk [11]. The second is a trial (PROBIT) in which hospitals were randomised to receive routine care or a breastfeeding promotion intervention that increased the duration and exclusivity of breastfeeding [12]. The infants in both trials have been followed up in later childhood.

Across all studies a notable feature is that there is considerable variation in the description of infant feeding and the definition of nutritional exposures. These differences impact on our ability to collate findings, and they provide challenges for the interpretation of the links between infant nutrition and adult health as discussed below.

Breast Versus Formula Feeding

Breast milk has a complex and variable composition that differs over time and between women. A key characteristic is its content of a wide range of bioactive constituents that include anti-microbial and anti-inflammatory factors, enzymes, hormones and growth factors [13]. When considering observational evidence of differences in outcomes between breastfed babies and those fed on breast milk substitutes, there may be particular challenges in interpreting measures of breast milk exposure. Firstly, the composition of breast milk substitutes has changed markedly over the past century and, in older studies, may also have differed significantly between individuals and between populations. Apparent differences in health outcomes that are attributed to breastfeeding may therefore capture two differences in exposure—both variation in exposure to breast milk—but also lack of exposure to

the breast milk substitutes used in the study populations at the time. For example in the past, diluted cow's milk was often fed instead of breast milk, whereas today use of formula milks is routine. Formula milks continue to evolve in their composition and the marked compositional differences, when compared with breast milk, require careful evaluation. A second problem is the definition of duration and exclusivity of milk feeding, as mixed feeding of breast and formula milk is common, and studies differ in the way that dose effects of breast milk are described. The inconsistent definitions of variation in exposure to breast milk and breast milk substitutes may contribute to misclassification of individuals, and therefore to inconsistency across studies that examine health outcomes in relation to breastfeeding. A third issue is the social gradients in patterns of infant feeding, particularly in breastfeeding, that are found in high-income countries today. For example, in the national study of infant feeding in 2010, 91% of UK women who had completed full-time education over the age of 18 years initiated breastfeeding, compared with 63% of women who left school at 16 years or younger [14]. Such marked differences in family background are likely to impact on other aspects of lifestyle, including patterns of physical activity and diet in later childhood, which also have implications for long-term health, and may confound associations between breastfeeding and later outcomes. The older historical cohorts that have prospective records of infant feeding are therefore particularly important in this respect, as such social gradients in infant feeding were much less evident in the past. Important insights will also come from comparison with low- and middle-income countries where patterns of confounding factors differ [15, 16].

Weaning Practice and Diet Quality in Infancy

Much of the existing literature is based on comparisons of types of milk feeding in infancy, and we currently know less about the importance of variations in weaning practice or whether there are long-term effects of qualitative differences in the weaning diet. The age at introduction of solid foods and the type of first solids are often documented, but the assessment of food and nutrient intake during later infancy is less common, and the process of weaning—that is the gradual transition from a milk-based diet to a diet based on solid foods—is not well described [17, 18]. Partly this may be a reflection of the technical challenges encountered in assessing intake in such young children, but as dietary patterns and intakes are changing rapidly in late infancy it may be difficult to determine the key stage and exposures that require definition. An important observation is that weaning practice, including the timing of introduction to solid foods, and type of weaning diet, is linked to the pattern of milk feeding in earlier infancy. Breastfed babies are commonly introduced to solid foods later than infants who are formula fed [19, 20], and factors that relate to the duration of breastfeeding, such as maternal education, also influence the nature of the weaning diet [18, 20]. It is therefore important to consider both milk feeding and variations in the weaning diet when examining the influences of infant diet and nutrition on later health.

Infant Growth

The healthy infant grows rapidly after birth, although the factors that determine the pattern of growth and the relative gains in lean and fat mass in this period are poorly understood [10]. Growth monitoring is widely used to assess the nutritional status of infants and children and as an indicator of health and well-being. There are international growth reference curves that have been used for many years to enable judgement of adequacy of growth throughout childhood—although we do not yet have a complete understanding of what is optimal in terms of patterns of early growth [21].

Growth Standards in Infancy

There has been considerable debate about growth reference data and the populations of infants on which these should be based. A particular concern is that, compared with formula-fed infants, those who are breastfed differ in their pattern of postnatal growth [22–24], and they achieve a lower weight by the end of infancy [23]. The definition of a 'normal' growth reference may therefore depend on the balance of the types of milks fed and the duration of milk feeding in the reference populations. To address this issue, new growth data were published by the World Health Organisation in 2006; these are the basis of reference curves that are now recommended worldwide [25, 26]. Using growth data collected from healthy infants in six diverse populations, the patterns of growth were shown to be very comparable. The infants in each centre were predominantly breastfed. Their pattern of growth is now seen as a standard—that is a description of how infants should grow, rather than a reference as used in the past [21].

The age at which solid foods should be introduced is widely debated [27]. However, lower energy intakes are needed by infants who are growing more slowly—and energy requirements in infancy are considered to have been overestimated in the past [28]. The review by Kramer and Kakuma in 2002 (updated in 2009) [29] shows there are no deficits in weight or length gain in infants who are exclusively breastfed for 6 months, and this remains the basis of the recommendation to start solid feeding at this age.

Rapid Weight Gain in Infancy

Babies of lower birth weight often exhibit 'catch-up' growth, gaining weight rapidly in infancy. This accelerated weight gain may be beneficial to survival in the short term, but has been shown to be associated with greater fat deposition and adiposity in later childhood [30, 31]. Singhal and Lucas [32] have proposed that it is the effect of rapid postnatal growth that is particularly damaging in relation to long-term outcomes such as cardiovascular disease. For example, in an intervention study of preterm infants, feeding a high-nutrient diet was shown to promote weight gain, but this was also associated with insulin resistance [33] and higher blood pressure [34] when the children reached adolescence. Additionally, systematic reviews of infant growth studies have shown that rapid infant growth is predictive of obesity in older children and adults [35, 36]. However, since more rapid weight gain is observed in formula-fed infants in later infancy, differences in long-term outcomes associated with rates of infant growth could be due to variations in patterns of milk feeding (section 'Growth Standards in Infancy'), and it may be difficult from existing observational data to determine their separate roles.

Low Weight Gain in Infancy

Poor growth in infancy has long been recognised as a cause for concern and an indicator of failure to thrive in infancy. However, in addition to evidence of poor outcomes associated with rapid weight gain (section 'Rapid Weight Gain in Infancy'), low gains in infancy also appear to be damaging. For example, in a follow-up study of men born in Hertfordshire, UK, low weight at 1 year was associated with higher mortality from cardiovascular disease [37]. More recently, using records of childhood growth and hospital admission and mortality data, the long-term consequences of poor infant growth have been explored in a study of men and women born in Helsinki, Finland between 1934 and 1944 [38, 39]. This study confirmed that men who had coronary heart disease in adult life had grown poorly in infancy, and relative to the other men in the cohort, had a low body weight and were short at 2 years

of age. However, an important additional finding was that their risk of heart disease was greatest if they then went on to gain weight rapidly in childhood [39]. In a study of young Indian adults this pattern of growth, where poor weight gain in infancy is followed by rapid gains in childhood, has also been linked to impaired glucose tolerance and diabetes [40]. These data highlight the importance of adequate weight gain in infancy, but they also provide clear evidence that further studies are needed to identify optimal paths of growth from birth to adulthood that are associated with lifelong health.

Infant Feeding, Growth and Reverse Causality

An issue that needs to be recognised in linking patterns of infant feeding to growth is that of reverse causation, as the decisions to stop breastfeeding or whether to introduce solid foods into the diet may be influenced both by the rate of an infant's growth and maternal perceptions of adequacy of the supply of breast milk. It has been suggested that infants who grow more rapidly may cry more frequently from hunger, prompting supplementation with formula milk and/or solid foods. Thus, prolonged breastfeeding may be a marker of a slower growth trajectory, rather than causally related to the rate of growth [41]. With the possibility of influence in both directions, the association between feeding pattern and infant growth may be difficult to address. Observational studies provide evidence that early cessation of breast feeding is linked to rapid growth [42]. However, in a recent analysis of data from the PROBIT trial, the reverse association was found; smaller infants were more likely to be weaned or to have discontinued breastfeeding at the subsequent follow-up [41]. These contrasting findings demonstrate the difficulties in understanding the basis of infant feeding decisions. To date, the mechanisms that underlie the slower growth rates observed in breastfed infants are unexplained.

Infant Nutrition and Health Outcomes

Variations in infant feeding have been linked to a range of health outcomes both in the short and longer term. Differences in rates of infection between breastfed and formula-fed babies have been recognised for many years, but in the past decade a new evidence base has been established that links variations in infant nutrition to health outcomes much later in life.

Infection

Breast milk has been described as the 'communication vehicle' between the maternal immune system and the infant [43]. It contains a diverse range of bioactive factors that include immunoglobulins, lymphocytes, neutrophils, cytokines and other anti-inflammatory compounds [13, 43]. The infant's immune status is protected not only by the antimicrobial properties of breast milk, but also by the actions of bioactive components that promote immune development and facilitate development of tolerance, and an appropriate inflammatory response [43, 44]. It is not surprising that breastfeeding is therefore associated with fewer infections in infancy, particularly gastrointestinal and respiratory infections [45]. The differences are most marked in the developing world, where access to clean water may be an issue. For example, tenfold differences in diarrhoea mortality under 6 months have been described between exclusively breastfed and non-breastfed infants [46]. However, even in the developed world, consistent differences in infection rates are evident. For example, in the UK Millenium Cohort of infants, studied up to 8 months, an estimated 53% of hospital admissions for diarrhoea and 27%

for respiratory tract infections would have been prevented by exclusive breastfeeding [47]. Recent UK data shows that there are also marked differences in the prevalence of less severe infections in infancy according to the duration of breastfeeding [48]. The importance of breastfeeding for protection from gastrointestinal infection was confirmed among infants in the PROBIT trial, although the rates of respiratory infection did not differ [49]. Because the bioactive components of breast milk influence immune development, it is also possible that protective effects continue beyond the period of breastfeeding. Early observations suggested that this was the case, as rates of infection were found to remain lower in children who had been breastfed in infancy [50, 51], but in more recent studies, such evidence of prolonged benefit has not been confirmed [47].

Much less is known about other aspects of infant feeding and infections in infancy. It is possible that the immature infant may be vulnerable to infection arising from the effects of early weaning, and early introduction of solid foods has been linked to greater risk of respiratory infection [52]. However, this has not been seen in other studies, and among infants in the Millenium Cohort, risk of hospitalisation for infection was not greater in those receiving solid foods [53].

Allergy and Atopy

There has been intense interest in the role of infant feeding in the aetiology of asthma, eczema and other atopic conditions, with a view to understanding whether appropriate infant feeding, particularly breastfeeding, could be protective. For high-risk children, breastfeeding is commonly recommended, although its role in atopic conditions is still not well understood. The pathogenesis of immune-mediated diseases, that include allergic conditions, involves a defect in tolerance induction [54]. A number of potential mechanisms link breastfeeding to tolerance induction, including the presence of antigens and tolerogenic factors in breast milk, as well as effects on gut microbiota and permeability [54]. However, the evidence for a protective role of breastfeeding is mixed [55, 56], and in the PROBIT trial, whilst there was a marked difference in exclusive breastfeeding at 3 months (44.3% in intervention vs. 6.4% in control group) there were no differences in risk of asthma or allergy in the children followed up at 6.5 years [57]. One possibility is that the misclassification of infant feeding exposures is particularly problematic in studies of atopic disease. Hypersensitivity reactions may not show a dose dependence, and they may be affected by frequency and timing of exposures [57]—both of which may be poorly characterised. For infants who are not breastfed, formula milks containing hydrolysed protein and prebiotics have been recommended for the prevention of atopic outcomes, although there is currently little evidence of benefit when compared to exclusive breast feeding [58, 59].

In terms of other aspects of infant feeding, there is evidence that very early introduction of solid foods may increase the risk of eczema, but there are few data to support an association with other allergic conditions [60]. The age at which solid foods should be introduced and the need for delayed introduction of allergenic foods remains controversial [56, 60, 61].

Intelligence and Cognitive Development

Brain growth is rapid in the first year of life, and slow growth in infancy predicts poor cognitive performance in later life and lower educational attainment [62–64]. This has led to considerable interest in the influence of infant feeding on cognitive development, in particular breastfeeding, which has been linked with higher intelligence in a number of studies [65]. The benefits of breastfeeding may be due to the presence of long-chain polyunsaturated fatty acids in breast milk, as these are found in high

concentrations in the brain, and they accumulate during the period of rapid brain growth. Other bioactive constituents in breast milk, such as nucleotides, may also have important roles in neurocognitive development [66], although we currently know little about these.

In high-income countries, breastfed children are commonly observed to have better performance in tests of cognitive function. However, the decision to breastfeed and the duration of breastfeeding are strongly linked to family background, particularly to maternal intelligence, which is often not considered as a confounder [67]. In a meta-analysis of observational studies in 2006, Der et al. showed that when maternal intelligence is accounted for, the apparent differences in the children's performance are no longer evident, suggesting that a positive association with breastfeeding is due to effects of residual confounding [67]. In 2008, data from the PROBIT trial were published, which showed that the intervention was associated with a difference of 5.9 points for full-scale IQ when the children were assessed at age 6.5 years [68]. Although the findings have been debated [69], the experimental design of the study means that the data lend strong support to benefits of breastfeeding for cognitive development. Further evidence of a causal link between breastfeeding and intelligence has come from the recent comparison of UK children in the ALSPAC cohort with Brazilian children in Pelotas [16]. In both cohorts, despite differences in the effects of social background on breastfeeding that were marked in the UK but not observed in Pelotas, there was a consistent association between breastfeeding duration and IQ. Brion et al. comment that adjustment for confounders attenuated the association in both cohorts, thus residual confounding is still a possibility. They recommend that further large studies are needed from populations that differ in confounding structures [16].

There is little evidence of links between other aspects of weaning practice and cognitive development. In one study, children whose weaning diet was characterised by higher intakes of fruit, vegetables and home-prepared foods had higher scores on tests of full-scale and verbal intelligence at age 4 years. This association was independent of a range of confounding factors, including maternal IQ and breastfeeding duration [70]. Although weaning practice is also socially patterned, and there could be effects of residual confounding, these data suggest that the quality of the weaning diet could affect brain development when growth velocity is high. Alternatively, as dietary patterns 'track' in childhood, this association may reflect continued exposure to a diet that provides an optimal supply of micronutrients that are important for cognitive development. Further work is needed to determine the influence of qualitative differences in the weaning diet on cognitive development.

Body Composition and Obesity

As a number of epidemiological studies have shown a lower risk of obesity in children and adults who were breastfed, infancy has become a focus of public health interest as a critical period that could be targeted for its prevention [71, 72]. There are good mechanistic reasons why being breastfed might be protective. One possibility is that as breastfed babies control the amount of milk they consume, they learn effective self-regulation of energy intake, which remains with them in later life [73, 74]. Secondly, breastfeeding is associated with slower weight gain in infancy and with later risk of obesity (sections 'Growth Standards in Infancy' 'Rapid Weight Gain in Infancy'). Although this might appear the simplest explanation, it may not be straightforward, as one study identified the critical period associated with later adiposity as early infancy [75], when differences in weight gain between breastfed and formula-fed infants may not be apparent [23]. Another possibility is that the bioactive components in breast milk have long-term programmed effects on function. For example, early exposure to leptin and adiponectin in breast milk could be involved in setting endocrine responses to feeding and appetite regulation [76]. Little is currently known about such programmed effects, but the finding that preterm infants fed human milk have lower leptin levels in adolescence than those fed preterm formula may be of importance [77].

Early meta-analyses and systematic reviews that linked breastfeeding to later body composition in high-income populations showed that the evidence of a protective effect on obesity was reasonably consistent across studies [78, 79]; Harder et al. estimated that risk of becoming overweight in adult life was reduced by 4% for each additional month of breastfeeding [80]. However, effects on mean BMI are small [81], and recent analyses of observational data from low- and middle-income countries have not confirmed the inverse association. In data pooled from five prospective birth cohort studies of more than 10,000 young adults in low- and middle-income countries, there was no association between being breastfed and later adiposity, nor was there any evidence of benefits of a longer duration of breastfeeding [15]. This difference in findings was also evident in a comparison of UK children in the ALSPAC study with a contemporary cohort of children born in Pelotas, Brazil—where, unlike the UK, there was little social patterning of breastfeeding [16]. Longer duration of breastfeeding was associated with lower BMI in the children studied in the UK, but this association was not found in the Brazilian children. These new findings are in accord with the PROBIT trial which showed no difference in BMI in the children in the intervention and control groups [82], suggesting that residual confounding could be the explanation for the inverse associations previously seen in observational studies.

However, further data are needed. Firstly, BMI may be too crude a measure of differences in body composition, particularly in childhood. In prospective studies in which fat mass has been measured directly using DXA, differences in adiposity in children have been found in relation to their duration of breastfeeding, even after adjustment for a range of known determinants of adiposity and other confounding factors [83, 84]. Importantly, this association may not be evident when using BMI as a marker of fat mass [84]. Secondly, studies of siblings have shown differences in adiposity in relation to breastfeeding, which cannot be explained by differences in social background or lifestyle [85, 86]. In this respect, future studies of adiposity using direct measurement techniques will be important, particularly in populations that differ in their confounding structures and influences on infant feeding practice.

Less is known about other aspects of infant feeding in relation to later obesity. Although early introduction of solid foods has been linked to obesity in individual studies [15, 51], this is not a consistent finding across all studies [84, 87]. Recent data from Project Viva cohort study in the US suggest that the inconsistency could arise from differential effects found in breastfed and formula-fed infants [88]. Among formula-fed infants, introduction of solid foods before 4 months was associated with a sixfold increase in risk of obesity at 3 years (adjusted odds ratio 6.3, 95% CI 2.3–6.9), whereas no difference in risk was found in the breastfed infants. The authors suggest that effective self-regulation of energy intake by breastfed infants leads to a reduction in milk consumption when they are given solid foods. In contrast, formula-fed infants increase their energy intake. These findings need to be replicated, but they highlight the need to consider the combined influences of milk feeding and the weaning diet when evaluating the role of infant nutrition in long-term health outcomes.

Cardiovascular Disease

The evidence collated over the past decade has enabled an evaluation of the links between variations in infant feeding and cardiovascular disease and its risk factors in adult life [10]. The primary sources of data are observational, from historical cohorts that had documented reports of infant feeding as well as adult data collected at follow-up. The principal exposures that have been considered are duration and exclusivity of breastfeeding, plus the comparison of breastfed individuals with those fed breast milk substitutes in infancy. There is little information on other aspects of infant feeding in relation to later cardiovascular disease.

Blood Cholesterol

Because breast milk contains cholesterol, there are marked differences between breast and formula-fed infants in their exposure to dietary cholesterol in early infancy. As might be expected, studies of breastfed infants show that they have higher total cholesterol concentrations when compared with other infants [89]. It has been proposed that the early exposure of breastfed infants to dietary cholesterol could result in programmed effects on endogenous cholesterol synthesis, leading to differences in regulation, that are evident later in life. Meta-analyses of observational data that link type of milk feeding to total cholesterol concentrations in adult life support this proposition. Although children who were breastfed or formula fed in infancy do not differ in their total cholesterol concentrations, in adult life, breastfed individuals have lower blood cholesterol concentrations (−0.18 mmol/L, 95% CI −0.30, −0.06 mmol/L) [89]. A further meta-analysis by Owen et al. in 2008 showed that the evidence of a protective effect of breastfeeding is robust to adjustment for a range of adult confounders that included smoking and BMI [90]. Although the differences in cholesterol were small, and there were insufficient data to examine the dose effects of duration of breastfeeding, the effects were more marked among adults who had been exclusively breastfed, who were likely to have been breastfed for longer. The age dependence of the protective effect identified in the meta-analysis [89] suggests that the children in the intervention studies [11, 12] are too young to determine whether there are differences in total cholesterol resulting from differences in breast milk exposure in infancy. In a follow-up study of the preterm infants randomised to breast milk or preterm formula, differences in total cholesterol between the groups at age 13–16 years were of borderline significance [91], but there were differences in other lipoproteins, including a lower ratio of LDL to HDL cholesterol in the breast milk group.

Blood Pressure

Meta-analyses of observational data show that breastfeeding is associated with small reductions in systolic blood pressure in later life [92, 93]. A smaller difference in diastolic blood pressure in relation to breastfeeding is evident in some studies, but this is a less consistent finding [92, 93]. The mechanisms that link breastfeeding to later blood pressure are unknown, but may be due to programmed effects of the bioactive or other dietary constituents in breast milk that are absent from formula milk [34]. In the meta-analysis by Martin et al. in 2005, the difference in SBP attributed to being breastfed was −1.4 mmHg (95% CI −2.2, −0.6), although the authors noted that there were differences in effect size according to size of study, raising concerns about publication bias [93]. The follow-up study of preterm infants at age 13–16 years, randomised to breast or preterm milk in infancy, provides further support for the findings of the meta-analyses, as in a non-randomised analysis, the proportion of human milk consumed was inversely related to later mean arterial blood pressure [34].

However, these findings differ from those of the PROBIT trial in which the children were followed up at 6.5 years [82], where, despite a much higher prevalence and duration of exclusive breastfeeding resulting from the intervention, there were no differences in systolic or diastolic blood pressure between the children in the intervention and control groups. Furthermore, in the recent comparison of children in the ALSPAC and Pelotas cohorts, whilst an inverse association was found between breastfeeding duration and SBP in the UK children that was independent of confounders, this was not evident in children from Pelotas [16]. Fall et al. also show weak and inconsistent findings between duration of breastfeeding and SBP or risk of hypertension, in their analysis of data from young adults in low- and middle-income populations [15]. These new findings, together with heterogeneity across studies observed in the meta-analyses [92, 93], raise the possibility of residual confounding that could explain the inverse association between breastfeeding and blood pressure. However, further data are needed, particularly to address effects of exclusive breastfeeding [15].

Blood Glucose and Type 2 Diabetes

There is one meta-analysis and systematic review of observational studies that has examined the association between breastfeeding and risk of type 2 diabetes [94]. This study by Owen et al. in 2006 included studies mainly conducted in the US and Europe, and showed that being breastfed was associated with a reduction in risk (OR 0.61, 95% CI 0.44, 0.85). This effect was reasonably consistent across studies, and among non-diabetic participants, being breastfed was associated with slightly lower fasting insulin concentrations later in life [94]. A protective effect of breastfeeding may be explained by the bioactive components of breast milk [95] or the content of LCPUFA, which in the past were absent from formula milks. For example, breastfeeding is associated with greater LCPUFA levels in skeletal muscle membranes, which in turn have been shown to be associated with lower fasting plasma glucose [96].

But the recent analysis of data from birth cohorts of young adults in low- and middle-income countries do not confirm the findings of the meta-analysis, as there was no association between being breastfed, or duration of breastfeeding on plasma glucose concentration or risk of type 2 diabetes [15]. There are differences in breastfeeding initiation rates between the two sets of analyses, as breastfeeding was almost universal in the low- and middle-income countries, which may be important, but the disparate findings also raise the possibility of residual confounding as an explanation for the association previously observed. In contrast, new data from a follow-up study of 9-year-old children in an Indian cohort show that longer duration of breastfeeding in infancy was associated with lower 2-h plasma glucose concentrations in a glucose tolerance test, indicating protective effects of breastfeeding that are consistent with earlier studies [97]. Further data on contemporary populations in low- and middle-income countries are clearly needed, particularly among those undergoing rapid transition to urbanised and Western lifestyles.

Cardiovascular Disease

Although breastfeeding is associated with reductions in a number of risk factors for CVD, consistent effects of breastfeeding on cardiovascular disease have not been demonstrated. In a systematic review and meta-analysis of four observational studies from the UK and US in 2004, Martin et al. showed there was no association between breastfeeding and mortality from cardiovascular disease [98]. Following this review, a follow-up study of women in the Nurses Health Study showed that there were small reductions in risk among those who had been breastfed (adjusted hazard ratio 0.91 (95% CI 0.83–1.01) for any cardiovascular event) [99]. It is not clear why these associations differ from those described for cardiovascular risk factors, although there may be particular challenges in defining nutritional exposures in infancy in cohorts of older adults. At present there are limited data to be able to address this.

Cancer

In comparison with cardiovascular disease, fewer studies have addressed the link between infant feeding and risk of cancer although it has been proposed that exposure to breast milk could be protective, resulting from effects on the developing immune system [100]. In a meta-analysis of studies from high-income populations, being breastfed was associated with a lower risk of childhood cancer: pooled OR 0.91 (95% CI 0.84, 0.98) for acute lymphoblastic leukaemia, 0.76 (95% CI 0.60, 0.97) for Hodgkin's disease [100]. However, with the exception of a reduction in premenopausal breast cancer identified in a meta-analysis [101], risk of adult cancers has not been shown to be associated with breastfeeding [10, 101].

Conclusion

There is a growing recognition of the need for a lifecourse approach to understand the aetiology of adult disease, and there is now a significant evidence base that links patterns of infant feeding to differences in health outcomes both in the short and longer term. In particular, observational data show that being breastfed is associated with lower rates of infection in infancy, childhood cancers and with reductions in blood pressure, cholesterol and lowered risks of obesity and diabetes in adult life. Although the effects on cardiovascular risk factors are modest, if causal, they would confer important benefits on health at a population level. Given the difficulties in assessing exposure to breast milk and other associated aspects of infant feeding (section 'Breast Versus Formula Feeding') it is likely that there is considerable misclassification of individuals, and the identified associations may be significantly underestimated. There are few data to show whether other aspects of infant feeding behaviour, such as age at introduction of solid foods, are determinants of later outcomes.

However, much of the existing evidence of the benefits of breastfeeding has come from high-income countries, where there are clear social gradients in infant feeding, particularly in breastfeeding duration—and, despite appropriate statistical adjustments, the possibility of residual confounding remains. New data from low- and middle-income populations of children and young adults, where the determinants of infant feeding behaviour differ, suggest that for blood pressure, BMI and risk of diabetes, confounding may be an explanation for the associations seen in the meta-analyses (sections 'Body Composition and Obesity', 'Blood Pressure', 'Blood Glucose and Type 2 Diabetes') [15, 16]. In comparison with high-income countries, low- and middle-income countries also differ in prevalence of breastfeeding and in their patterns of adult disease, and many are undergoing rapid transition to Western lifestyles [102]. It will be important to continue to follow up these and other comparable study populations in the future, to assess the effects of transition and to determine associations with morbidity and mortality at older ages. The evidence that links infant feeding to all long-term health outcomes is currently incomplete. Whilst further data are needed, misclassification of nutritional exposure in infancy remains a key challenge. Future progress will depend on new studies that provide detailed prospective data on duration and exclusivity of breastfeeding, as well as appropriate characterisation of the weaning diet.

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Chapter 2
Nutrition in Infants: Risks and Management

Rakesh Sharma

Key Points

- Infants grow very fast in the first year of life during first 6 months. It creates a significant demand of nutrients but mother breast milk or commercial formulas meet all nutrient requirements.
- Breast-fed infants require vitamin D supplementation since birth and iron supplementation with cereal or milk during first 6 months.
- Bottle-fed infants require iron-fortified formula or supplementation by 4 months of age. Fluoride supplementation is needed throughout childhood if water supply does not have fluoride.
- Premature or small-for-date infants require special nutrition planning. Eating frequency among infants in early weeks is every 2 h while old infants can stay longer up to 4 h without foods. Calm environment and social interaction encourage the infants to serve themselves. With growth, switching to solid foods between 4 and 6 months is dependent on baby size and appetite. A plain rice cereal diluted to thin gruel fed without sugar is good choice of solid food. Cereals may be added to other solid foods according to the physical development and eating skills gradually develop. Vegetables and fruits are added soon after cereals are established. Egg yolk and strained meats or beans with custard are next food types given to baby.
- Babies learn to chew and swallow strained solid foods such as commercial strained foods. Such modification in foods provides adequate vitamin, minerals, and proteins as nutrients. Meal planning and diet preparation is an art. Strained foods should be served at various times in a day. Inadequate feeding and loss of appetite may cause physical problems and risk. Overfeeding may be a risk of obesity, weight gain, and excessive load on intestinal and kidneys. After first year of age, infants are ready to shift from formula to whole milk and to learn drinking from a cup, eat chopped food. The transition to table food can be made by serving chopped foods without seasonings under supervision of parents.
- Prospective randomized trials support that a nutrient-enriched diet in infancy can increase fat mass later in childhood. It indicates a causal link between faster early weight gain and a later risk of obesity. The link has implications for the management of infants born small for gestational age, and suggests that the primary prevention of obesity could begin in infancy.

Keywords Breast milk • Infants nutrition • Formula fed infants • Vitamin deficiency

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R.R. Watson et al. (eds.), *Nutrition in Infancy: Volume 1*, Nutrition and Health,
DOI 10.1007/978-1-62703-224-7_2, © Springer Science+Business Media New York 2013

Introduction

Infancy is the stage of life with abrupt transition from fetal period to the neonatal phase during first year of childhood. Infancy creates a sudden need of necessary nutrients from external sources. Provision of adequate energy and nutrients is needed in the first year of life to support the most rapid growth and development period in a person's life. From birth to 6 months of age about 108 calories per kilogram per day are needed; by 12 months a baby needs about 100 calories per kilogram per day. Since babies can eat only a small volume of food to support rapid growth, they require nutrient-dense, highly caloric foods. Fat must contribute at least 30% of total calories to meet the demands of growth and development. Babies should double their birth weight by 4–6 months of age and triple it by 1 year. The key of proper infant growth is right proportion of essential and supplemented nutrients supply through mother milk or alternate nutrition formula. Unfortunately, growing dependence of infants on alternate milk formulas or artificial milk feeding is putting infants at the risk of obesity. On average, their length increases by 50% in the first year of life. The present chapter puts forth the nutritional demands in infancy and importance of breast feeding during early first year of infancy. A comprehensive alternate of mother milk and importance of nutrients in mother and cow's milk is highlighted. In the following section, importance of vitamins in infant growth and growing threat of weight gain and obesity is highlighted due to lack of maternal nutrition.

Maternal Nutrition and Breast Feeding

Mother's breast milk is the best source of nutrients for a newborn. A full-term infant's digestive system has been specially designed to digest breast milk. Whether by breast or by bottle, feeding on demand is best. Infants can self-regulate their food intake to match their nutritional needs, based upon internal hunger and satiety cues. Parents need to pay attention to their baby's cues and feed them accordingly. If a baby is bottle fed and signals that he is full by pulling away or easily becoming distracted, consumption of the entire bottle is not necessary.

For the first 4–6 months, babies should be fed only breast milk or correctly prepared infant formula. Children under the age of 12 months should not have cow's milk. Between 4 and 6 months of age, children are usually developmentally ready to try moist, soft foods. To easily identify allergies, one food should be introduced at a time, with a 3-day wait before the introduction of another new food. Parents should encourage the child to try new foods, one at a time. During the first year or so, children will learn to chew, swallow, and manipulate finger foods; drink from a cup; and eventually feed themselves. Of course, they will make lots of mess while learning these skills, so patience is important. Bottle-fed infants should be weaned from the bottle by 12–14 months of age. There is no specific time to wean a breast-fed child; the longer a baby is on breast milk, the better it will be for her health and well-being [1, 2] (Table 2.1).

Milk, Formulas, and RDA

In first year of life, dietary adequacy is nutrients provided from maximum 1 quart or 944 mL milk or formula with RDA in the diet as given in Table 2.2. Appetite beyond this amount should be supplemented with solid food to provide infant development and growth. Energy value of 1 quart of human milk provides to meet needs of infants until weight about 14 lb according to the RDA recommendation. Infants who need a higher calorie intake prior to the initiation of solid foods between the ages of 4 and 6 months can be given additional milk or formula to supply energy needs. Mother milk is considered best for nursing infants without any supplementation and serves as balanced infant diet.

Table 2.1 RDA of vitamins and minerals to meet the needs of a 1-year-old infant[a]

	RDA		Estimated safe and adequate		
Nutrient	0–6 months	6–12 months	Nutrient	0–6 months	12 months
Energy (cal)	kg × 108	kg × 98	Biotin (μg)	10	15
Protein (g)	13	14	Pantothenic acid (mg)	2	3
Vitamin A (RE)	375	375	Copper (mg)	0.4–0.6	0.6–0.7
Vitamin E (mg)	3	4	Fluoride (mg)	0.1–0.5	0.2–1.0
Vitamin K (mg)	5	10	Chromium (μg)	10–40	20–60
Vitamin C (mg)	30	35	Molybdenum (μg)	15–30	20–40
Thiamin (mg)	0.3	0.4	Sodium (mg)	120	200
Riboflavin (mg)	0.4	0.5	Potassium	500	700
Niacin (mg eq)	5	6	Chloride (mg)	150	300
Vitamin B6 (mg)	0.3	0.6			
Folate (μg)	25	35			
Vitamin B12 (μg)	0.3	0.5			
Calcium (mg)	400	600			
Phosphorus (mg)	300	500			
Magnesium (mg)	40	60			
Iron (mg)	6	10			
Zinc (mg)	5	5			
Iodine (μg)	40	50			
Selenium (μg)	10	15			

[a]Reproduced from [3]

Table 2.2 Recommended daily allowances of supplements on human milk and cow's milk formula for 1-year-old infant[a]

	Amount per quart		
Nutrient supplements	Human milk	Cow's milk	Goat milk
Energy (cal)	727	632.5	168
Protein (g)	10.4	14.2	8.7
Vitamin A (RE)	686	606	451
Vitamin D (μg)	5	10	–
Vitamin E (mg)	2	2	–
Vitamin K (mg)	–	–	–
Vitamin C (mg)	47	52	3.0
Thiamin (mg)	0.1	0.5	0.12
Riboflavin (mg)	0.4	0.6	0.7
Niacin (mg equiv)	1.9	7.0	0.7
Vitamin B6 (mg)	0.09	0.4	0.11
Pantothenic acid (mg)	0.76	0.77	0.76
Folate (μg)	49	47	0.7
Vitamin B12 (μg)	2.8	0.9	0.16
Calcium (mg)	312	434–507	326
Phosphorus (mg)	132	302–387	270
Magnesium (mg)	22	39–49	34
Iron (mg)	0.9	12	0.12
Zinc (mg)	4–5	3–5	0.73
Iodine (μg)	28	94	–
Copper (mg)	–	–	0.112
Iron (mg)	0.11	0.12	0.12
Sodium (mg)	110	119	122

[a]Reproduced from [23]

However, milk has low or inadequate thiamine, niacin, vitamin B6, most of minerals than RDA. Partly, growing demand of iron is met from deposited iron in infants. Other good source is cow's milk to meet vitamins and minerals consistent with RDA values but it has high protein content.

There are several government nutrition assistance programs that are available in health centers or clinics, schools, child-care centers, and licensed day-care homes. These programs assist families in meeting the nutritional needs of their children [5–7]. Interested readers should read the federal public documents [5–7]. Some important programs are cited as examples:

- The Supplemental Nutrition Program for Low Income Women, Infants, and Children is a government program that provides nutrition education, vouchers for food, and referral for services for eligible women and children [8]. Eligibility includes having a nutritional risk and an income that is less than the poverty level multiplied by 1.85.
- The Child and Adult Care Food Program provides reimbursement to child-care providers—child-care centers and family day-care homes—for each child to have two meals and a snack. The provider must follow menu guidelines and report the menus in order to be reimbursed.
- The National School Meal Program (NSMP), which includes lunch, breakfast, and special milk, is offered in almost every school in the country [9]. The *lunch* provides one-third of a child's daily nutrient requirements; when *breakfast* is also provided, 40% of the requirements are met. If a school does not have a cafeteria, food may be brought in from a central kitchen or at least the special milk program will be available. With the increase of after-school programs, the NSMP is assisting in providing *after noon snacks* for those programs. In the summer when school is not in session, day camps, recreation centers, and schools can sponsor the *Summer Food Program*, which provides lunches for children to eligible programs.

Recommended Supplements

Infants need basic nutrients such as energy, milk protein, vitamins, minerals, carbohydrates as given in Table 2.2 as guide to interested readers. Majority of nutrients are supplied through maternal nutrition or breast feeding. Alternatively, supplements are given either as cow's or goat milk. Goat milk is gaining popularity. Goat's milk is believed to be more easily digestible and less allergenic than cow's milk.

As infant grows, absorption of iron (nonheme) also increases as well as the (heme) iron from milk "protein" when milk containing vitamin C is given. Vitamin C rich formula also helps the body to absorb nonheme iron present in milk.

In the following section, recommended requirements in normal infants of normal weight and small-for-date are given.

Infants of Normal Weight

Supplementation of the milk-based diets for infants of normal weight at birth depends on the milk being fed. Cow's milk is alternate to human milk [10, 11]. Of specific mention, vitamins K, D, C, A, folate, iron, fluoride, calcium, and protein are major supplements in cow's milk presented in Table 2.2 [12]. However, a parenteral administration of vitamin K (0.5–1 mg phytylmenaquinone) should be done routinely in hospital at delivery. Some known examples are cited on supplementation:

- Breast milk has low vitamin D so 5–7.5 μg/daily or 200–300 IU should be supplemented as cow milk-based formula 1 quart daily.
- Breast milk has sufficient vitamin C but cow milk is inadequate in vitamin C. It needs 2 fl oz (4 table spoons) of orange juice daily.

- Low folate levels in milk-based formula need supplementation of 25–35 μg to offset inadequacy.
- Iron demand increased during infancy after 4 months because stored iron in red blood cells is exhausted and replaced with new erythrocytes. To meet this iron demand, infants are fed with iron-fortified cereals six spoons to provide 14 mg iron during 4–6 months age [13]. Fluoride supplementation may be needed if drinking water has inadequate fluoride content. American Academy of Pediatrics Committee on Nutrition recommends that children of 2 weeks through 2 years of age need supplementation of 0.25 mg fluoride per day.

Premature or Small-for-Date Infants

Nutrition needs of premature or small-for-date babies require more supplementation due to their limited ability to absorb calcium, protein, fat, and vitamins A and D [14]. Some known examples are cited on supplementation:

- Premature babies need vitamin D supplementation up to a level of 10 μg (400 IU) daily, at least until milk intake is about 1 quart each day. A supplement of 17 mg vitamin E is recommended for the first 3 months of premature baby's life.
- Iron deficiency appears soon after iron stores are exhausted in first 2 months. Iron-fortified formula with added sufficient vitamin E is recommended along with high polyunsaturated fatty acids.
- Increasing demands of proteins and infants need proteins at least (3–5 g/kg weight) rich in histidine, tyrosine, arginine, taurine amino acids, and calcium (60-mg/100 calories in feeding formula) to meet requirements in premature infants in first weeks of life.
- Vitamins A and D may pose risk. As an example, hypervitaminosis D (due to 45 μg daily intake) may cause loss of appetite, vomiting, weight loss. High blood calcium levels may cause calcium deposits in blood vessels, lungs, kidneys. Hypervitaminosis A due to high intake of fortified milk (around eight times above the RDA) causes loss of appetite, blurred vision, loss of hair, cracked and dry skin, headaches, nausea and irritability. Symptoms easily disappear soon after discontinuing vitamin A supplement.

In the following section, feeding schedule, growing sensory experience, transition to solid foods, importance of socialization and risks are highlighted.

Feeding Schedules

Feeding schedules of babies require basic considerations such as: How often should a baby be fed in regular intervals and awake cycles? Moreover, premature babies need to eat every 1 ½ to 2 h at first, whereas large newborns may want to eat at least every 3 h and sometimes every 2 h for the first few days [15]. Growing infants like 8 lb babies eat every 4 h and breast-fed babies may eat more frequently. Other important issue is proper feeding and completing feed while baby is awake otherwise baby may not get feed if gone asleep during feed. Other side of urging or persuasion of accepting feed may cause overfeeding. It certainly needs longer playtime or slow feeding or rocking a baby or conversation to pass time between feedings to wakeful babies. With growth of infants, older babies can be fed with less longer intervals or eliminating middle-of-the night feeding and given solid food. Premature babies 2 months or a little longer in age can sleep through without the middle-of-the night feeding. Other factor is feeding place free from disruptive environment such as shouts, bangs, phone ringing, etc. Sights, sounds, music, and smells are new experiences. Major problem is growing infants is combating dental growth or teeth eruption. Keeping milk bottle all times near to sleeping baby makes habit of milk draining into the baby's mouth with risk of dental caries or "nursing bottle syndrome." Feeding schedules and participation of parents in feeding process also strengthens family bonding.

Solid Foods

Practice in infant feeding change time to time. Solid foods are delayed until at least 4–6 months of age. Cereals should be introduced to infant diets based on development progress in feeding skills, sensory experiences, and nutritional needs. As an example, nipple reflex, swallowing, extrusion reflex, and chewing. After 4 months, extrusion reflex extincts out and lip closure control plays a role after about 8 months such as drinking from a cup and swallowing. It needs a lot of practice to baby and feeder. Chewing food or regular diet different from milk is development skill including rotatory motions, vertical motion of jaws by 6 months of age. Feeding skills involves hands, tongue, mouth, grasping objects, feeding themselves finger foods [15].

Sensory Experience

Before introduction of solid foods into infant's life, feeding acquaints the sense of taste, smell, touch only with human milk and/or milk formula and orange juice. Later infants on cereals, pureed food diluted with milk, vegetables, fruits, and flavors get tactile perception in the mouth.

A significant pleasure is mounted with palate of food colors, aroma, flavors, and textures in early experiences. With growing age after 1 year, infants set their attitude toward food and reject unfamiliar food.

Nutritional Aspects in Infancy

Human milk or commercial formula provides necessary nutrients to meet the demands comfortably for first 4 months of life. Later demand increases and 1 quart milk is not sufficient for their growth and increasingly active bodies. After 6 months of age, nutrients are added such as iron through cereals with vitamins and minerals in milk. However, introduction of solid foods and obesity is controversial if fat cells are increased in 6 months during second half of the first year age. Issues of extra calories from solid foods and development of excess fat cells or obesity are still not resolved [16]. If relationship of excess fat cells and later obesity were to be proven, solid food at 6 months age or later seems feasible. In the following description, we describe the advantages of addition of solid foods in infant diet:

- Cereal is added between 4 and 6 months of age when a quart of formula or breast milk cannot satisfy the baby. Cereals are processed richer in thiamine, riboflavin, niacin, and iron in milk diet.
- Cereals are flakes, dehydrated form added in 4–6 months of age. Mostly cereals are added with thiamine, riboflavin, niacin, and iron to enhance nutrition value during first year. Cereals can vary as a very dilute mixture with flakes, thick paste, semisolid properly diluted cereal easy to chew and swallow.
- Cereals include rice, barley, oatmeal, grains, and other easily digestible feeds.
- Cereals should be allergen free. Rice is first introduced in small amount as thin gruel. With time, grain in cereals can be changed in increased amounts mixed with breast milk, ready-to-feed formula.
- Vegetables and fruits can be added to diet on a regular basis by 6 months or later. Each pureed fruit or vegetable should be added half a spoon to one spoon daily. Babies like vegetable and fruit varieties as mixture as sense of adventure with food if they are given different experiences in eating. However, in the beginning, single fruits or vegetables are good choice to identify allergic response.

- Meats and egg yolk are added with fruits and vegetables in baby feeds as dietary source of iron, copper, and vitamins in diets at the age baby reaches 6 months. Flavors and textures of added meats or egg yolks are also significant.
- Cottage cheese and high meat dinners may be served as main course of meal near at the end of first year as source of protein and energy. Strained meat has high protein quantity.
- Infants around 9 months old, they enjoy pick up foods and putting in mouth. Foods made of flour are rich in B vitamins and iron. Hand textured breads are more comfortable to babies experiencing teething problems. Zwieback or teething biscuits are recommended for babies with small appetite.
- Potatoes and pasta are added to meals at 8 or 9 months. These are easy to chew, with good texture, in small servings are acceptable at meals.
- An occasional dessert of fruits or custard can be fed, avoiding some items as cookies, cakes, candies.
- Strained baby foods are convenient foods. Strained fruits, vegetables, meats, egg yolks, pasta and meat combinations, combo meat dinners, fruit and cereal combinations often complete the infant nutritional needs. However, commercial companies have introduced to add flavors with added sugar. To keep low cariogenic effects of sugar and low renal solute load, commercial solid dehydrated flakes of strained baby foods were introduced as instant baby formulas. Instant baby foods can be diluted with fluoridated water to reconstitute according to the baby age. It can be stored tightly covered in container for later use without risk of spoilage due to low moisture content.
- Pureed baby food is strained food and can be easily prepared at home.
- During second half of first year, babies are ready for a diet based on Daily Food Guide, diet may look quite different from what is served at family table. Milk still serves greater portion in diet at the limit of 1 quart daily.

Daily Feeding of Solids

With growing age, infants need more varieties of foods in diet. A typical diet is given in Table 2.3 for a 7 months aged baby [17]. Daily menu may differ with families, preference of parents and baby feeder. Feeding infants with diets or foods supplemented with nutraceuticals [18] and complementary feeding practices is not established yet [19].

Table 2.3 Recommended intakes of vitamin A among lactating women, observed average intakes, and corresponding range of vitamin A in breast milk of women from developed and less-developed countries

Vitamin A amount	μg RE	RDA for lactation month 0–6
RDA	1,300	
FAO/WHO	900	>6–12
RDA	1,200	
FAO/WHO	900	
Maternal dietary intake		
Developed countries	1,543	
Less-developed countries	660	
Concentration of vitamin A in breast milk		
Developed countries	1.75–2.45 μmol/L	
Less developed countries	1.05–1.75 μmol/L	

Sources: *RDA* recommended dietary allowances; *FAO* Food and Agriculture Organization; *WHO* World Health Organization

Socialization and Transition to Adult Food

By 10 months of age, a gradual transition to chopped foods (junior foods) or coarsely mashed foods should be started to acquaint babies with pleasant textures that may require more chewing than is needed for strained foods [18]. Table foods without large supply of junior foods can be done by taking away baby's portion from cooked whole family food before mixing seasonings. Examples are eggs, cheese, boiled vegetables, deboned meats/fish, cooked fruits, avocado, banana, and boiled pastas to make junior foods. Sharing on common table with other family members, infants quickly become familiar to family meal. Infants and diets expand as they experience the whole range of foods eaten by others in the family. It gives them sense of togetherness. Transition to adult food is an empirical approach. It depends on growing child's taste, psychology, environment, social circle, family, parenthood, and food availability. Baby begins to eat enough vegetables, fruits, and milk. Transition to adult food may also give risks. For example, soups deserve attention in infant's diets at the end of first year. Soups further make babies full that they fail to eat food they need to obtain adequate nutrients. Replacing junior foods with concentrate soups is not good practice but risk of undernutrition [17]. Other example, pasteurized whole milk is good choice after first year. Low fat and nonfat milk is not good choice but cow milk along with low breast milk is good to infants till age of two [16]. Other example is intestinal bleeding due to an unwanted protein in milk. Unpasteurized cow milk has a protein which causes intestinal bleeding and high renal solute load to cause anemia and strain on the kidneys of infant.

Nutritional Risks in Infants

The importance of providing a broad range of foods in the diet without overfeeding is a key concept during a second half of the first year. With growing number of infant dietary supplementation, new challenges and risks have surfaced. Major challenges are weight control and management without sacrificing good nutrition during infancy. An anthropometric measurement such as infant weight for length is an appropriate measure of weight gain. Weight control can be achieved by two ways. Excessive weight gain is not really a good sign of baby growth but feeding according to the appetite of baby is right practice. One is food control using daily food table. Other way of exercise such as walking or crawling among babies gives them encouragement to muscular coordination exercise and physical activity. Weight gain varies from baby to baby; average weight gain is about 6 oz each week during first 6 months of life. The rate of growth slows in second 6 months. Height and weight gain tables for early childhood are available as standard. Although infants grow at different rates, growth charts are very helpful in monitoring the growth pattern and weight of individual children. First risk of weight gain is obesity. At the end of first year, babies may adopt transition to adult food such as learning to drink from a glass or cup, to hold finger foods in the hands and carry them to mouth, to want to eat food from the table.

On other hand, nutritional supplements and health risks of mothers also affect infant's health sooner and later in adolescence stages. In the following section, major causes of infant mortality are given with evidences including maternal and dietary supplements of vitamin A, lipids nutrients, increased risks of obesity, and ischemic heart disease. Present day, dietary supplements are advocated as measures of good nutrition in Infancy. In the following section, maternal status of vitamin A, requirements in infants, vitamin A deficiency, and overfeed risks are described in infants.

Maternal Vitamin A

Vitamin A is an essential nutrient because of its critical role in reproduction, the immune system, and vision, as well as in the maintenance of cellular differentiation [19]. These roles are particularly critical during periods of infancy and early childhood. Recently, awareness on maternal vitamin status has gained popularity in context with infant growth. Breast milk is the only source of vitamin A during the neonatal period for the exclusively breast-fed infant. It is the principal source for many infants from developing countries as long as breastfeeding continues. The ability to meet infant requirements, therefore, depends on the concentration and volume consumed, both of which are influenced by maternal vitamin A status and dietary intake.

Requirements of Vitamin A

The necessary nutrients in infants can be adequately provided from maternal reserves of women eating at concentrations above the United States recommended dietary allowance (RDA) of 800 μg retinol equivalents (RE)/day (2,700 IU). Vitamin A is stored for subsequent use when the diet provides amounts in excess of need and it provides a margin of safety. The median intake of vitamin A from food for lactating women in the United Kingdom is reported at 686 μg RE/day [20] and in the United States at 880 μg RE/day [21].

Consequences of Vitamin A Deficiency

Vitamin A deficiency may not be evident from observable signs in the mother, but the rapidly developing infants become vulnerable to subclinical deficiency. Night blindness during growth could signal of risk and warrant special attention [22]. Studies are needed to establish the vitamin A status of infants and pregnant women who report night blindness.

Lactation Requirements During Infancy

Vitamin A needs during lactation exceed because of increased demand by maternal tissues but to replace that lost daily in breast milk. Estimates of requirements during lactation, therefore, have been based on calculations of how much would be needed to replace that excreted daily in breast milk. The increased daily need according to the FAO/*WHO* is 300 μg RE/day, raising the recommended safe daily intake of vitamin A to 900 μg RE/day (3,000 IU) [23]. According to the United States RDA committee, a dietary increment of 500 μg RE/day (RDA of 1,300 μg RE, 4,330 IU) in the first 6 months of lactation and 400 μg RE/day (*RDA of* 1,200 μg RE, 4,000 IU) in the second 6 months fully meets the lactational demand [3]. Newman [24] summarized average daily intake data of unsupplemented lactating women from 19 studies in developed countries and 32 studies from developing countries and reported a difference of more than twofold, 1,543 μg vs. 660 μg RE/day, respectively. The average intake in developing countries, therefore, is about two-thirds of the recommended safe daily intake and less than half the average intake of lactating women in developed countries (Table 2.3).

Effect of Maternal Diet

Recent data indicated that the amount of vitamin A in breast milk is directly related to the maternal dietary intake, particularly at low concentrations of intake [25]. Providing supplemental vitamin A, either daily at physiological doses through a vitamin A-rich diet [26] or fortified foods [27, 28] or as a high-dose supplement immediately after birth [29], can increase breast-milk vitamin A concentrations. Breast-milk vitamin A concentrations in developed countries exceed an average of 2.1 μmol/L, whereas those from developing countries average under 1.75 μmol/L and are often near 1.05 μmol/L [24].

Prevalence of Nutritional Deficiency in Industrialized vs. Less Developed Countries

In industrialized countries, maternal nutrition status of pregnant and lactating mothers is considered major factor in infant growth and reduced risks in adolescence. Dietary surveys are available to assess the prevalence of deficiency among pregnant and lactating women and effect on growth rates of infants. Recently, the modified relative dose–response (MRDR) test showed 11% abnormal responses that suggested subclinical deficiencies [30]. However, additional information is needed using more specific and sensitive assessment methods to survey deficiency states among lactating women in the industrialized world. In industrialized countries, the vitamin A status of infants and children up to age 4 years is not established. The available data indicates that serum vitamin A values stabilize during the first 2 week of postnatal life and are homeostatically controlled after that, with an age-related increase at least through the first 6 months [30]. Application of more sensitive dose–response assessment methods to evaluate the vitamin A status of premature infants confirms their minimal body stores at birth that normally build postnatally in response to dietary intake [31]. Available data from the NHANES blood vitamin A surveys in the United States also suggest that vitamin A deficiency is not a public health problem in infants [32]. However, the NHANES surveys have not applied more sensitive assessment methods to determine if a subclinical problem exists, especially among certain high-risk groups. Very limited studies using the MRDR test in selected low-income participants in the Women, Infants, and Children's program report little evidence of subclinical deficiency [33], but these data are inadequate for determining population prevalence. In contrast to the situation in industrialized countries, in many developing countries vitamin A deficiency remains the primary cause of initiating childhood blindness and corneal disease [34, 35]. In addition, subclinical deficiency is a problem contributing to a risk of infant mortality from common childhood infections [35, 36]. The subclinical problem becomes manifest from 6 months onward even among breast-fed infants. It suggests that lactating women in these countries also have subadequate vitamin A status. Recent evidence from Indonesia indicated subclinical vitamin A deficiency among lactating women [29].

Vitamin A Deficiency in the Infants and Early Childhood

The regulated delivery of vitamin A to the fetus during pregnancy limits infant body stores of the vitamin at birth. Although the stores are somewhat higher in the full-term newborns of well-nourished mothers than of undernourished mothers, most available data suggest that the difference is small [37]. As noted earlier, infants born prematurely are especially vulnerable to limited body stores. Preterm infants are at a high risk for bronchopulmonary dysplasia, and vitamin A supplementation protects against this condition [38]. Without continued supplementation, suboptimal vitamin A status may

Table 2.4 Calculated vitamin A from breast milk relative to intake vitamin A requirements for newly born till over 14 months old infants

Infant Age	Milk daily (pmol/L)	VA daily (μg)	VA "excess" (μg)	Intake Vitamin A (mg)	Intake excess
0–6 months					
	700 mL	1.75	350	170	31
	700 mL	0.05	210	30	6
	700 mL	0.70	140	−40	−7
6–12 months					
	500 mL	1.75	250	70	13
	500 mL	1.05	150	−30	−5
	500 mL	0.70	100	−80	−15
1–2 years					
	250 mL	1.75	125	−175	−9

Intake from milk minus requirement: 180 μg/day required for 0–1 years of age, and 300 μg/day required for 1–2 years of age

persist for many preterm infants, possibly with health consequences [39]. This has been well described in the United States, but how it applies in the developing world, where the survival of preterm infants is rare, is not clear.

The limited body stores of vitamin A at birth may increase rapidly postpartum, depending on the diet [24, 37]. Colostrum and early breast milk are remarkably rich sources of vitamin A, exceeding 3.5 μmol/L. The concentration in early breast milk declines 50% over the first 4–8 weeks postpartum [24]. Early feeding practices, e.g. feeding colostrum and early milk, can therefore significantly augment the neonatal body stores at a time when requirements per kilogram to support growth are the highest experienced in postnatal life. Mothers are strongly urged to breast feed their infants exclusively for the first 4–6 months for many nutritional, immunological, and other health and sociological benefits well described elsewhere. The preformed vitamin A in breast milk, even from a poorly nourished mother, is adequate to meet basic physiological needs and to avoid clinical deficiency during the first half of infancy as given in Table 2.4. This is evident from both epidemiological studies [40, 41] and empirical calculations [24]. Breast milk from a malnourished mother who is deficient in vitamin A, however, may not be adequate to maintain and build body reserves in the rapidly growing infant. Thus, empirical calculations suggest that at the end of 6 months, the body stores of infants fed from mothers whose milk contains varied vitamin A concentrations can vary substantially as presented in Table 2.5. When the milk concentration is <1.05 μmol/L (30 μg/dL), the nursing's body reserve may be under the estimated critical concentration of 17.5 nmol/g to meet physiological needs in the latter half of infancy. Nursing infants of supplemented mothers were half as likely to have inadequate body stores by 6 months of age. It is indeed notable that 10% of those infants nursed by supplemented mothers showed evidence of inadequate body stores at 6 months and that this percentage paralleled the prevalence of supplemented women with breast-milk vitamin A concentrations <1.05 μmol/L. Benefits for the mother and infant alike, therefore, are strong reasons for improving the vitamin A status of lactating women, preferably through diet; however, where this is not easily accomplished and an early contact with the medical system occurs, improved vitamin A status may be managed through direct supplementation. Infants from age 6 months to 6 years who are depleted of body stores of vitamin A are at increased risk of death if they become infected. In areas where vitamin A deficiency constitutes a public health problem, the evidence is now convincing that improving the vitamin A status of such populations will generally decrease mortality rates by >20% [42]. Correcting the deficiency reduces deaths associated with diarrhea, measles, and other infections, and with protein-energy malnutrition by modifying the severity of these disorders, although not necessarily decreasing their incidence or prevalence. The effects of clinically evident vitamin A deficiency (xerophthalmia) during early childhood are recognized by professionals.

Table 2.5 Calculated total liver vitamin A from infants fed breast milk with different vitamin A concentrations at different periods during infancy

	mg (μg/g)	mg (μg/g)	mg (μg/g)
	1.75 μmol/L	1.05 μmol/L	0.7 μmol/L
Birth	3.5 (39)	3.5 (39)	3.5 (39)
3–6 months	34 (162)	9 (43)	
6–l2 months	47 (174)	3 (11)	–20

Vitamin A deficiency remains the leading cause of blindness during infant ages in the developing world, and it can occur as early as age 2 months in a nonbreast fed infant improperly fed in a deprived environment. Visual impairment is preventable but may not be reversible.

Iron Requirement for Infants

Most breastfeeding infants do not need any water, vitamins, or iron in addition to breast milk for at least the first 6 months. Human milk provides all the fluids and nutrients a baby needs to be healthy. By about 6 months of age, however, you should start to introduce your infant to baby foods that contain iron. Iron deficiency is rarely seen in breast-fed babies during the first 6 months of life. Iron is present in your milk. Although human milk does not contain large amounts of iron, it is very well absorbed. Approximately 50% of the iron in mother's milk is absorbed. Iron in human breast milk is well absorbed by infants. It is estimated that infants can use greater than 50% of the iron in breast milk as compared to less than 12% of the iron in infant formula. The amount of iron in cow's milk is low, and infants poorly absorb it. Feeding cow's milk to infants also may result in gastrointestinal bleeding. For these reasons, cow's milk should not be fed to infants until they are at least 1 year old. Gradual introduction of iron-enriched solid foods should complement breast milk from 7 to 12 months of age. Infants weaned from breast milk before 12 months of age should receive iron-fortified infant formula. Infant formulas that contain from 4 to 12 mg of iron per liter are considered iron fortified. As your infant grows, you can increase the absorption of iron (nonheme) from "plant" foods as well as the (heme) iron from "protein/meat" foods when a food containing vitamin C is eaten at the same meal or snack. Serving cereals with a fruit that contains Vitamin C would aid in the absorption of the iron contained in the cereal product.

Eating foods that are high in Vitamin C will help the body absorb nonheme iron that is present in most foods served in a meal. The majority of iron that most people receive is nonheme iron; this type of iron has less bioavailability and is absorbed in smaller quantities by the body. Vitamin C also helps to utilize iron.

Potential for Maternal Supplementation to Improve Infant Outcomes in Developing Countries

A potential exists to improve the status of infants through maternal diet and/or high dose supplementation. Preferred intervention is through a diet that provides a safe concentration of intake throughout pregnancy and lactation. A vitamin-deficient mother may still obtain benefits from low-dose vitamin A supplementation. Her status will improve and, in turn, influence to some extent her infant's stores. High-dose supplementation of the lactating mother immediately postpartum may be the safest and most effective approach to improve her status and that of the nursing infant. Single boluses of 60,000–90,000 μg RE (200,000–300,000 IU) have been given with no evidence of toxic effects on either the mother or her nursing infant [24, 37].

Some people advocate direct infant supplementation in the first half of infancy as a more direct means of assuring adequate vitamin A status by 6 months of age. This recommendation includes infants from vitamin A-deficient areas even when the mother also has been supplemented with high-dose vitamin A. A cost-effective delivery system exists through immunization systems, such as the WHO Expanded Program of Immunization (EPI). Currently, the policy of the WHO supports supplementation at any contact from age 6 to 12 months with 30,000 μg RE (100,000 IU) and particularly emphasizes using the measles immunization contact for this purpose where measles case fatality rates exceed 1% [43]. Vitamin A supplements during late infancy and early childhood meet an urgent need for children under 5 years, growth-monitoring sessions, and other community programs that gather mothers and their infants into group activities. These opportunities should be used to increase awareness and provide educational programs to improve infant care and feeding practices. Communities and families must be empowered to be dependent in meeting their families' needs for an adequate diet and basic human rights. In the following section, risks of weight gain and obesity is described in infants.

World Health Organization Recommendations: Infancy Weight Gain and Obesity

Rapid early postnatal infant weight gain predicts well the increased risk of obesity. However, the exact timing of adverse rapid postnatal weight gain is unclear. Previous prospective cohort study in 248 (103 males) singletons and their mothers showed height and weight at birth, 6 months, 3 and 6 years were associated with weight gain during infancy (0–6 months) and early childhood (3–6 years) [44]. Increased weight gain during infancy and early childhood both independently showed association with larger body mass index (BMI), fat mass, relative fat mass, fat-free mass (FFM), and waist circumference at 17 years ($P<0.005$ for all; adjusted for sex, birth weight, gestational age, current height, maternal socioeconomic status, and maternal fat mass). Rapid weight gain in infancy, but not in early childhood, also predicted taller height at 17 years [45]. Rapid weight gain in both infancy and early childhood is a risk factor for adult adiposity and obesity [46]. Rapid weight gain in infancy also predicts taller adult height. Rapid weight gains in infancy and early childhood are different processes and may allow separate opportunities for early intervention against obesity risk later in life [47].

Overweight and obesity in infants and adolescents are rapidly increasing in prevalence worldwide and are related to a wide range of adverse outcomes [46]. Perinatal life has been identified as a key period for the development of obesity. High birth weight is associated with an increased risk of later obesity. Conversely, lower birth weight and slim size at birth have been linked to increased central fat, impaired glucose tolerance, and features of the metabolic syndrome later in life [47, 48]. Low-birth-weight intrauterine growth-restricted infants usually compensate by showing rapid catch-up growth during the first year of life [46, 49]. Postnatal rapid weight gain seems a risk factor for later obesity, elevated blood pressure in adolescent males, impaired glucose tolerance in young adults, and increased mortality from coronary heart disease [50]. However, the exact timing of rapid postnatal weight gain in relation to later obesity risk is unclear.

Rapid weight gain, or upward percentile crossing, during the first 2 years of life has been linked to general and central adiposity at age 5 years [51]. More recently, rapid weight gain during the first week or 1 month of life was shown to be associated with an increased risk of overweight and obesity, on the basis of BMI (in kg/m^2), in childhood and in young adulthood [52]. However, it has been debated whether rapid weight gain during infancy or early childhood (the period of the "adiposity rebound" at 3–6 years) may contribute to obesity and the adult metabolic syndrome [53]. It is unknown whether rapid postnatal weight gain is associated with a general increase in body size, i.e. increase in fat mass (FM), FFM, and height or a selective increase in these components of body composition [54–57].

In a healthy contemporary birth cohort study, rapid weight gain during both infancy (0–6 months) and early childhood (3–6 years) were related to long-term changes in body composition. A gain in weight of 1 SD score in infancy and in early childhood was associated with an increase in FM of 1.8 and 3.4 kg, respectively, and with an increase in FFM of 1.0 and 1.4 kg, respectively, at age 17 years [44]. Upward weight percentile crossing at these early ages also predicted larger BMIs and waist circumferences in young adulthood, whereas rapid weight gain in infancy also predicted taller adult height [57, 58].

Although the effect of weight gain in early childhood on obesity risk appeared to be greater than that of weight gain in infancy, rapid weight gain occurred more commonly during the shorter infancy period (25.4%) than during early childhood (8.8%) similar with other studies [59]. Thus, the population attributable risk (an estimate of the proportion of all overweight subjects that could be prevented if each risk factor were removed) was slightly higher for rapid weight gain in infancy (15.7%) than for rapid weight gain in early childhood (11.7%).

It is believed that rapid weight gain in infancy leads to obesity risk later of obesity. Rapid weight gain in infancy and early childhood are at least partly mediated by different mechanisms supported by inverse interrelation and by their differing effects on childhood height [60–63]. Rapid weight gain in infancy, or "catch-up," can be explained by compensatory mechanism following intrauterine growth restraint [64]. It was based on the fact that children who show rapid weight gains in infancy remain shorter, lighter, and thinner at birth than other children at adolescence. In contrast, children with rapid weight gains in early childhood remain same in size at birth from other children [65]. A previous population study suggested that rapid weight gain in infancy is mediated by decreased satiety and food composition [66], and another study reported that energy intake and sucking behavior, but not total and nonsleeping energy expenditure, predict infancy weight gain [67]. Duration of breastfeeding and the introduction of complementary foods influence the weight gain between birth and 1 year. Maternal weight gain during pregnancy seems associated with weight gain in infancy. Lower weight gain in infancy may partly underlie the protective effects of breastfeeding and of lower nutrient milk formulas on later obesity and cardiovascular disease risk.

Rapid weight gain in infancy, but not in early childhood, predicted an increase in height at their age of 17 years was health related [61]. Rapid weight gain in infancy was shown to be associated with subsequent higher insulin-like growth factor I concentrations [68], and this major childhood growth factor could mediate the subsequent gains in lean body mass and height. Considering its high prevalence, rapid weight gain in infancy could have heterogeneous effects on subsequent statural growth and body composition. It is possible that interindividual differences in insulin-like growth factor I secretion or activity could lead to variations in height and lean mass gains and in disease risks in response to rapid weight gain in infancy.

Rapid weight gain in early childhood was also consistently and independently associated with an overall increase in FM and FFM but not in height [69]. The determinants of rapid weight gain such as birth size, early growth, obesity during early childhood are largely unproven [70]. Compared with the infancy period, different environmental factors are likely to be important, including childhood food consumption patterns [67] and a sedentary lifestyle [68]. However, the causal associations of environmental factors during infancy with blood pressure, coronary heart disease, cardiovascular disease, and physical activity in adolescence remain to be demonstrated [71–74].

In a recent longitudinal study, physical activity-related energy expenditure, assessed by the doubly labeled water method, did not predict future weight and FM gain in children [75]. Future studies using other robust methods of assessing physical activity during daily living may help to clarify this issue. Food intake, especially of energy-dense foods, may also contribute. For example, the consumption of sugar-sweetened soft drinks among children has more than doubled during recent decades [76]. Excessive intake of sweetened drinks is associated with greater childhood weight gain [77], and the odds of becoming obese may increase by as much as 60% with each additional daily serving of sugar-sweetened drinks [78]. Similar findings were recently reported in adult women [79].

Prospective studies incorporating careful characterization of childhood growth; body composition; and endocrine-, metabolic-, social-, nutritional-, and energy expenditure related factors would advance our understanding of paradox and these complex associations. Identification of the mechanisms that underlie rapid weight gain in early life is likely to be important to understand how to prevent obesity throughout life.

Most of observations of independent associations between rapid weight gain in infancy and childhood with body composition and height at infancy age 1–2 years are consistent and valid by continuous and stratified analytic approaches. Now science of infant growth and childhood development is advancing for potential confounding factors including environmental, social, physical, behavioral, endocrine, metabolic, and nutritional factors with known variables that are plausibly associated with infancy and childhood growth. Furthermore, all data suggest the weight gain in offspring may be overestimated or less predictive decreased risk of recall bias or unreliable measurements. Birth weight and body composition in adolescence samples has remained major focus in the larger cohort studies on the basis of the availability of early growth measurements. Birth weight and BMI of females during infancy and adolescence were not significantly different from Swedish reference data [69]. Fat mass and prevalence of obesity robustly predict overweight and obesity risk related to rapid weight gain in infants. However, the unadjusted relative risk of rapid weight gain in early childhood seems significantly related to the risk in young adulthood, and the relative risks. Previous report suggested that rapid weight gain, or upward percentile crossing, in infancy and in early childhood both predict increased adiposity and obesity risk in young adults [53]. We believe that rapid weight gain in infancy and childhood may be mediated by different factors and may provide separate opportunities for targeted interventions to prevent the development of obesity.

Present Developments and Future Prospective

Weight gain, rapid growth, sugar control, maternal nutrition, and infant feeding are major factors in infant growth regulated by infant nutrition. Federal agencies and governments are focusing on developing infant nutrition programs, advice on maternal diets, and breastfeeding schedules [80–82]. Preclinical and clinical evidences now strongly suggest mother milk during first 6 months, continued breast feed during 1–2 years with added dietary supplements including dietary nucleotides [80], lipid-based nutrients [83], lamb-based infant food [84], long chain fatty acid and fish oil-rich foods [85–89], osteogenic vitamin D and minerals [90–95], iron [96–100], zinc [101, 102], fluoride [103], iodine [104]. Very recently, dietary supplements in disproportion have been identified as risks to infants including iodine deficiency [104] and anthocyanins [105]. With experience, preclinical studies on infants suggest new evidences of new emerged nutritional factors as responsible of risks for obesity [106, 107], ion transport and enterocyte proliferation [108], weight gain, malnutrition, heart [109], and neuropsychological risks [110]. Moreover, such empirical association has implications for the management of infants born small for gestational age and suggests that the primary prevention of obesity could begin in infancy [107]. Breast feeding still serves as gold standard of protective measure in infancy against inflammation [111] and obesity [112]. Infant feeding schedule with right mixing solid foods approach plays a significant role to keep low risk of obesity [113–115]. In future, federal and nongovernment agencies will play significant role in designing and implementing food programs for maternal nutrition including pregnant, lactating mothers at care centers with improved infant feeding schedules during 6 months, 6–12 months, and 1–5 years in order to keep low risks of diseases and health consequences during infancy, childhood, and adolescence. Present time challenge is growth acceleration as a consequence of relative over nutrition in infancy with increased risk of later obesity [116]. In recent report, fat mass was main determinant in early growth promotion and later body composition in infants born small for gestational age [107]. Report showed a subset of children ($n = 153$ of 299 in study 1 and 90 of 246 in study 2) randomly assigned at birth to receive either

a control formula or a nutrient-enriched formula (which contained 28–43% more protein and 6–12% more energy than the control formula) at 5–8 years of age. Fat mass was measured by using bioelectric impedance analysis in study 1 and deuterium dilution in study 2. Fat mass was lower in children assigned to receive the control formula than in children assigned to receive the nutrient-enriched formula in both trials (mean (95% CI) difference for fat mass after adjustment for sex: study 1: −38% (−67%, −10%), $P=0.009$; study 2: −18% (−36%, −0.3%), $P=0.04$). In this nonrandomized analysis, faster weight gain in infancy was associated with greater fat mass in childhood [107]. Infant mortality and keeping low risks of common induced diseases still remains a challenge since four decades and it needs attention to develop protective measures to keep low risks of them. In a review report, rise in ischemic heart disease in England and Wales was associated with increasing prosperity, and mortality rates are highest in the least affluent areas [117]. Of the 24 common causes of death, only bronchitis, stomach cancer, and rheumatic heart disease were related to infant mortality. Ischemic heart disease was strongly correlated with both neonatal and postneonatal mortality. These diseases are associated with poor living conditions in present time and infant mortality from them is declining due to role of nongovernment organizations and effective social service network. It is suggested that poor nutrition in early infant life increases susceptibility to the effects of an affluent diet.

Conclusion

Growing infant in first 6 months has very high demand of nutrients. In third world countries, infant growth is related with socioeconomic-geographical factors. More than two-third breast-fed infants in rural population further require vitamin D and iron supplementation with commercially available cereal or milk formulas during first 6 months due to poor nutrition of lactating mothers. Additional requirement of fluoride supplementation is needed throughout childhood if water supply does not have fluoride. In premature or small-for-date infants require special infant diet preparation and nutrition planning. For infant growth, meal service etiquettes, motivation and additional factors play a great role in reducing risks:

- Calm environment and social interaction encourage the infants to serve themselves.
- With growth, switching to solid foods between 4 and 6 months according to baby size and appetite.
- A plain rice cereal diluted to thin gruel fed without sugar is good choice of solid food.
- Cereals may be added to other solid vegetables and fruit foods according to the baby's physical development and eating skills.
- Egg yolk and strained meats or beans mixed with custard to provide adequate vitamin, minerals, and proteins as nutrients.
- Motivation to chew and swallow strained solid commercial strained foods. Modification in foods provides adequate vitamin, minerals, and proteins as nutrients.

Inadequate feeding may cause malnutrition and loss of appetite while overfeeding may be a risk of obesity, weight gain, and excessive load on intestinal and kidneys. Lactating mothers need awareness:

- After first year of age, infants are ready to shift from formula to whole milk and to learn drinking from a cup, eat chopped food. The transition to table food needs supervision of parents but it is a risk if highly nutrient-enriched diet in infancy can also increase fat mass later in childhood.
- Faster early weight gain may also result a later risk of obesity.
- Management of infants born small for gestational age needs awareness that the primary prevention of obesity could simultaneously begin infancy.

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Chapter 3
Nutritional Concerns of Aboriginal Infants and Children in Remote and Northern Canadian Communities: Problems and Therapies

Noreen Willows and Malek Batal

Key Points

- Great disparities in health outcomes exist between First Nations, Métis and Inuit (collectively referred to as Aboriginal in this chapter) and the general Canadian population.
- Among the Aboriginal population the prevalence of many infectious diseases (e.g., tuberculosis) and lifestyle-related chronic conditions and diseases (e.g., obesity and type 2 diabetes mellitus) is higher than among the general Canadian population.
- A higher percentage of Aboriginal infants and children suffer from poor health (e.g., high prevalence of overweight and obesity and much higher rates of preterm birth, stillbirth, and infant death).
- Aboriginal infants and children in northern Canada have high rates of nutrient deficiencies, particularly iron and vitamin D.
- Increased availability of traditional game, fish and fowl would likely increase young children's vitamins A and D, iron, magnesium, and zinc status.
- Breastfeeding has the potential to protect children from overweight and obesity and is a nutritionally sound and culturally appropriate strategy to combat nutrient deficiencies, with the possible exception of vitamin D.
- Breastfeeding promotion may alleviate some of the health problems experienced by Aboriginal infants and children in northern regions such as otitis media and dental caries.
- Breastfeeding promotion will not be effective unless barriers to breastfeeding are addressed.
- The promotion of maternal health, including the provision of excellent prenatal and postnatal care, in addition to improved socioeconomic and living conditions has the potential of improving the health of Aboriginal infants in Canada's north.

Keywords Aboriginal • Canada • Infants • Nutrition • Northern Canada • Breastfeeding • Health

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R.R. Watson et al. (eds.), *Nutrition in Infancy: Volume 1*, Nutrition and Health,
DOI 10.1007/978-1-62703-224-7_3,

Health Concerns of Aboriginal Peoples in Canada

In Canada, "Aboriginal peoples" is the term used to describe the descendants of the original inhabitants of North America. The Canadian Constitution recognizes three groups of Aboriginal people—Indians (i.e., First Nations), Métis and Inuit, each with unique heritages, languages, cultural practices, and spiritual beliefs [1]. In the 2006 Canadian Census, the number of people who identified themselves as Aboriginal surpassed the one-million mark. The Aboriginal population is growing nearly six times faster than the non-Aboriginal population. This great rate of population growth will continue given high birth rates, a low median population age, and a large proportion of the population that is comprised of children [2].

Among the Aboriginal population, the prevalence of many infectious diseases (e.g., tuberculosis) and lifestyle-related chronic conditions and diseases (e.g., obesity and type 2 diabetes mellitus) is higher than among the general Canadian population [3]. Based on observations from the historical record, lifestyle-related chronic diseases such as type 2 diabetes mellitus were uncommon or virtually unknown less than a century ago [4]. Today, obesity-associated conditions such as the metabolic syndrome and diabetes are observed even among Aboriginal children [5]. Aboriginal peoples, similar to many indigenous populations worldwide, are undergoing rapid cultural changes including the nutrition transition resulting in both overnutrition (i.e., excess caloric intake) and undernutrition (e.g., micronutrient deficiencies) which may co-occur within individuals or within households [6, 7]. The poorer health of the Aboriginal population must be understood within the context of these modifications to often health-promoting traditional lifestyles, in addition to oftentimes limited access to culturally appropriate health services and traditional foods, food insecurity, and poverty [6, 8, 9].

An unacceptably high percentage of Aboriginal infants and children suffer from poor health [10, 11]. Infant mortality is a key indicator of the health of a population. Despite a long-term decline in Aboriginal infant mortality rates, the Aboriginal population still has infant mortality rates that range from 1.7 to over four times the overall non-Aboriginal rates. The elevated postneonatal infant mortality rate among Aboriginal infants includes a greater proportion of deaths from congenital conditions, sudden infant death syndrome (SIDS), and infections [11]. Clearly focusing on infant and child health is paramount to improving the general well-being of Aboriginal peoples.

Health Concerns of Aboriginal Populations in Northern Canada

Aboriginal persons in Canada's North (Yukon, Northwest Territories, Nunavut, Nunavik) are experiencing detrimental health problems as a result of rapid changes to their social, cultural, and physical environments. Among the Inuit, injury and social pathologies including domestic and other violence, suicide, and substance abuse contribute substantially to suboptimal health [12]. The same issues occur in many First Nations communities [13]. Poverty contributes to inadequate nutrition, and many health problems and their poor management [3, 6, 14].

Although in Canada the Aboriginal population as a whole has poorer health and health practices than the non-Aboriginal population, obesity, daily smoking, and infrequent physical activity are more prevalent for Aboriginal peoples in northern Canada than for Aboriginal peoples in southern Canada [3, 10]. Whereas type 2 diabetes mellitus prevalence in the Inuit population was once lower than the Canadian average, data from the International Polar Year Inuit Health Survey for Adults 2007–2008 shows that diabetes prevalence among Inuit is now comparable to that of the general Canadian populace [15]. Similarly, obesity is common among First Nations in northern regions [7, 10].

Aboriginal infants and children in the Canadian North and in the northern parts of many Canadian provinces have numerous health challenges and suboptimal living conditions. In 2001, the majority

(79%) of Inuit children 0–14 years of age were rated by caregivers as being in excellent or very good health. This was lower than the average (87%) for all children in Canada [16]. The 2007–2008 Nunavut Inuit Child Health Survey (www.inuithealthsurvey.ca) provides a comprehensive overview of the cultural, socioeconomic, and health indicators of Inuit preschoolers aged 3–5 years. In the survey, caregivers' assessment of their child's health was excellent (22.8%), very good (31.6%), good (37.3%), fair (7.7%), and poor (0.5%) [17]. Many children in the 2007–2008 Nunavut Inuit Child Health Survey lived in homes that were crowded and/or in need of major repairs [17]. Nearly 70% of the preschool children resided in households that were food insecure, and 25.1% lived in homes that were severely food insecure implying reduced food intake and disrupted eating patterns. Caregivers reported that children in severely food insecure households had times in the past year when they skipped meals (75.8%), went hungry (90.4%), or did not eat for a whole day (60.1%) [14]. Given these abject living conditions, it is not surprising that 41.6% of children aged 3–5 years were reported to have been hospitalized at least once (not including for delivery), and that within the past year, 40.7% had been taken to the health center or hospital for a respiratory problem [14].

A number of studies over the past 20 years have documented a high prevalence of overweight and obesity in Aboriginal children living in the North and the northern parts of the provinces of Ontario and Quebec, including among children as young as 2 years old [5]. Rising rates of obesity in Inuit children forewarn of future increases in the prevalence of T2DM, heart disease, and high blood pressure in Inuit-inhabited regions [14, 15, 18]. One explanation for why obesity is so common among Aboriginal children may be that the poor often have few affordable healthy food choices available so eat low-cost high-calorie market foods [19]. Indeed, the explanation offered as to why Inuit preschool children in Nunavut are predominantly overweight or obese despite living in homes with food insecurity is the consumption of readily available energy-dense and highly processed foods in the Arctic [14, 17]. Undoubtedly, strategies to improve early childhood nutrition and increase children's physical activity are essential to reverse this trend toward even very young children having excess body weight [5].

Inuit-inhabited areas of Canada have much higher rates of preterm birth, stillbirth, and infant death compared to the rest of Canada and other rural or northern areas [10, 11, 20]. Indeed, the rate of infant death in Inuit-inhabited regions is 16.5/1,000 live births, equivalent to the rate in the general Canadian population in 1971 [20]. Excess infant mortality in Inuit regions is observed for congenital anomalies, immaturity-related conditions, asphyxia, SIDS, infection, and external causes [20]. Maternal smoking is more prevalent among Inuit women than among other women in Canada and is an important risk factor for preterm birth, SIDS, and postnatal respiratory tract infections [10, 20].

Breastfeeding and Infant Health

A vital food for Aboriginal infants is human breast milk. We therefore center our discussion in the remainder of this chapter on how breastfeeding promotion may alleviate some of the health problems experienced by Aboriginal infants and children in northern regions, while being mindful of the myriad issues faced by Aboriginal mothers that may preclude women from breastfeeding their children, or providing them with optimal care in other ways. We raise some of the concerns surrounding breastfeeding in northern Aboriginal populations, such as environmental contaminants in breast milk and associations of breastfeeding with vitamin D deficiency. We also discuss the nutritional and cultural significance of traditional food harvested from the land and sea as important complementary and weaning foods to ensure infant health.

Breast milk is the most secure and economically advantageous form of infant nutrition in northern and remote regions where infant formula is expensive to purchase, or where the quality of the water supply used to make infant formula is questionable [21]. Health Canada promotes breastfeeding as the

best method of feeding infants as it provides optimal nutritional, immunological, and emotional benefits for the growth and development of infants [22]. The First Nations and Inuit Component of the Canada Prenatal Nutrition Program of Health Canada promotes breastfeeding; however, the program is limited to mothers of infants up to 12 months of age who live on reserves[1] or in Inuit communities, particularly those identified as high risk [23].

Despite the essential role of breast milk to infant health [24–26], too few Aboriginal infants in Canada are breastfed. Data from the First Nations Regional Health Survey (RHS) collected in 2008–2010 indicates that 57.5% of children living on-reserves are breastfed. As the education level of First Nations women increases, so does the likelihood that they breastfeed their children. About 50% of mothers with less than a high school education breastfeed their children, compared to 71% with a diploma/certificate and 75.4% of mothers with a university degree. The RHS did not provide specific breastfeeding information for northern communities [27]. The most recent data (2007–2008) about breastfeeding in off-reserve[2] Aboriginal mothers indicated that 81.5% initiate breastfeeding, somewhat lower than the rate of 88.3% among non-Aboriginal mothers [28]. Again, data were not provided for only northern regions. Findings from the 2001 Aboriginal Peoples Survey revealed that the percentage of 0–3-year-old Inuit children who had been or were being breastfed (66%) was lower than the national average at the time (80%); however, when Inuit children were breastfed it was for a longer period of time [16]. The differences in rates of breastfeeding initiation between Inuit and other Canadians are possibly attributable to higher rates of adoption among Inuit. Recent data from Nunavut indicate that while only 67.6% of Inuit children receive any breast milk, among nonadopted infants there is an 80.6% rate of breastfeeding initiation. The mean number of months a breastfed Inuit child is fed any breast milk is considerable at 17.4 months (95% CI: 15.3–19.7 months) [17].

Benefits of Breastfeeding

Aboriginal populations in Canada suffer from higher incidences of SIDS than non-Aboriginal groups. The morbidity/mortality rates experienced by Canadian Aboriginal populations were reported to be 3–7 times that of non-Aboriginals, with upper track respiratory infection and SIDS reported as the chief causes [29]. Breastfeeding has been found to protect from SIDS, however the association is not always consistent. In a meta-analysis of 23 scientific publications, 19 found a protective effect of breastfeeding on SIDS with bottle-fed infants being twice as likely to suffer from SIDS [30]. Similarly, in a recent meta-analysis, breastfeeding was found to reduce the risk of SIDS by about 50% [31]. On the other hand, a number of studies have argued that the protective effect of breastfeeding is often confounded by other variables; particularly maternal smoking [32] and that the association between breastfeeding and SIDS [33] is either weak or inexistent as reported in a prospective study completed in New Zealand [34]. In view of the magnitude of the problem of SIDS among Aboriginal communities, however, public health messages should take into account the possible protective effects of breastfeeding.

Infants in the North suffer disproportionately from bacterial and viral infections [10]. Reduction in infectious disease may be of particular importance to Aboriginal infants living in remote locations with limited access to health professionals. In particular, otitis media is endemic among Inuit, First Nations, and Métis children in northern Canada with prevalence rates in some communities as high as

[1] A reserve is a tract of land, the legal title to which is held by the Crown, set apart for the use and benefit of an Indian band.

[2] A term used to describe people, services, or objects that are not part of a reserve.

40 times that found in the urban south [16, 17, 35, 36]. Ear infections or ear problems were the most common chronic health conditions reported for Inuit children 0–14 years old in the 2001 Aboriginal People's Survey, with 11% of children having them [16]. Data from the 2007–2008 Nunavut Inuit Child Health Survey indicated that 36.4% of preschoolers had a past-year ear infection or earache, and 12.3% suffered from six or more episodes [17]. Hearing loss attributable to chronic otitis media is common among First Nations and Inuit children and adults in northern regions [35].

Conditions associated with otitis media are bottle feeding, exposure to cigarette smoke, and upper respiratory tract infections [35]. For decades, there has been evidence that bottle-fed Inuit infants were at greater risk than breast-fed infants for otitis media [35]. One study from the 1970s found that the prevalence of otitis media in Inuit infants was inversely related to the age at which bottle feeding was started. Indeed, there was a significant decrease in the prevalence of otitis media with increasing age at the onset of bottle feeding, and no Inuit child bottle fed for the first time after the age of 6 months acquired the disease [36]. Given these facts, health promotion strategies to prevent otitis media would include the targeting of breastfeeding, access to clean water, immunization, smoking cessation, adequate nutrition, hygiene, improved housing, and reduced household overcrowding [35].

Inuit and First Nations preschool aged children have a high prevalence of extracted, filled, or decayed deciduous teeth [37–42]. Data from the 2001 Aboriginal People's Survey showed that approximately one quarter of Inuit children from Nunavut, Nunavik (northern part of the province of Quebec), and the Inuvialuit region of the western Canadian Arctic, and about 35% from Labrador were in need of dental care [16]. Most Inuit communities are not regularly serviced by a resident dentist; dentists from southern Canada fly into remote communities sporadically throughout the year. Thus, limited access to dental care was the most frequently cited reason for Inuit children not having a dental appointment [16].

The relationship between breastfeeding and dental caries has not been always clear. Breastfeeding was once considered a cause of dental caries [43]. Some studies have reported that breastfeeding has no effect on dental caries [44]. It is however clear that sugary drinks such as fruit juice, fruit juice punches and beverages from drink crystals, and soft drinks, often displace breast milk, and these sugary alternatives are directly associated with an increase in the number of dental caries in children [37, 39, 44].

Infant feeding practices can modify the rate at which infants grow and their adiposity. Willows et al., in a study of Cree First Nations infants in northern Quebec, found that bottle-fed infants had significantly greater weight gain between birth and 9 months compared to breast-fed infants. On average, formula-fed babies gained 724 g more weight than breastfed babies [45]. A study by Mai et al. that included Aboriginal children showed that children who were exclusively breastfeeding for <12 weeks were more likely to be overweight at age 8–10 years than children who were exclusively breastfed ≥12 weeks [46]. Given this and other evidence, the First Nations and Inuit Health Committee of the Canadian Paediatric Association considers that breastfeeding is the most natural component of a traditional Aboriginal diet and should be encouraged as a proven method of reducing obesity in children [47].

Some studies have indicated that breastfeeding may reduce the risk of developing type 2 diabetes mellitus, a disease commonly associated with excess body weight in the Aboriginal population. In a case–control study among Aboriginal Canadians, the risk of T2DM was lower among adolescents who had been breastfed for longer than 12 months compared to those who had not been breastfed after adjusting for maternal diabetes status (OR 0.24, 95% CI 0.13–0.84) [48]. In a cohort of Pima Indians in the United States, the offspring of women who were exclusively breastfed for at least 2 months had about half the prevalence of diabetes by 10–39 years of age compared to those who were not breastfed [49]. Given these findings, improved rates of infant breastfeeding could potentially reduce the risk for developing T2DM among Aboriginal infants.

Iron-deficiency anemia is prevalent among Aboriginal children in Canada and Native American Indian and Alaska Native children in the United States [45, 50, 51]. Dietary risk factors for anemia include bottle feeding with low-iron formula or cow's milk, the absence of iron-rich complementary foods following 6 months of age, and prolonged exclusive breastfeeding past 6 months of age [50–52].

Maternal anemia is associated with anemia in Cree First Nations infants in northern Quebec [21]. Data from the 1990s showed that among Inuit infants in northern Quebec the prevalence of anemia was 21.1%, 47.4%, and 37.7% at 2, 6, and 12 months of age, respectively. The corresponding values for iron-deficiency anemia at 2, 6, and 12 months were 1.3%, 24.4%, and 26.3%, respectively. Breastfed infants were better protected against iron deficiency than infants bottle fed with cow's milk or low-iron formula [52].

To reduce iron deficiency in Aboriginal infants, multiple health promotion activities that are mutually reinforcing are required. Strategies to improve the iron stores of newborns could include improving women's access to nutritious foods prior to, during, and following pregnancy; supplementing pregnant women with iron; and delaying umbilical cord clamping at birth [53]. Universal supplementation of women of childbearing age with iron might be appropriate to prevent iron deficiency in mothers and their infants [53]. The limited data suggest that supplement use among Aboriginal mothers in the North is low. One study found that only 38% of Inuit mothers in Nunavut took prenatal vitamins or multivitamins during pregnancy and not all of those women took iron [17]. Considering the potentially low use of iron supplements, promoting the consumption of locally available iron-rich foods (marine mammals, game meat, and wildfowl) is also necessary.

To prevent anemia, nutritional interventions in infancy must begin with the promotion of breastfeeding or iron-fortified infant formula for infants whose mothers choose not to breastfeed or who have been adopted by family members. After that, interventions to ensure the introduction of iron-rich solids such as meat and iron-fortified infant cereals beyond 6 months of age are required while avoiding the early introduction of cow's milk [53, 54]. Iron-fortified cereals are expensive to purchase in remote communities; however, wild meats, many of which were, and continue to be, part of traditional Aboriginal child feeding practices are a culturally appropriate alternative [17].

Specific Issues with Breastfeeding in Northern Regions

Inuit consume marine mammals and fish, which results in exposure to environmental contaminants concentrated through the food chain [55]. These same contaminants appear in breast milk [56]. Many health effects of environmental contaminants are subtle and difficult to detect. Often, benefits and harm need to be carefully considered. The potential disease producing effects of contaminants in breast milk need to be weighed against the health-promoting and disease-preventing benefits of breast milk. To lower the concentration of contaminants in breast milk, women could be advised to substitute the most polluted food items with other traditional foods.

The major source of vitamin D for most humans is sun exposure [57]. Given the high latitude of northern Canada, Aboriginal infants and children in the region may be at risk for vitamin D insufficiency due to insufficient cutaneous production. Indeed, the prevalence of vitamin D insufficiency (<75 nmol/L plasma 25-hydroxy vitamin D) among Inuit preschoolers included in the 2007–2008 Nunavut Child Inuit Health Survey was 78.6% in the summer months and 96.8% in the winter months [58].

Historically, Aboriginal people living in the Arctic and other northern regions spent months without sunlight, or wearing thick, fur clothing that blocked sunlight yet maintained good vitamin D status by eating cold-water fishes and sea mammals. Today, due to changing eating habits, diseases such as rickets associated with vitamin D deficiency occur in Inuit and other northern populations. In Canada, the prevalence of rickets among children 1–2 years is estimated to be 12 cases/100,000 with the highest incidence rates occurring in the Yukon Territory (150 cases/100,000), Nunavut (141 cases/100,000), and Northwest Territories (79 cases/100,000) [59]. In Nunavut, rickets caused by inadequate vitamin D intake are common enough that vitamin D inadequacy is a recognized public health problem [60].

To reduce childhood rickets and infants with vitamin D inadequacy, strategies to improve the nutrition of both infants and women of childbearing age are required. This is because infants acquire body

stores of vitamin D transplacentally and that the concentration of vitamin D in breast milk depends on the mother's vitamin D status [61]. Maternal risk factors for child rickets in Canada include limited sun exposure and a lack of vitamin D from diet or supplements during pregnancy and lactation [59].

Infants who are formula fed receive adequate vitamin D from formula regardless of sun exposure [62]. In contrast, breast milk typically contains an insufficient amount of vitamin D to prevent rickets in infants with limited sun exposure [63–66]. Almost all (94%) cases of child rickets in Canada between July 1, 2002 and June 30, 2004 occurred among children who had been breast fed without receiving vitamin D supplementation; no case of rickets was reported among breast-fed infants who regularly received vitamin D supplements [59]. The Canadian Paediatric Society recommends that breast-fed infants who reside above the 55th latitude receive 800 IU/day of vitamin D from October to April when little vitamin D is formed from sun exposure [67]. Information could not be found about the percentage of Aboriginal infants above the 55th latitude who receive vitamin D supplements; however, one study among Cree infants living at approximately 53° north in Quebec found that 70% were given a supplement containing vitamin D; 41% of these supplemented infants were given supplements daily [68]. More research is required to find out how to encourage parents to systematically provide their infants with vitamin D and other required supplements.

The Canadian Paediatric Society recommends that the risk of vitamin D deficiency in infants also be minimized by supplementing mothers with vitamin D during pregnancy and lactation so that breast milk contains enough vitamin D [67]. Hollis and Wagner suggest supplementing lactating mothers with up to 4,000 IU/day of vitamin D to ensure adequate vitamin D in breast milk for newborns [64]. Approximately 70% of the biological mothers participating in the 2007–2008 Nunavut Inuit Child Health Survey reported taking a prenatal vitamin or multivitamin during pregnancy. Among women taking any vitamins or supplements, only 26% reported taking vitamin D [17]. The low percentage of women supplementing with vitamin D suggests that more work needs to be done to convince mothers of the importance of supplements and to ensure their availability and use. Although traditional food sources of vitamin D could be promoted (e.g. fatty fish and aquatic mammals such as walrus, whale, seals, and polar bears), their consumption is often infrequent or they are consumed in small quantities meaning that they would be an inadequate substitution for supplements to ensure vitamin D adequacy [7, 69–71].

Conclusions and Future Directions

In this chapter we discussed some of the health problems related to poor nutrition among Aboriginal children in northern Canada. Unfortunately, Canada does not have a national strategy to address infant and childhood nutrition. Until that time, it will be up to communities, regions, territories, and provinces to make decisions to improve the well-being of infants.

The promotion of maternal health including the provision of excellent prenatal and postnatal care is an integral component of infant well-being. Enhancements to maternity care for First Nations, Inuit, and Métis women and their families, including prenatal care, access to midwifery services, birth services that are close to home, and postnatal services are needed [11]. Programs to reduce alcohol and other substance abuse among Aboriginal women of child-bearing age and to promote smoking cessation and awareness of the dangers of environmental tobacco smoke are strongly recommended [20]. Because the health of mothers is not just conditional on the delivery of health services but also on poverty reduction strategies and efforts to increase educational attainment, improvements in the social determinants (e.g., income and education) are undeniably important. That is, investments in improved socioeconomic and living conditions are required to improve the health of Aboriginal infants in Canada's north. Breastfeeding provides the highest attainable standard of health for infants; and being breast fed is thus a basic human right. Breast milk is also an important component of food security

among Aboriginal people in Canada given that breastfeeding provides a positive economic advantage to families living in poverty in that it is free. Breast milk is a secure and self-reliant food source that is ecologically sound, nutritionally efficient, and complete. That breast milk contains environmental contaminants suggests that to optimize the health of Aboriginal infants in northern Canada strategies to improve the environment are essential.

The health of Aboriginal peoples would improve with increased consumption of traditional and nutritious market foods. Traditional foods are rich in vitamins and minerals but are often consumed in insufficient quantities by adults and children to ensure nutrient adequacy [69]. Even so, among preschool Inuit children, those with greater intake of traditional food consumed more vitamins A and D, iron, magnesium, and zinc [72]. Despite their superior nutritional value to many market foods, traditional foods may not be consumed even if desired due to fear of the presence of contaminants, species decline, the cost of procurement, or the absence of a hunter in the household [69, 73]. In northern communities, the excessive cost, poor quality, and lack of variety or availability of perishable commercial foods are barriers to the purchase of lean meats, milk and dairy products, and fresh fruits and vegetables [73, 74]. Interventions to improve the nutritional status of Aboriginal infants and their caregivers must reflect these realities. Policy initiatives to help create and sustain supportive food and geographic environments are essential to make it easier for Aboriginal parents and caregivers to make healthy food choices for themselves and their children. To alleviate food insecurity in the Aboriginal population, community and government initiatives to address poverty and food access are required.

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Chapter 4
Breastfeeding and Infant Health in the Indian Subcontinent: Problems and Solutions

Zaynah Tahmina Chowdhury, Melissa A. Henderson, and Ronald Ross Watson

Key Points

- Rates of proper infant feeding are low among India, Pakistan, and Bangladesh, all of which belong to the Indian subcontinent.
- Breastfeeding has many benefits that protect against morbidity and mortality, especially in impoverished populations.
- Recommended breastfeeding practices include initiation of breastfeeding within 1 h of birth, exclusively breastfeeding for the first 6 months, and continued breastfeeding until the infant is 2 years of age.
- Barriers to practicing optimal breastfeeding include prelacteal feeding, food insecurity, poor maternal health, lack of awareness, and lack of access to care.
- Solutions exist at the national and local level, and the focus should be community based.

Keywords Breastfeeding • Prelacteal feeding • Colostrum • Food security • Maternal health • Indian subcontinent

Introduction

The fourth Millennium Development Goal set by the United Nations aspires to reduce child mortality by two-thirds between 1990 and 2015 [1]. The World Health Organization (WHO) and United Nations Children's Fund (UNICEF) estimate that exclusive breastfeeding (EBF) for the first 6 months after birth could prevent the deaths of 1.5 million infants worldwide each year [2, 3]. According to the WHO, proper breastfeeding practices include initiation of breastfeeding within 1 h of birth, EBF for the first 6 months, and continued breastfeeding until the infant is 2 years of age [4]. EBF is the practice of feeding only breast milk (and medicine when prescribed) to the infant, and is recommended as the best feeding method for infants, as it protects against morbidity and mortality [5]. Other benefits include the immunological properties of breast milk, the long-term benefits of breastfeeding, and the decreased transmission of HIV in HIV-exposed infants when they are exclusively breastfed [4]. Unfortunately, EBF is not as widely practiced as it should be.

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R.R. Watson et al. (eds.), *Nutrition in Infancy: Volume 1*, Nutrition and Health,
DOI 10.1007/978-1-62703-224-7_4, © Springer Science+Business Media New York 2013

Table 4.1 Infant feeding trends among Indian subcontinent nations [7]

	India	Pakistan	Bangladesh
% Received early breastfeeding (colostrum)	22	24	42
% Exclusively breastfed (EBF) for 6 months	46	37	43
% Breastfed for 24 months	73	53	91
% Ever breastfed	97	94	98

Table 4.2 Selected characteristics of Indian subcontinent countries

Variable	India	Pakistan	Bangladesh
Population [8–10]	1.2 billion	187 million	158 million
Population rank [8–10]	2nd	6th	7th
% Urban [8–10]	30	36	28
% Living below poverty line [8–10]	25	24	40
Infant mortality rate (per 1,000 live births) [11–13]	48	72	51
Under-5 mortality rate (per 1,000 live births) [11–13]	66	87	52
Leading causes of infant death [14]	Preterm birth	Preterm birth	Birth asphyxia
	Birth asphyxia	Birth asphyxia	Preterm complications
	Pneumonia	Neonatal sepsis	Neonatal sepsis
	Neonatal sepsis	Pneumonia	Pneumonia
	Congenital anomalies/diarrhea	Congenital anomalies[a]	Congenital anomalies
% Low birth weight [15]	28	32	22
Children under 5 [15]			
Underweight	44%	31%	41%
Stunting	48%	42%	43%
Wasting	20%	14%	18%
Overweight	2%	5%	1%

[a]Diarrheal disease ranks 7th

This chapter focuses on three countries from the Indian subcontinent: India, Pakistan, and Bangladesh. In developing countries especially, EBF can save lives, and offers significant benefits for infant health [6]. However, in discord with the WHO recommendation, just 44% of mothers in India, 42% of mothers in Pakistan, and 50% of mothers in Bangladesh predominantly breastfeed for under 6 months [7].

Table 4.1 highlights basic trends in infant feeding among the three nations. While infants in Bangladesh are more likely to have been breastfed within 1 h, breastfed for 24 months, and breastfed in general, India has the highest rate of EBF for the recommended 6 months. Pakistan has the lowest rates of the three in all categories, with the exception of early breastfeeding.

While it is important to consider the many differences and similarities across the Indian subcontinent, it is also necessary to take into account the varying beliefs, lifestyles, accessibility, and environments present within regions of each country presented. Examples of barriers are somewhat universal; however, exceptions always exist. This chapter includes a general overview of the barriers, and later, solutions, regarding breastfeeding in India, Pakistan, and Bangladesh. Table 4.2 compares the three nations on selected demographic variables.

Based on demographic comparisons (Table 4.2), India is the most populous among the three nations, with the highest rates of underweight, stunting, and wasting in children under the age of 5. Pakistan has the highest urban proportion as well as the highest rates of infant mortality, under 5 mortality, low birth weight, and percent of overweight children under 5. Bangladesh has the highest percentage of people living in poverty, but ranks lower than India and Pakistan in all other demographics.

The Indian subcontinent represents one of the world's most populated regions with some of the world's most challenging public health issues. Among the three nations reviewed in this chapter, urbanization is occurring rapidly, mainly due to migration of the rural population as a result of underemployment/unemployment in rural areas [16–18]. Collectively, at least one quarter of the population is living below the poverty line [8–10]. Bangladesh is the most densely populated country in the world, with high demands for employment and access to care. According to the World Bank, India accounts for 20% of the world's children and 40% of malnourished children worldwide [19]. In Pakistan, one in ten children will not celebrate his/her fifth birthday, mostly due to infectious diseases and poor nutrition. Pakistan is still recovering from a devastating flood in 2010, which has caused extensive damage to the Pakistani economy, health sector, and its residents who were already challenged by the 2005 earthquake [20, 21].

There are several barriers to consistent breastfeeding and proper complementary food practices. Many mothers in the Indian subcontinent do not breastfeed due to lack of the following: proper information, infant feeding counseling, adequate health care services, and qualified health care workforce to properly address breastfeeding difficulties [22]. The societal atmosphere is not entirely nursing friendly. For example, in India, community centers and workplaces lack motherhood support systems such as maternity leave and do not have breastfeeding rooms or nurseries on site. As a result, women are less inclined to breastfeed and are more likely to turn to formula where available. Corporations aggressively promote formula within India, just as they do in so many other nations, noted as a large barrier to breastfeeding [22].

In Bangladesh, recent WHO data indicates that about 60% of all deaths among children under the age of 5 can be attributed to malnutrition, of which improper infant and young child feeding practices play a key role [23]. Although the prevalence of any breastfeeding in Bangladesh is around 98.3% [24], the major obstacles to achieving optimal breastfeeding compliance are a low prevalence of EBF and a high prevalence of prelacteal feeding [25].

Problems

Prelacteal Feeding

Prelacteal feeding is the practice of feeding infants other food prior to breast milk, and typically occurs within the first day of life [26]. The practice is tied to beliefs among many cultures, predominantly Hindu and Muslim, and has been found to be significantly associated with home births [27].

India

Common prelacteal foods in India include castor oil, honey, sugar water, diluted cow's milk, goat's milk, and wet nursing [28, 29]. Castor oil is typically followed by another mother's milk, devoid of colostrum. Prelacteal feeds are often given via fingertip, which may increase infection risk in unsanitary conditions. During the 1970s and 1980s, India's national infant feeding protocol encouraged prelacteal feeding of sugar water, which continues to influence current practices [28].

In India, the period between birth and the first few months of life is a culturally significant time filled with strong traditional practices that may pose barriers to infant survival. In many households, a tradition known as *Banthana* is observed, which consists of discrete periods based on rituals, diets, mobility, seclusion, and health interventions to protect the mother and infant from pollution, which is believed to have occurred during birth [28]. Following delivery, mother and child are thought to be extremely vulnerable to natural and supernatural illnesses including *drishti* (evil eye) and *bheeti*

shanke (terror and superstition), among other afflictions. In hopes of purifying the infant via an induced bowel movement, prelacteal foods are given prior to breastfeeding, typically during the first 3 days of life [28].

Pakistan

In Pakistan, the most common prelacteals are honey, ghutti (herbal paste), and arq (rose water) [27]. Prelacteal feeds are used in hopes of reducing colic or initiating a bowel movement [30]. In a study conducted among health workers at a Baby Friendly Hospital in Karachi, 9.13% of doctors, 19.2% of paramedics, and 34.9% of mothers indicated that prelacteal foods should be given prior to breastfeeding [31]. This study illustrates how widespread belief in prelacteals remains, especially among health workers who are supposed to receive training on WHO best practices. This example reflects a common disconnect between policy, understanding, and practice.

Bangladesh

The giving of prelacteal foods is a popular cultural tradition in Bangladesh, and thus reduces the true prevalence of EBF [25]. There are two major justifications for not practicing EBF: the strong tradition of giving water or sweet food to the infant soon after birth, and the perception of not producing breast milk for the first 3 days after birth [32]. Family members and health staff sometimes advise prelacteal feeding, which intervenes with proper EBF protocol. This poses as a barrier at times since the higher social status of health staff makes it difficult for mothers to ignore their advice [33].

In a study done by Saha et al., researchers found that 8% of female participants have given prelacteal feed, including honey, mustard oil, sugar water, milk, or water [34]. Honey and sugar water are given to sweeten the infant's tongue and help develop a pleasant personality later in life, and mustard oil is given to clean the mucus from the infant's mouth immediately after birth [32]. Also, while knowledge of the benefits of giving colostrum is quite high, the actual practice is much lower in comparison [32]. This discrepancy is not only due to a perception of inadequate breast milk in the first few days after birth, but also due to the idea that colostrum is not real milk and should be discarded [32].

Colostrum and Early Breastfeeding

Colostrum, which is the first milk secreted from the mother's breast, is an essential component of infant health and is often referred to as an infant's first immunization. A recent study done in Ghana provides strong epidemiological evidence for this argument: researchers determined that 22.3% of all neonatal deaths could be prevented if breastfeeding was initiated within 1 h of birth, regardless of EBF practices within the first month of life [35]. However, due to its yellow, pus-like appearance, it is not uncommon for colostrum to be misidentified as spoiled and avoided. Misconceptions regarding its importance on behalf of mothers, elders, and healthcare providers act as a key barrier to colostrum consumption.

India

In India, initial breastfeeding is often suspended until the mother has bathed on the third day, a ritual believed to trigger the drop down effect of breast milk. The ritual pollution period continues until 40 days have passed since delivery, leaving the 28-day neonatal period unacknowledged [28]. Reported reasons for delayed feeding include maternal exhaustion and a widespread belief that milk is unhealthy

(spoiled) immediately following delivery, often due to the yellow-tinged colostrum [28]. Research by Kesterton and Cleland in rural Karnataka shows that more than 60% of mothers indicated spoiled milk as the main reason for delayed breastfeeding [28]. The same study reported that only 23.4% of mothers breastfed within 3 h after birth, 26.6% fed between 3 and 24 h, and 47.6% fed between days 1 and 3 [28]. Research indicates that the trend in delayed breastfeeding is declining among younger, more educated mothers [28]. In many cases, little autonomy exists for mothers due to the strong presence of tradition, belief in ritual pollution, and lack of experience, whereas decision-making and caregiving rely on grandmothers and elders [28].

Research in India has shown delayed breastfeeding to be significantly associated with home delivery and limited to lack of literacy among mothers [36]. No significant association has been determined between early breastfeeding and religion, trained birth attendant (TBA) presence, parity, spacing, gender, or gender preference. A 2006 study identified common reasons for delay in early breastfeeding to include family restrictions (38.8%), and social customs and religious beliefs (25.2%), which also influenced colostrum discard (30.2% and 25.6%, respectively) [36].

Additional barriers for both initial and continued breastfeeding include difficulties in infant positioning and attachment [37]. A study conducted in rural Wardha found that these challenges were common for mothers experiencing feeding problems, including twisted infant neck, poor holding technique (e.g. mother held head only), infant's body was turned away from mother, infant not held closely, infant's chin did not touch breast, infant's mouth partially closed, infant's lip not turned outward, and little areola visibility [37].

Pakistan

In Pakistan, like India, breastfeeding is commonly delayed for up to 3 days, partially due to the fear of giving the infant spoiled milk. In one qualitative research study in a low socioeconomic status (SES) setting in Karachi, a participant indicated that her mother told her not to use the first milk from her breast, as it was "dirty because it had been stagnant for 9 months" [30].

Research has indicated an association between delayed early breastfeeding and delivery location [27]. In a 2010 study of infant feeding practices among urban squatters in Karachi, only 16.8% of mothers breastfed within 2 h of giving birth [27]. When analyzed based on delivery location, early breastfeeding was less common in home births (8%) vs. institutional births (24%) [27]. While early breastfeeding was low in both settings, home births are more strongly associated with delays in early breastfeeding. A study conducted by Hanif et al. attempts to explain the surprisingly low prevalence of early breastfeeding despite institutional delivery [31]. Among 515 health workers and mothers at a Baby-Friendly Obstetrics and Pediatrics Department of a Civil Hospital in Karachi, knowledge of proper feeding practices existed; however, misconceptions remained. When asked if colostrum should be given to infants, 91.7% of doctors, 89.9% of paramedics, and 88.8% of mothers said yes. When asked when breastfeeding should be initiated, 90.4% of doctors, 88.9% paramedics, and 69.3% of mothers responded that it should occur within the first half hour [31]. It is important to note that responses to surveys and interviews regarding recommended practices can be skewed by social desirability bias, in which respondents may be more likely to respond to questions based on what they think is the correct response. Health professionals may have indicated what they believed to be proper responses to the survey, although messages delivered to mothers may differ, if given at all [31].

Bangladesh

In Bangladesh, breastfeeding promotion programs and projects have been in existence for many years. There are a number of recommended practices that are the basis for these programs, but cultural and societal barriers often bar these recommended actions from being followed properly. For example, the

recommended practice of giving breast milk within 1 h of birth is often met with a lack of awareness on the part of the mother, as well as responses including: putting the baby to the breast but finding that there was no milk, the milk came in late, the placenta was delivered late, the mother and child must be bathed immediately, the mother was not well after the delivery, there was a delay in bringing the baby to be fed, family decisions about what or when to feed the baby, the baby was too ill or weak to suck, or the midwife discouraged breastfeeding for the first 3 days [38]. Similar issues prevent mothers from following the practice of not giving other fluids or food within the first 3 days after birth, as well as exclusively breastfeeding for the first 6 months after birth (although many reasons for not practicing EBF involve low lactation or the perception of inability to breastfeed) [38]. Mothers often make the mistake of improperly positioning the infant during feeding and removing the infant from the breast early so s/he is unable to finish feeding, which leaves the infant's caloric needs unfulfilled [38].

Perceptions of insufficient breast milk play a key role in feeding practices in Bangladesh. A study done by Rasheed et al. categorized breastfeeding practices into three categories: full breastfeeding trajectory, continuous mixed feeding trajectory, and intermittent feeding trajectory [39]. Researchers found that when mothers perceive their breast milk to be inadequate, they continuously feed nonhuman milk during the first 0–4 months after birth (continuous mixed feeding trajectory), and when breastfeeding is going well, mothers will sometimes feed nonbreast milk foods intermittently to their child from 0 to 4 months and continuously from 4 to 6 months (intermittent feeding trajectory) [40]. Few women in the urban slums of Dhaka thought their breast milk was sufficient for their infants, so EBF and feeding mostly breast milk and some water (full breastfeeding trajectory) was rare [33]. Mothers in the full breastfeeding trajectory came from poorer households than those in the intermittent breastfeeding trajectory; poorer mothers would like to feed food other than human milk but usually cannot afford to [39]. Multiparous (and thus older) mothers are more likely to be part of the continuous mixed feeding trajectory, for a number of possible reasons; they receive less help with housework, so the workload constraint may be the reason for reduced feeding frequency. As a result, lactation decreases and thus the perceived breastfeeding ability is negative, so mothers resort to feeding nonhuman milk [39].

Exclusive Breastfeeding

India

In India, protective factors for EBF include higher levels of education, employment, more antenatal clinic visits, radio exposure, and vaginal delivery [41]. Factors such as higher household wealth index, delivery in a health facility, and living in the northern region of India have been shown to be negatively associated with EBF [41].

Pakistan

Although early initiation of breastfeeding is uncommon in Pakistan (37% according to the WHO) [11–13], studies often report higher rates. Reasons may include regional differences in EBF and the potential for social desirability bias on the part of self-reporting participants [27, 42]. Despite WHO recommendations that infants should be breastfed exclusively for the first 6 months of life, beliefs and practices among Pakistani health care workers and mothers vary [3, 31]. In a survey conducted by Hanif et al., only half of doctors indicated that complementary feeding should begin at 6 months of age, while only 28.3% of paramedics and 25.2% of mothers believed so [31]. Nearly 43% of doctors reported that complementary feeding could occur at 4 months. When asked if breastfeeding should be continued for 24 months, nearly 70% of respondents among all groups agreed [31].

While the Pakistani government has attempted to reduce formula promotion within hospitals through policy adoption (e.g. Baby Friendly Hospital Initiative), these endeavors have not necessarily translated into practice. In 2010, responses to a study conducted among healthcare staff at a Baby Friendly Hospital in Karachi revealed a lack of policy awareness and practice [31]. When asked if healthcare staff could receive gifts, free samples, donations, or formula company-sponsored trainings, 76.65% of doctors and 32.3% of paramedics responded yes. When asked if promotional material regarding formula milk, feeding bottles, and pacifiers should be permitted in the hospital, 83.75% of doctors and 25.2% of paramedics also responded yes. While Baby Friendly Hospitals are encouraged to provide lactation management trainings, less than half (47.7%) of doctors and just over half (53.5%) of paramedics indicated that they had participated in such trainings [31]. In another study among 427 healthcare workers in 12 urban Islamabad hospitals, the vast majority of participants were unaware of Pakistan's national breastfeeding policy (70.5%) or the International Code (79.6%) [43]. Awareness appeared to increase with duration of employment among employees of 10 years or more (OR = 2.48), especially for pediatricians (OR = 7.00) [43]. Researchers also found that it was common for healthcare workers to receive small gifts (e.g. pens, pencils, calendars) from infant formula companies (38.4%), free samples of infant formula (15.9%), and formula company sponsorship for trainings and conferences (12.4%) [43]. Lack of policy awareness was associated with reception of gifts (OR = 1.64) and free samples (OR = 1.86) [43]. These results illustrate gaps that exist between policy and practice among paramedics and doctors in Baby Friendly Hospitals specifically.

As is the case with many public health interventions, acquiring knowledge about recommended practices is only half the journey to achieving healthy behaviors. In a small qualitative study in Karachi, focus groups were held with six breastfeeding mothers to better understand protective factors and barriers to continued breastfeeding [44]. When asked which factors contributed to their commitment to proper feeding practices, mothers responded with knowledge of the benefits, familial support (e.g. mother-in-law's willingness to bottle feed expressed milk), support from the husband (e.g. willingness to care for infant while mother rested), privacy to feed at work, and personal motivation [44]. Reported challenges included lack of privacy at home, lack of ability to breastfeed in public, lack of time due to work or household duties, physiological changes (e.g. tiredness, tender breasts, back pain), and social pressure to bottle feed. Concerns with privacy at home were attributed to a common Pakistani custom of a joint family system, in which extended family members such as grandparents live with the immediate family unit. Social pressures to bottle feed were identified specifically as the belief that bottle-fed infants are chubbier and therefore healthier than exclusively breastfed babies [44]. While this study is small, it offers insight into potentially universal protective factors as well as challenges for continued and EBF.

Bangladesh

Demographic, health, and social factors all affect the prevalence of EBF. For example, higher education most often leads to higher social status, which increases the exposure to advertisements (e.g. baby formula), thus leading to lower EBF rates among a wealthier and more educated demographic [25]. Younger mothers have been found to breastfeed for a shorter duration, perhaps due to a lack of experience breastfeeding or discomfort with the practice [24]. Caesarian section birth, belonging to the Islamic faith, and mothers who have not used any contraceptives are also associated with a lower duration of breastfeeding [24].

Infectious diseases including diarrhea and acute respiratory infections cause more than two-thirds of all deaths in Bangladeshi children aged less than 1 year [45]. Exclusively breastfed infants are less likely to be exposed to contaminants and environmental pathogens, thus serving as a protection from infectious disease [25]. Longer duration of EBF has also resulted in a larger thymic index at 52 weeks. The thymus is a lymphoid organ that is essential for the production of T-lymphocytes, and is thus

greatly responsible for the stability of the immune system. The thymus is extremely sensitive to undernutrition, and since many of the children of Bangladesh live in environments that put them at a risk of being immunocompromised, EBF should be stressed as a preventive measure of retracting infectious disease [46].

Delivery Location and Access to Care

Delivery location plays an important role in maternal and infant health. Births in institutional settings are more likely to be accompanied by a TBA, also known as a "skilled" birth attendant, improved sanitation, access to services if complications occur, and opportunities for education by trained workers [47]. Despite these advantages, home births remain the more commonly practiced form of delivery, in part due to lack of access to care (especially in rural areas), lack of financial resources, and cultural norms [47]. Still, as promotion of institutional deliveries continues and community health workers (CHWs) become a larger part of the health sector, deliveries accompanied by a TBA offer an important opportunity for mothers (and elders) to learn proper infant feeding and care techniques that can improve their child's likelihood of survival.

India

Between 2005 and 2006, approximately 75% of births in India occurred in rural areas vs. 25% in urban areas [11], a trend that is similar to the overall population distribution of India [8]. The slight skew toward rural births may reflect either that more women live in rural areas or women tend to return to rural areas for delivery. In addition, there appears to be a slight increase in trained birth attendance over the past decade. An estimated 73% of urban births and 37% of rural deliveries were assisted by a TBA; however, large variations exist regionally [11]. For example, in the state of Kerala 99% of births were assisted by a TBA whereas in Nagaland, only 25% were attended by a TBA [11]. The majority of births in India occur in homes (61%) vs. health facilities (38.6%) [11]. While the home birth trend is slowly reversing nationwide, home births are still more popular, largely due to their cultural familiarity [28]. Research has shown that widespread acceptance of TBAs has yet to be achieved. A study in rural Karnataka revealed little local recognition of the terms *dai* or TBA, likely because the terms are more common in institutional settings [28]. While TBAs are revered in some areas, they remain stigmatized in others, and may or may not hold onto traditional practices despite formal training. Many prefer to assist in deliveries in barns rather than homes, returning to the belief that delivery is a pollution-filled exercise that could pollute the home. In addition, barns provide easier cleanup than homes. In Northern India, TBAs may assist in infant care following delivery by a relative [28].

Pakistan

In 2007, 38.8% of births in Pakistan were attended by a TBA [15]. Involvement of relatives during the birthing process may limit access to care and may pose a significant barrier to breastfeeding education. Among urban births, 60% were attended by a TBA, whereas only 30% were attended in rural areas of Pakistan [12]. Overall, 65% of Pakistani births occurred in the home [12]. The role of CHWs not only includes trained birth attendance, but also health behavior promotion before and during pregnancy (e.g. prenatal care consultations and community-wide education on proper infant care practices). It is also important to note that hospital deliveries do not guarantee improved TBA care or infant care education, often due to the short amount of time mothers spend in the hospital. Women who cannot pay for hospital fees are particularly subject to poor treatment and neglect [28].

Bangladesh

In Bangladesh, approximately 80% of deliveries occur in rural areas, during which only 13% are assisted by a TBA [13]. Among urban deliveries, only 37% are attended by a TBA [13]. Hospital-based breastfeeding promotion does not reach most Bangladeshi mothers because 85% have home deliveries [13]. Private-sector hospitals are usually too expensive for the poorer population, but free services from public hospitals are also rarely utilized by this population. This may be because public hospitals are officially free for the public, but patients may have to pay unofficial charges, or it may be that nongovernmental organization (NGO) services and home births are more appealing to women from this population due to the level of care they receive in comparison to hospital births [48].

Food Security

Food security, or the accessibility of sufficient, safe, and nutritious food [49], has been associated with infant and maternal health [50]. While it is believed that there is enough food in the world to supply everyone's food needs, inadequate distribution of those resources is problematic, both internationally and at the household level [49]. The ongoing global economic crisis and climate change has affected food prices worldwide, but its impact has disproportionately affected the poor. In each of the three nations highlighted in this chapter, the percent of the population living below the poverty line represents a large proportion of the population likely living in food insecurity [8–10]. If a mother is not well nourished, she may not be able to provide nutritious breast milk, may supplement her milk with premature complementary foods, or may not breastfeed at all.

India

One quarter of India's population lives below the poverty line, and nearly 42% are living under $1 a day [15]. The indirect resulting dietary consequences of rising food prices include a decreased consumption of nutrient-dense foods and higher consumption of cheaper staple foods, or a decrease in food consumption overall for the poorest population [51]. Not only does this imply a decrease in child nutrition, but maternal undernutrition becomes an issue as well. Micronutrient deficiencies increase with a decrease in micronutrient consumption, and this has an adverse effect on cord blood and breast milk status [51, 52]. For example, maternal anemia is relatively common in India; based on Demographic Health Survey data, maternal anemia was prevalent in 58.6% of women during pregnancy [11]. Iron content is greatly reduced in the breast milk of severely anemic mothers so, accompanied with the already low iron content in newborns born to anemic mothers, this could potentially have serious consequences for the infant at a time when iron demands are high [52].

Pakistan

Between 2005 and 2007, more than one quarter of the population was consuming less than the minimum dietary energy consumption, and in 2002 only 17% of the population was consuming an appropriate amount of iodized salt [15]. In 2001, the WHO reported that 50.9% of children under 5 years of age and 39.1% of mothers were anemic Also, 7.8% of women were reported as having clinical vitamin A deficiency, and 12.5% of preschool age children were reported as having subclinical vitamin A deficiency, putting them at risk for night blindness [15].

Bangladesh

Approximately half of the population of Bangladesh is food insecure [34]. Much of this food insecurity can be attributed to a lack of sufficient food from the country's own crop production and cash income, as well as other resources required to obtain ample food supplies [53]. There are seasonal dimensions of food security in Bangladesh; at certain times of the year food production is affected by drought and flood, which indirectly influences the cycle of food production and seasonal variation in food availability and prices [53].

About 31% of the population experiences chronic poverty, which is characterized by low food intake, undernutrition, and lack of basic health services [54]. Around 19% of rural households cannot afford three full meals a day, and about 10% survive on two or less meals a day for most months out of the year [34]. Hunger and childhood malnutrition rates in Bangladesh are among the highest in the world. According to a study done by Saha et al., greater household food security was associated with worse feeding practices from 3 to 6 months but better infant feeding practices during 6–12 months [34]. Infants in more food secure households were given other liquids (e.g. juice, milk, formula, etc.) with breast milk before 6 months, possibly because they were able to afford feeding liquids other than breast milk [34]. Infants in food insecure households were found to have greater morbidity, and therefore a greater duration of EBF [34].

Maternal Health

Depressive disorders are a major source of disability among low-income mothers in developing countries [55]. In 1951, a postwar study in Germany published by the Lancet cultivated an interest in the role of maternal mental health on child nutrition. The WHO defines maternal mental health as, "a state of well-being in which a mother realizes her own abilities, can cope with the normal stresses of life, can work productively and fruitfully and is able to make a contribution to her community" [56]. Although mental health remains a relatively underserved area of public health research, several studies have investigated the relationship between maternal mental health and infant nutrition.

According to the WHO, incidence of depression among women doubles during pregnancy, and nearly triples in the year following delivery [56]. Maternal depression has been associated with several adverse infant health outcomes. Prenatal maternal depression increases the risk of low birth weight as mental stress may lead to poor maternal self-care such as poor diet, low weight gain, and lack of sleep [57, 58]; a decreased likelihood to seek prenatal care and even delivery assistance; increased risk of substance abuse; increased risk of suicide; and physiological damage due to increased stress hormones [56]. These factors may result in poor fetal growth, preterm birth, and related complications [56, 57, 59]. Postpartum depression has been associated with infant undernutrition at 6 months, especially among lower SES groups [57, 60]. It may also be associated with early cessation of breastfeeding [57, 61], higher rates of infant diarrhea [57, 62], disturbed mother–infant bonding, and subsequent hindered child development [57, 63, 64]. Following delivery, depressed mothers may continue to suffer from aforementioned poor self-care behaviors, be less likely to make eye contact and personal contact with infants, or may be less likely to recognize infant distress, all of which may result in poor feeding practices, and subsequently poor physical and developmental growth [56].

Mothers with depressive symptoms tend to view infants as more irritable or "temperamentally difficult" [55]. However, in high-income countries children who are considered more irritable are often heavier, likely because parents associate irritability with hunger and feed the child more often [55]. Thus, maternal perceptions of infant temperament and the relation with infant feeding vary, and further studies are required [55].

India

Familial support is often influential in infant care, largely because it is not uncommon for mothers to feel exhausted following delivery. While the presence of grandmothers can also support beneficial infant care practices such as active feeding (responsiveness to infant hunger cues), many traditions encouraged by elders may be harmful to infant health such as colostrum discard and delay of complementary feeding [65].

Pakistan

In urban areas of Pakistan, researchers have determined a significant association between high levels of maternal mental distress and undernutrition among 9-month-old children despite sufficient food security [66]. Research has also shown an association between prenatal maternal depression and poorer infant growth, increased risk of diarrheal infection and diarrheal episodes [67]. After adjusting for low birth weight, maternal depression is significantly associated with growth retardation, regardless if the infant was born with a low birth weight. In addition, it appears that maternal depression has a somewhat dose–response relationship with poor infant health; however, this relationship is also cyclical. The more stressed a mother feels, the less healthy her infant becomes, which then compounds even greater stress, according to researchers [67]. In a study conducted in urban Rawalpindi, maternal depression was identified as being a greater risk factor for poor infant growth than low birth weight, frequent diarrhea, and SES.

Bangladesh

In Bangladesh, birth weights are lowest during seasons when there is a short supply of food, so maternal depressive symptoms may be related to food insecurity, and thus indirectly birth weight may be related to food insecurity as well. Household food security has nutritional consequences for the caregivers as well, so compromised maternal health could influence infant care and infant feeding practices, including a negative impact on breastfeeding [53]. In a study done by Black et al., maternal depressive symptoms were found to be associated with poor infant growth from 6 to 12 months [55]. Maternal depression was also more prevalent among the lower income and less educated mothers.

Solutions

Studies assessing provider awareness of policies, policy guidelines, adherence, and beliefs have illustrated large gaps between policy development and implementation [31, 41, 43]. Many policies lack implementation and evaluation, so it would be beneficial to re-examine the Baby Friendly Hospital Initiative and other international/national policies. Hospitals deemed “Baby Friendly” by the WHO lack significant improvements in feeding outcomes (e.g. early breastfeeding and avoidance of prelacteal foods). Researchers suggest that this points to a failure of the Baby Friendly Hospital Initiative, which was intended to promote WHO newborn feeding recommendations [27]. Other international and national policies should also be re-evaluated for their appropriateness, adherence, and effectiveness [22]. Initiatives promoting EBF should be incorporated into international and national programs such as the Baby Friendly Hospital Initiative, Integrated Management of Childhood Illness, Saving Newborn Lives Initiative, and Family Planning Programs [23]. In addition, assessments used by these initiatives should be adapted to include infant positioning to guide interventions [37].

It would be beneficial to horizontally integrate maternal health into other health programs to ensure the sharing of resources between ministries, monitoring quality, and the implementation of new programs [23, 27]. Health workers can utilize other medical settings to support EBF and continued breastfeeding, such as during hospital, prenatal care and well-baby visits [23]. Although it may be too late for a mother to practice early breastfeeding with her newborn, the information could be beneficial for future pregnancies.

Another method of promoting proper infant feeding at the national level is to encourage celebrities to support proper infant feeding practices through media campaigns [23, 68] such as television, video, and radio outlets as well as mobile vans common in the region [38]. This is becoming an increasingly popular method in regard to other health campaigns such as polio eradication and slowing the spread of HIV/AIDS. Garg et al. also suggest addressing misconceptions regarding infant feeding and care at the secondary education level by incorporating a reproductive life cycle curriculum [68]. In addition, educational campaigns (communication material and channels) that stress the benefits of breastfeeding are good for encouraging a longer duration of breastfeeding [24, 39]. While this is an important approach that should be considered, it is important to address the lack of access many girls have to education in this region.

Various stakeholders in both the private and public sector should come together to discuss and collaborate on innovative ways to address infant feeding and health, while also generating plans for interdisciplinary accountability. Stakeholders should include, but are not limited to, health sector leadership, health sector trainers/institutional representatives, formula company executives, CHWs, and leaders of nonprofit organizations engaging in this line of work. Singer et al. suggest utilizing a nonpartisan nonprofit organization or similar agency as the evaluation/noncompliance officer [68, 69].

All families need consistent access to food to prevent undernutrition, morbidity, and mortality [53, 55]. Food supplements for food insecure families may be a way to combat the ongoing struggle of food insecurity among vulnerable populations [37]. In times of seasonal food insecurity as well as during the wake of natural disasters, greater accountability must be held in the distribution of resources, especially to rural areas, which receive less government oversight. While governments are likely stretched thin to accommodate their burgeoning populations, and corruption may be present, local NGOs with proven accountability should be contracted to assist in the distribution of food supplements, especially in times of unexpected chaos.

Increased attention to and investment in mental health is often overlooked when assessing solutions for improving child nutrition [57]. For example, screening and treatment for depressive symptoms will likely decrease the effects of depression on the health of a mother and, subsequently, her offspring [55]. This ties in with food security as well; consistent access to food decreases the prevalence of depression, thus resulting in better feeding practices [55].

It is imperative that strategies also address the community level, where national policies tend to lose their effectiveness and resources are limited. As discussed, home births remain common across the Indian subcontinent, which requires a higher emphasis on training of local health care providers. CHWs are becoming an increasingly common way to address local health needs across the globe. Breastfeeding promotion and infant care training should be given to community members through CHWs, who can relate to the local culture and beliefs regarding breastfeeding and infant care, while also imparting their skills and knowledge to help women and children lead healthier, happier lives [28, 68]. In addition to training CHWs on how to promote various health messages, counseling skills should also be cultivated. Specific methods should include practical training on how to breastfeed [39], the importance of proper positioning and duration of feeding, the benefits of breastfeeding (e.g. colostrum is like a baby's first immunization, breast milk is good for a child's physical and brain development), the dangers of not following recommended practices, and ways in which mothers can overcome barriers to feeding (e.g. insufficient breast milk) [38, 39]. CHWs and women should begin a relationship during prenatal care in hopes of addressing concerns early.

In addition to CHWs, it is important to train other trusted health care providers such as traditional midwives and *dais* in EBF and infant care [68]. Influential health workers such as these and other local leaders should be encouraged to reinforce specific priority messages whenever possible, and at the same time deterred from giving incorrect advice [38]. Women's groups are also an excellent resource for breastfeeding promotion and support for women [23, 68]. Where possible, one-to-one breastfeeding counseling could be employed, although cost-effectiveness varies [23, 68]. Above all, breastfeeding and infant care outreach must be culturally appropriate and regionally tailored [28]. These interventions should, as a priority, target mothers, family elders, and women of reproductive age, including adolescents [28, 65, 70].

While these opportunities for promotion can occur regularly, Dongre et al. also suggest utilizing special holidays to draw wider attention to infant feeding and health issues, such as Village Health Nutrition Day to educate breastfeeding mothers and potential mothers [37].

In hopes of better understanding the barriers to proper infant feeding, it is important to pursue further research into the perceived benefits, barriers, and behaviors of mothers and the health care providers that serve them [27]. Important topics for research should include why women choose to deliver at home, perceived acceptability of TBAs, the role of various service providers (e.g. CHWs, hospitals, NPOs) and evaluation of programs both successful and unsuccessful. Due to the diversity of this region, both culturally and economically, researchers face a challenge in assessing these topics without over-generalizing results. Solutions must be locally tailored, and research must follow suit.

Conclusion

Although these countries are all within the Indian subcontinent, each has its own unique regional, cultural, and socioeconomic characteristics. While this chapter does not attempt to generalize problems and solutions, there are evidence-based themes that appear throughout. In general, themes include prelacteal feeding, EBF, delivery location, maternal health, and food security. Some of the ways infant feeding can be improved in these areas include policy re-evaluation, horizontal integration of maternal health into other health sectors, media campaigning, stakeholder collaboration, food supplementation, increasing government accountability, strengthening the community health workforce, and use of alternative avenues for breastfeeding promotion. Most importantly, further research into the ways in which women have overcome the barriers to breastfeeding and characteristics of successful interventions should be conducted. Community-based research involving local stakeholders (e.g. current and potential mothers, elders, CHWs, and TBAs) should be employed to better understand the problems and solutions, while also giving voice to women who can then become more empowered to engage in the health of their children, themselves, and their peers.

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Chapter 5
Infant Nutrition in the Middle East

Malek Batal and Laura Hjeij Awada

Key Points

- The Middle East and North Africa region (MENA) is diversified in terms of economy and health indicators.
- Significant undernutrition with high levels of acute and chronic child malnutrition often coexists with overweight and obesity in the same country.
- Breastfeeding has the potential of addressing some of the health concerns in the region in light of its decreasing prevalence and duration.
- Lack of filtered water, poor housing environment, low parents' (mother and father) educational level, the absence of antenatal visits during pregnancy, and early discontinuation of breastfeeding are associated with stunting and wasting in parts of the region.
- Obesity and diet-related conditions such as diabetes, hypertension, and cardiovascular diseases are on the increase in the MENA region.
- Abundant energy and fat intake, lack of physical activity, and urbanization have been reported as the top three factors associated with overweight and obesity in the region's children and adolescents.
- A cross-nation strategy to combat malnutrition is needed for the region.

Keywords Middle East • North Africa • Arab • Nutrition • Malnutrition • Overweight • Obesity • Breastfeeding • Infants • Preschool age • Children

Introduction

The Middle East and North Africa (MENA) region covers countries of Western Asia and North Africa. An ethnically and socioeconomically diversified region, MENA encompasses more than 360 million Arab, Persian, Jewish, and Kurdish inhabitants dispersed across nations that range from the oil-rich to the resource-scarce [1, 2]. Opinions vary as to what and how many countries make up this region [2–4]. For the purpose of the current chapter, a commonly recognized map of the region (refer to Fig. 5.1) is adopted. The region has witnessed great progress on multiple socio-health indicators over the last decade; this is shown by an average life expectancy of 71 years, an under-5 mortality rate of

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R.R. Watson et al. (eds.), *Nutrition in Infancy: Volume 1*, Nutrition and Health,
DOI 10.1007/978-1-62703-224-7_5, © Springer Science+Business Media New York 2013

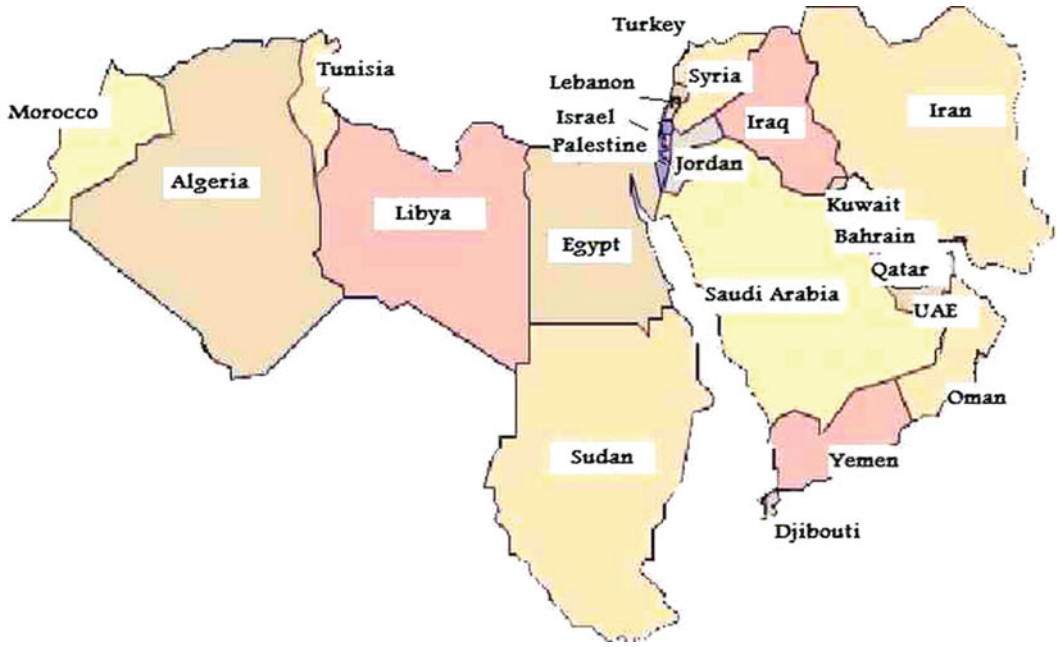

Fig. 5.1 Map of the Middle East and North Africa (MENA) region

38/1,000, and a decline in the prevalence of underweight and stunting in children under 5–12% and 25%, respectively [2, 5]. Despite this encouraging trend, malnutrition, whether in deficiency (undernutrition) or excess (overweight/obesity), remains a chief contributor to the national and global burden of disease. Both these conditions can coexist in the same county forcing it to deal with the high cost of treating diet-related diseases while trying to set up a national plan to combat nutritional deficiencies [3, 6].

Child nutrition and growth, a primary indicator of a population's health status, varies greatly between different MENA states due to the parallel effect of urbanization and economic growth on this region [3, 7, 8]. According to the World Health Organization (WHO), countries like the Islamic Republic of Iran and the Gulf Cooperation Council (GCC) states are in an advanced nutritional stage with low rates of undernutrition and micronutrient deficiencies and high levels of obesity and overweight; on the other hand, poorer countries such as the Palestinian Territories, Iraq, and Yemen seem to be witnessing the double burden of disease as they continue to suffer from significant undernutrition with high levels of acute and chronic child malnutrition as well as fast rising obesity rates [3].

This chapter portrays feeding patterns among children aged 0–12 years old in the Middle East and North Africa region; it presents the potential socioeconomic determinants of those patterns and their direct and long-standing nutritional outcomes. It illustrates the vast scope of severe health complications associated with the co-occurrence of over and undernutrition in this age group and identifies the augmented hazard of premature illness and death later in life [9].

Breastfeeding

The WHO and the American Academy of Paediatrics recommend that babies be exclusively breastfed (EBF) for the first 6 months of life [10]; noncompliance to these guidelines contributes to "over a million avoidable child deaths each year" [11]. Continuation of breastfeeding (BF), along with other complementary food providing essential vitamins and minerals, is encouraged until the age of 12 or 24 months [10]; studies have shown that longer duration of BF lead to a decrease in the likelihood

of overweight and obesity in young adolescents [12]. In the MENA region, consisting mainly of developing countries with a relatively high prevalence of malnutrition and infectious diseases, BF can have sizable protective benefits [13]. Exclusivity and total duration rates of breastfeeding are both in decline, falling below the minimal universal guidelines mentioned earlier [1]. The rates of EBF and BF differ across countries in the region however. For example, countries that were categorized by WHO as belonging to the "advanced nutritional transition" group like the Islamic Republic of Iran [14, 15], the Kingdom of Saudi Arabia (KSA) [16], and Israel [10] had a BF rate that was higher than countries like Lebanon [17], Yemen [18], and Turkey [19]. Studies from different countries point to the following factors as negatively affecting EBF during the first 6 months of life: a caesarean delivery, the use of pain killers by the mothers, hospitalization of the newborn, shorter maternity leaves, and nonencouragement by the family and the hospital staff [10, 14, 17]. As for the duration and continuation of breastfeeding, studies from different MENA countries agreed on the fact that mothers living in rural areas breastfed longer than those residing in cities [17, 20]. However, the effect of the mother's education on the continuation of breastfeeding was different across countries. In Israel, the duration of breastfeeding increased with an increased level of the mother's education [10] while there existed a negative correlation between those two factors in Lebanon [17], KSA [21], and the United Arab Emirates (UAE) [20]. In general, there does not seem to be a high compliance rate to the WHO BF recommendations in the MENA region with variability across countries and across regions in the same country [22].

Undernutrition: Stunting, Wasting, and Micronutrient Deficiencies

Child growth is a recognized indicator of a child's nutrition and health status [8]. Undernutrition, known to be linked to more than one third of universal child deaths, can be expressed in children by different measures: stunting (low height for age) as an indicator of chronic malnutrition, wasting (low weight for age) as a symptom of acute severe undernutrition, and signs of vitamins and minerals deficiencies [3]. In the MENA region, undernutrition is one of the most dangerous public health concerns [3, 6]; however, the prevalence of its three indicators indicated above varies across countries. According to several recent studies in the region, Yemen, Oman, Gaza-Palestine, and Djibouti (countries with the lowest Growth Domestic Products (GDPs) in the region) have the highest rates of stunting and wasting, while Libya, KSA (both oil-rich), and Turkey (relatively highly industrialized) have the lowest rates for these malnutrition indicators [6, 21, 23, 24]. Major predictors of undernutrition in children less than 12 years old are the lack of filtered water, poor housing environment, low parents' (mother and father) educational level, the absence of antenatal visits during pregnancy, and early discontinuation of breastfeeding [7, 25, 26]. Large disparities exist also within countries; studies agree that wasting and stunting are more prevalent in rural areas [23] where unprivileged populations with no social security coverage [21] reside. Vitamins and minerals insufficiencies are widespread among the region's population and most precisely among children. Iron (45% of population), iodine (54% of population), and Vitamin A (22% of preschool children) are the three major micronutrient deficiencies [3]. A cross-sectional study conducted in Gaza in the Palestinian Territories, one of the most politically unstable regions in the MENA, showed that 72.85% of children <2 years old were anemic [27]. Another study carried out among the Bedouin preschool children living in the Jordanian desert showed that 57.5% of them suffered from anemia, 29.5% from vitamin A deficiency, 28.4% from iron deficiency, and 17.1% from vitamin E deficiency [28]. Undernutrition has profound implications on a country's economic growth and productivity; it is associated with enormous public health costs and dramatic losses in human capitals; increased efforts should be made in the MENA region to improve the nutritional status of children [3, 23]. A successful example is the 3-year intervention plan meant to lessen malnutrition in rural areas of Iran which resulted in a sizable decline in wasting, stunting, and underweight among children less than 3 years old [29].

Overnutrition

Obesity and diet-related conditions such as diabetes, hypertension, and cardiovascular diseases are on the increase in the MENA region among the general population [3]. Child obesity, an increasing global concern, is thought to be associated with genetic, socioeconomic, and environmental factors [30]. Abundant energy and fat intake, lack of physical activity, and urbanization have been reported as the top three factors associated with overweight and obesity in the region's children and adolescents [30, 31]. A study published in the Eastern Mediterranean Health Journal (EMHJ) stated that the obesity rates among preschool children, school children, and adolescents in the region were 9%, 25%, and 45%, respectively; these alarming rates call for an immediate national and regional response targeting obesity in schools, and at the family unit level through nutrition education targeted at children and their caretakers [32]. Unlike in more developed regions of the world, obesity rates are higher among boys belonging to families of higher socioeconomic status (SES) whose parents have advanced levels of education [33, 34]. In fact, these findings concur with another study's outcomes that compared the relation between SES and obesity in highly developed versus developing countries; results illustrated a negative association (lower SES associated with larger body size) in highly developed countries and a positive association between SES and obesity in developing countries [35]. KSA, UAE, and Bahrain preschool and school age children obesity rates are among the highest in the world [32, 34, 36]. This stresses the importance of early detection of obesity and overweight as data show that detecting obesity in childhood by focusing on children with above-average waist circumference can lead to early intervention which protects them from developing high blood pressure and other signs of the metabolic syndrome (MS)[1] as adolescents [37–39]; note that MS is much higher in obese subjects than normal weight children [39]. Intervening at a young age also saves healthcare costs; a study conducted in Israel reported that obese children had more doctor visits, got hospitalized more, and used more medication than normal weight counterparts [39]. Therefore, reducing the risk for chronic diseases and lessening the load of a costly health bill are two key motives for MENA countries to combat obesity. The Arab Taskforce for Obesity and Physical Activity, based in Bahrain, prepared a 5-year strategy for combating obesity and promoting physical activity in the Arab countries which constitute the majority of MENA. This strategy states that action is needed in several areas. First, it addresses schools as a place for children's education about healthy eating; second, it focuses on primary-care health clinics as centers for detecting overweight and obesity in children through regular measurement and weighing for immediate intervention; it addresses also food preparation through institutions where food is served by promoting healthier cooking methods [40].

Conclusion

The Middle East and North Africa region has the 2nd highest mean Body Mass Index (BMI) after North America and the 2nd highest mean waist-to-hip ratio after South America [40]. These two measures demonstrate that the state of overweight and obesity has reached an alarming level in this part of the world [32]. On the other hand, high levels of acute and chronic malnutrition in addition to widespread micronutrient deficiency are still persistent in certain countries of the MENA [3]. Epidemiological and experimental research has shown that there is a causal relationship between

[1] Metabolic Syndrome (MS): a syndrome marked by the presence of usually three or more of a group of factors (such as high blood pressure, abdominal obesity, high triglyceride levels, low HDL levels, and high fasting levels of blood sugar) that are linked to an increased risk of cardiovascular disease and type 2 diabetes—called also insulin resistance syndrome and syndrome X.

Table 5.1 Life expectancy and under five mortality rate across the region in 2009 based on data from the World Bank [42, 43]

Country	Life expectancy at birth (in years)	Under five mortality rate (per 1,000 live births)
Algeria	73	32
Bahrain	76	12
Djibouti	56	94
Egypt	70	21
Iran	72	31
Iraq	68	44
Israel	82	4
Jordan	73	25
Kuwait	78	10
Lebanon	72	12
Libya	75	19
Morocco	72	38
Oman	76	12
Palestinian Territories	74	30
Qatar	76	11
Saudi Arabia	73	21
Syria	74	16
Tunisia	74	21
Turkey	72	20
United Arab Emirates	78	7
Yemen	63	66

stunting (chronic malnutrition) and overweight in children [6]. Knowing that, public health agencies should tackle the multidimensional causes of malnutrition and promote healthy eating patterns and physical activity among children of the MENA countries. Incorporating well-being programs into overall health and development efforts of governments will guarantee an optimal health of its youngest and most vulnerable inhabitants [1].

Due to the cultural, political, and socioeconomic disparities within the region, MENA is one of the most researched and least understood regions in the world [1]. The complex picture of infant and child nutrition with the superimposition of both deficiency on one hand and excess on the other pose a challenge for policy makers and healthcare planners in setting feasible policies and programs for improving nutrition of this vulnerable group. It would be pertinent, however, to encourage few simple measures such as the following: First, pregnant women need to be educated about the great protective value of breastfeeding at their antenatal visits; informing them about the importance of EBF during the first 6 months and the continuity until 1–2 years of the child's age is imperative [21]; second, managing overweight and obesity in preschool and school children through promoting healthy eating and physical activity has the potential of slowing down the rise in childhood obesity and its negative consequences while contributing to the decrease in healthcare costs [39–41]; and finally, combatting undernutrition through well-planned economic and nutritional programs will contribute to the decrease of the unacceptably high rates of child morbidity and mortality in large swaths of the region [25].

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Chapter 6
Complementary Local Foods for Infants in Developing Countries

Peter Orji Uvere and Henrietta Nkechi Ene-Obong

Key Points

- The emphasis on complementary feeding over the years is a reflection of the advantages that adequate feeding within the 6–23 month window of life confers on the overall development of the child and the larger community.
- This attention on infant feeding dates back to prehistoric times and explains why a lot of development has taken place in the complementary food world.
- These developments have not trickled down to the rural and urban poor in much of the developing world in order to improve the locally available complementary foods for infants.
- This chapter therefore considers developing world complementary foods, their processing and how the nutritional quality and feeding practices may be improved in addition to some strategies to disseminate the new technologies to the rural and urban poor.

Keywords Developing countries • Infants • Local complementary foods • Improvement • Technology dissemination

The Infancy Period

Infancy is the developmental period that extends from birth until eighteen to twenty-four months. It is a time of extreme dependence on adults. Many psychological activities are just beginning—language, symbolic thought, sensorimotor coordination and social learning, for example. This makes it necessary for conditions that may lead to irreversible faltering in linear growth and cognitive deficits to be addressed. Poor nutrition during this critical period is one such factor and contributes to significant morbidity and mortality in developing countries. Early detection of growth faltering and promotion of appropriate feeding practices are therefore important for prevention of malnutrition and the very survival of such children.

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R.R. Watson et al. (eds.), *Nutrition in Infancy: Volume 1*, Nutrition and Health,
DOI 10.1007/978-1-62703-224-7_6,

Infant Growth and Development

The pattern of a child's growth can be resolved into infant, child and pubertal phases based on endocrine influences. By the first year of life, the child increases in weight threefold and by 50% in length; and in head circumference by 10 cm. The growth rate slows in the second year of life and head circumference increases by 2 cm over the year. From 2 to 5 years of age, weight gain occurs at about 2 kg/year and height increases by 7–8 cm/year. When exclusively breastfed, babies grow more quickly than growth standard rates, but after 3–4 months, a relative deceleration in growth velocity becomes apparent [1].

Growth in infancy is a complex process; it is affected by factors such as diet, the nutritional status and health of the mother and the occurrence of infections. In addition, social factors (family structure and cohesiveness), economic status, cultural practices and biological factors (the sex of the infant, birth weight, birth order, birth interval and genetics) may also play significant roles in growth. The nutritional factors may affect growth in infancy both before and after birth. Maternal and infant nutrition are therefore intimately related. For breastfed infants, nutrition of the mother and that of her young are interrelated from conception until weaning. This makes the dietary intake of pregnant and lactating women very important to the child.

Assessment of Child Growth

Anthropometric measurements are commonly used for assessing growth and nutritional status of children. These include weight for age, height for age and weight for height. Low height for age (stunting) reflects the cumulative effects of numerous insults experienced by children during infancy and early childhood. It begins at birth and continues through the initial 40 months, after which time it is irreversible. In contrast, low weight for age (wasting) is reversible and can reflect either acute or chronic malnutrition.

Faltering in length extends through the first 3–4 years of life. In contrast, faltering in weight is concentrated between 3 and 12 months. After 12 months of age, a child may be stunted and of low weight/age, but his weight/height ratio improves. In other words, weight gain can be adequate even while the process of stunting continues for another 2 years. While failure to gain weight is a signal of inadequate nutrition, adequate weight gain does not necessarily mean that a child is growing normally. Thus, differences in the degree of growth failure in weight and height have implications for assessing the true prevalence of chronic malnutrition. This is also important for monitoring trends or evaluating the effects of interventions.

Nutritional Requirements During Infancy

Appropriate feeding practices to reduce malnutrition requires that infants should be exclusively breastfed for the first 6 months of life and thereafter, should receive adequate and safe complementary foods while breastfeeding is continued for 2 years or beyond [2] until the child is full dependent on family meal. This transition period is the most vulnerable when growth faltering starts in many children and is caused by many factors including late introduction, poor nutritional quality and insufficient amounts of complementary foods.

According to the FAO/WHO recommended nutrient intake (RNI) for developing countries, infants 0–24 months need about 400–500 mg calcium per day; for iron, 3.9–6.2 mg/day; zinc, 4.1 mg/day; vitamin A, 400 μg RE/day; thiamin, 0.3 mg/day; riboflavin, 0.4 mg/day; white for pyridoxin (B_6) it is

0.3–0.5 mg/day. Poor nutrition in the first two years can slow a child's physical and mental development for the rest of his/her life [3]. The nutrient requirement from complementary foods for infants that consume average intake of breast milk after the age of 6 months are: energy, 50–70%; protein, 20–45%; vitamin A, 5–30%; thiamine, 50–80%; riboflavin, 50–65%; calcium, 60%; vitamin B_6, 75–88%; zinc, 85%; and almost 100% for iron. Beyond these micronutrients, there is a developmental need for the polyunsaturated omega-3 and omega-6 fatty acids which are major building structures of membrane phospholipids of the brain and are important for visual and intellectual capabilities in infants and pre-schoolers. Similarly, the amino acid composition of dietary proteins contributes to the cerebral function for which tryptophan has a special role. Other essential amino acids are important for the formation of neurotransmitters.

Food Acceptance, Preference and Intake Patterns in Infants

Infants at birth depend on breast milk only for adequate nutrition during the intensive nursing period (first 6 months) of life. In order to continue normal growth and development beyond this period, additional food of varying nature must be provided [4] by the parents to help them make the transition from dependent to independent self-feeding at a time certain motor skills such as chewing and mastication have been developed. This transition occurs gradually over the first 2 years of life [5] and involves:

- A shift from a single to multiple food sources
- Increased opportunities for self-regulation of food intake
- New social contexts for eating involving peers and adult caretakers

The success of this transition can be attributed largely to the fact that the infant "comes equipped" with a set of predispositions and abilities that facilitate this dietary transition, promote the acceptance of solid foods and shape subsequent dietary patterns [6]. This is shaped by the availability of dietary variety, the quality of children's early feeding experiences and the ability of parents to accommodate their children's emerging independence. The ultimate food intake pattern of the child therefore depends on the child, the parents and the society in which the child lives.

Food Acceptance Pattern

The overall food acceptance pattern of a child is developed as the child comes into contact with the omnivorous diet in the family and society. It is mainly shaped by three factors:

- Opportunities for repeated exposure to new foods to make the food "familiar"; up to 5–10 exposures may be needed [7] to achieve this
- The social context of meals: Routine family meals teach children about foods their culture finds edible, the food combinations, meal times and what foods are typically eaten at these meals. Other social contexts include the attitudes of parents and older adults to food
- Associative learning: Children learn to associate foods with the post-ingestive effects of eating those foods. These include conditioned aversion [8] and the association of food cues with the positive consequences of ingestion [9]

Other factors which affect an infant's food acceptance pattern include: mother's level of education/literacy, age and household income.

Food Preference Pattern

Human infants are instinctively afraid of anything new and prefer to eat foods that are familiar. This helps them to avoid the ingestion of potentially harmful foods and may also explain why newborns cry at birth.

Human infants are however born with a well-developed sensitivity and preference for sweet and fatty foods but reject sour and bitter tastes. The recognition or preference for salt taste begins to appear at about 4–6 months of age and may be due to the maturation of salt-specific receptors on the tongue, early experiences with salted foods [5] and the salt flavour note in breast milk.

Infants as young as 6 weeks old can regulate their energy intake and can learn to associate the flavour cues in a food with the post-ingestion consequences, and hence regulate their intake accordingly in subsequent encounters with the food. The foods preferred by an infant are conditioned by the parents' attitudes and the foods available to them. But the amount consumed will depend on caregivers' feeding behaviours, internal satiety cues and characteristics of the diet. Additionally, children on average prefer seven different items on their plates, and six different colours which suggest that this preference for diversity could open opportunities for parents to encourage more nutritionally varied diets [10].

Infant Feeding Practices and Beliefs

Infant feeding practices in developing countries include breastfeeding and the use of complementary foods. The extent to which these are practised depends largely on the cultural norms of the communities.

Breastfeeding

Breastfeeding is the culturally accepted method of feeding infants in most developing countries of the world and the initiation rates are very high [11]. It exceeds 90% in almost every country and exceeds 95% in more than half of the countries. Breastfeeding practices are, however, far from optimal. On average, the proportion of infants under 4 months of age who are exclusively breastfed is the highest in Asia (up to 82% in Nepal) and the Near East/North Africa (63% in Morocco) followed by Latin America and Sub-Saharan Africa. There is significant variation within regions. For example, in Latin America and the Caribbean, the proportion of infants under 4 months of age who are exclusively breastfed ranges from less than 5% in Haiti to more than 50% in Bolivia, Guatemala and Peru. In Ghana, the proportion of those breastfeeding exclusively up to 6 months was below 32% [12]. This figure is woefully below the WHO/UNICEF's aim of achieving exclusive breastfeeding rate of 75% and above in sub-Saharan Africa.

Complementary Food Use

Complementary foods are used in addition to breast milk to make up for the deficits in nutrient requirements when the child's needs outstrip that provided by breast milk. The target range for complementary feeding is generally taken to be 6–23 months [2]. However, some discrepancies that draw

on cultural differences exist. Ghanaian mothers are known to use complementary foods starting with water and glucose solutions in the first few months of life [13]. Most mothers in Ghana give `koko', a maize-based fermented porridge, to their infants as early as the first month of life, a stage at which the child is supposed to be exclusively breastfed. In other parts of the developing world, complementary foods are similarly used and consist of home-made and factory-processed foods.

Breastfeeding and Timing of Weaning

Complementary foods are introduced mostly when the child attains 4–6 months, but may extend from 1 to 9 months. Factors determining the timing of complementary feeding include baby crying, baby not being satisfied, advice from the health clinics, the necessity for some mothers to return to work and maternal HIV status [14, 15].

Food Beliefs and Attitudes

Foods prepared at home are preferred by Zambian women who feel that they are fresher and contain all the nutrients. Cold foods and some foods such as *okra* prepared at home using sodium bicarbonate may cause stomach problems in the child [14] as does maize meal porridge. In Ghana, water and glucose solutions are used in the first few months of life to quench the thirst of the newborn after the exhaustive birth process or as a cultural gesture to welcome the child into the world [13].

In Ethiopia, before the initiation of breastfeeding, the newborn is often fed with butter up to 1–2 months of age and in some areas is continued even longer, mixed with a liquid made from fenugreek (*Trigonella faenum graecum*). This is to open up the throat, to grease it or to get rid of dirty things [16]. On the day of birth or a few days after birth, a liquid made of boiled fenugreek seeds is given to the child until he/she can walk. This is to get rid of intestinal dirt. Honey is forbidden in some areas in the belief that it will make children to stammer. According to Abate and Yohannes [16], eggs are believed to be the cause of intestinal parasites such as tapeworm; children who eat liver lose their teeth while eating the heart will make one to be forgetful. Sorghum and wheat are believed by some mothers to cause *Ascaris* infection.

Even though 35–40% of Indian families consume eggs and meat, it is traditionally believed that meat products and eggs cannot be given to infants due to the fact that infants fail to digest animal foods [17]. In Nepal, meat, fish, or eggs are infrequently given to children because of the belief about pure and impure food [18]. For example, in the Nepalese rural communities, vegetables and fruits are considered dangerous to the health of the infant and young children because it is regarded as cold food for young children [19]. A widely shared misperception was that infants under 1 year of age cannot digest animal source foods [20, 21]. In Bangladesh, food taboos are maintained by older family members especially the grandmothers who do not recommend oils/fats and eggs which are suitable for young children, thus further restricting food diversity [22].

In Guatemala, mothers prefer thinner complementary foods for children less than 1 year old and thicker foods for children more than 1 year old. When the child has a cough or fever, most mothers prefer thin, liquid complementary foods. When the child has diarrhoea, about half of the mothers believe that thinner complementary foods would replace the water the child lost with diarrhoea, whereas other mothers believe that thicker complementary foods would harden the stool or stop diarrhoea [23]. Infants are also believed to innately prompt mothers to begin introduction of certain foods.

Complementary Local Foods for Infants in Developing Countries

Complementary foods are food-based sources of nutrients other than breast milk that are provided to infants who are still breastfeeding [24]. Such foods are supposed to be nutrient dense because infants have high nutritional requirements relative to body size and consume small amounts of food at a time. Appropriate complementary foods can be readily consumed and digested by the young child from 6 months onwards and provide nutrients to help meet the growing child's needs. The most important nutrients are protein, iron, zinc, calcium, and vitamin A, the absence of which contributes to increased morbidity and mortality in children. In the developing countries, the raw materials used to prepare complementary foods are unrefined cereals or legumes that contain high amounts of phytic acid and phenolic compounds. They are monotonously consumed and contain negligible quantities of animal source foods because of some cultural factors. Fruits and vegetables rich in ascorbic acid and provitamin A carotenoids are not included because of the innate preferences of infants for sweet foods.

In most rural and urban poor settings, mothers are largely housewives and caregivers which restricts the choice of foods they consume and the foods provided for infants. The mothers' poor status and low intake of some micronutrients can affect the concentration of these micronutrients in human milk and by extension determines the infant's status [25]. In the case of iron and zinc, the concentrations of these trace elements in human milk are normally low regardless of maternal intake and stores, and therefore the infant's reserves at birth determine infant status [26, 27]. The need, therefore, for complementary foods becomes imperative [28] in order to improve the nutritional quality of intake when breastmilk is no longer enough and to help the child develop independent feeding capabilities based on chewing, mastication and swallowing.

Assuming an average intake of energy from breast milk, infants 6–8 months of age should on average receive 270 kcal/day, and those 9–11 months of age should consume 450 kcal/day from complementary foods [3]. Complementary foods should provide approximately 25–50% of total daily requirements for protein, riboflavin and copper; 50–75% for thiamin, calcium and manganese; and 75–100% for phosphorus, zinc and iron [29].

Developing World Complementary Local Foods

Cereals, often maize, is the major ingredient for African complementary foods, whereas rice is the major ingredient for the Asian complementary foods [30]. Sorghum and millets are used in complementary foods in countries such as Ethiopia, India, the United Republic of Tanzania, Uganda and some processed ones are based on these raw materials [31].

Porridge made with maize meal, which is a .bulky food low in nutrient density, is used as complementary food in many African countries [25, 32–34]. Nout et al. [35] summarised the preparation of African weaning foods as follows:

(a) Fresh flour + water → boil → consume (sweet porridge)
(b) Fresh flour + water → ferment overnight → boil → consume (sour porridge)
(c) Fresh flour + water → boil → ferment → consume (sour porridge)

Systems (a) and (b) are the commonly used while system (c) is used occasionally. The method of fermentation used in (b) is mostly of the uncontrolled and mixed character with lactic acid bacteria being responsible for the fermentation.

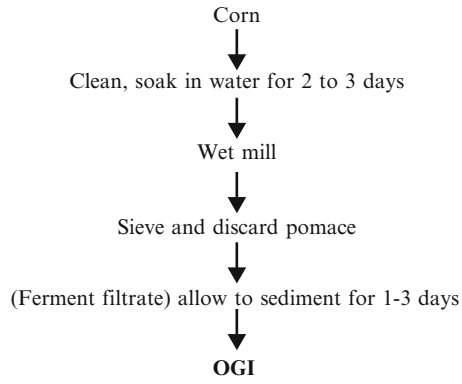

Fig. 6.1 Flow diagram for the preparation of ogi (*Source*: Haard et al., 1999)

Table 6.1 Proximate composition of maize and sorghum *ogi* obtained from study villages[a]

Type of ogi	Moisture (g)	Protein (g)	Fat (g)	Crude fibre (g)	Carbohydrate (g)	Ash (g)	Energy (kcal)	Protein energy (%)
Per 100 g wet weight								
Maïze	54.0±1.9	3.5±0.2	2.2±0.2	0.2± 0,1	39.8 ± 2,1	0.3±0.1	193.0±7.4	7.2±05
Sorghum	68.2±4.6	4.4±0.1	1.7±0.1	0.9±0.2	24.2±4.2	0.7±0.1	129.5±18.5	13.8±1.9
Per 100 g dry weight								
Maïze	7.6±0.5	4.8±0.5	0.4±0.1	86.5±1.0	0.6±0.3	420.0±2.7		
Sorghum	14.0±1.9	5.4±0.4	2,9 ± 0,2	75.6±2.1	2.1±0.1	406.9±0.1		

[a]Mean ± SD. *Source:* Brown et al., 1988

African Local Complementary Foods

In Nigeria, there are two popular indigenous complementary foods; hot-pap (*ogi*) and cold-pap (*agidi*). To prepare paps generally, the maize grains are soaked in cold water for 2–3 days (with 24 hourly change of water) and later ground to paste, wet-sieved through nylon cloth and the starch sediment collected (Fig. 6.1). Water is added and left for days with change of water at 24 h intervals. It is prepared by stirring a desired amount, in a limited amount of cold water before hot water is added and stirred continuously until a semi-liquid porridge (hot pap) is obtained [36]. There are variations to this process. The proximate composition of *ogi* is given in Table 6.1.

For cold-pap, after grinding the grains, the paste is wet sieved using clean, white cloth to get a very smooth paste which is allowed to settle at the bottom of the pot. The top water is removed while the paste is poured into boiling water and stirred to get a semi-solid porridge. This is then put inside banana (*Musa* spp. L., *Musaceae*) leaves, in a characteristic domed shape and steamed to solidification. In Ghana, the child is first started on water and glucose solution before the main traditional complementary food, *koko*—a fermented maize porridge [13] is used.

In East Africa, *uji* is a cereal gruel or porridge used widely for weaning children [37]. The traditional manufacture of fermented *uji* varies slightly from area to area. In Kenya, a flour mixture containing about 80% maize and 20% millet or sorghum flours is slurried in tap water at about 30% (w/v) level. The slurry is allowed to ferment spontaneously at room temperature for 1–3 days, diluted to give a slurry of about 6–8% flour mixture and boiled for 15–30 min until smooth and thick before sweetening with sugar. It is served hot. Traditionally, fermented *uji* suffers from problems of

Table 6.2 Grain based complementary foods in Ethiopia

Weaning foods	Raw materials
Gruel (starting complementary food)	Tef, sorghum, barley, maize, emmerwheat, and ensete (false banana used mainly in the south)
Porridge (in addition to gruel until the end of the second year)	Tef, sorghum, barley, maize, emmerwheat, and ensete
Fetfet[a] (thin leavened bread mixed with sauce of legumes)	Tef, sorghum, barley, maize, wheat, broad beans, chick peas[b], field peas[b], and lentil[b]
Ketta[a] (unleavened bread)	Tef, sorghum, barley, maize, wheat, ensete, and chick peas[b]
Dabo[a]	Tef, sorghum, barley, maize, wheat and emmerwheat

[a]Given as from 2 years until introduced to adult diet
[b]Used to produce sauce eaten together with the thin leavened bread

off-flavour and flavour irregularity and occasionally, insufficient acid production leading to a hazardously high pH product.

In some areas, mashed potatoes, bananas, or cassava are also used. Depending on the season and the area, a variety of beans, peas and vegetables are added. The energy contribution from fat is low. The liquid gruel usually contains around 5% dry matter, which results in an energy density of 0.2 kcal per gram of prepared gruel. For children above 1 year old, mothers may prepare thicker gruels. The upper limit for dry matter, however, is normally 20%, because, beyond this concentration, the gruel becomes difficult to stir. This provides an energy density of about 0.7–0.8 kcal per gram.

Obusera is the traditional fermented millet porridge of Uganda and is processed by one of three methods. The processing involves a combination of germination and fermentation resulting in a porridge with low viscosity, high nutrient density and the desirable sour taste [38].

In Ethiopia, traditional weaning practices start immediately after birth [16]: (a) before the initiation of breastfeeding, the newborn is often fed with butter. Water is also given, either alone or mixed with butter. Butter feeding continues up to 1–2 months of age and in some areas, is continued even longer, mixed with a liquid made from fenugreek (*Trigonella faenum graecum*). (b) On the day of birth or a few days after, a liquid made of boiled fenugreek seeds is given the child until he can walk. In some areas, fenugreek water is mixed with milk, butter or spices; (c) diluted milk (from cow and less frequently, goat and camels) and milk products are given as from 2 to 3 months and continued to at least 1–2 years of age. Apart from these, grain-based complementary foods are used in Ethiopia and are summarised in Table 6.2.

Maize or maize meal with groundnuts, *nshima* and *okra* are used in Zambia as complementary foods, According to Owino et al., [14] maize meal-based porridge is the main form of food for infants. *Nshima* is prepared from the flour of maize, sorghum, or millet which is boiled into a stiff porridge. The amount of flour in such a porridge is about 30% to give an energy density of 1 kcal/g and is given to children about 1 year in age [39]. To improve intake, it is diluted with water to a thin porridge containing 5% dry matter and giving 0.2 kcal/g. Porridge may be prepared with the addition of any or more of the following ingredients to maize meal: pounded groundnuts, cooking oil, sugar, fresh milk, salt, and eggs. In addition, from about 3 months onwards, cassava porridge with a little salt and/or sugar [40] may be used.

The traditional complementary food in Tanzania are based on maize, sorghum and finger millet. They can be classified into four groups [41]:

- Complementary foods composed of single foods, usually cereal flours made into thin porridges or gruels (*uji*)
- Double mixes of cereal or root/tuber flour or banana prepared as a mash, mixed usually with a little milk or animal fat

Table 6.3 Composition of the two types of meals for 100 g of rough ingredients

Composition	Control[a]	Treatment
Ingredient composition		
cassava meal (g)	–	43.4
maize meal (g)	40.0	30.0
soya flour (g)	20.0	18.6
sorghum flour (g)	20.0	-
sugar (g)	20.0	8.0
Macronutrient composition		
proteins (g)	12.9	11.3
lipids (g)	6.4	4.7
Carbohydrates (g)	58.0	65.6
energy (kcal)	350	342
moisture (humidity/water) (%)	7.9	9.0

[a]Traditional complementary food in Zaire

- Triple mixtures of cereal, fruit and vegetable mash
- Multimixes including all the ingredients mentioned, plus any other food that the mother finds suitable and that makes the food palatable and attractive

In Zanzibar of the Tanzanian Republic, the primary complementary food is maize porridge (*Ugali*), although foods made from local tubers and fried dough (*maandazi*) are also introduced early [42]. More children are fed starchy staples consisting of rice, porridge, cassava, *shelisheli* (breadfruit), potatoes, pancakes, sweet potatoes, pumpkins, plantains, or maize-flour. At 10–15 months, food made from local tubers and green vegetables may also be incorporated, but to a small extent. Meat and large fish are expensive and are, therefore, not regularly consumed. Fruits (mainly mangoes, pineapples and oranges) tend to be seasonal.

The traditional gruel in the Republic of the Congo (Table 6.3) is made from sugar, maize, sorghum and maize flours [43]. The high-energy-density gruel used for comparison (treatment) was prepared from mixed flours (maize, soya, sorghum) to which industrial amylase was added [44]. The energy densities obtained are 0.5 kcal/g for the traditional gruel and 1.0 kcal/g for the high-density gruel.

In Lesotho, the complementary foods include a fermented thin porridge known as *Motoho* and an unfermented porridge, *Leshele-shele* [45]. *Leshele-shele* is prepared by mixing a portion of finely ground sorghum or maize flour with water and boiling for 15 min to make a thin porridge. *Motoho* on the other hand, is prepared by mixing finely ground mealie (sorghum or maize flour) with lukewarm water and inoculated with a bacterial culture or inoculum from a previous preparation. The mixture is wrapped in a blanket and left overnight (11–13 h) to ferment. The following morning, a sieved mixture of the porridge is cooked in boiling water for about 20–30 min. Alternatively, a rough grind is incubated overnight with the starter culture, then reground finely and cooked as described.

Botswana has an interesting deviation from the all-cereal weaning diets: the traditional complementary food is milk from cow or goat, depending on availability. Weaning porridges include a fermented porridge, *ting* and the unfermented (*mosokwena*). Sorghum is the preferred grain; to make *ting*, sorghum is mixed with warm water to form a thick paste which is left in a warm area. To accelerate the fermentation, left-over from a previous fermentation may be used to start a fresh fermentation. The mixture is left overnight after which it is ready to use [46].

In South Africa, a soft porridge is made with maize meal (dry matter content approximately 14%) with usual addition of margarine, peanut putter, sugar, formula milk powder and eggs. In a survey by Faber [24], only 4% of the infants had nothing added to their porridge. Eighteen per cent of the infants consume fruit and vegetables, pumpkin and butternut during the 24-h recall period.

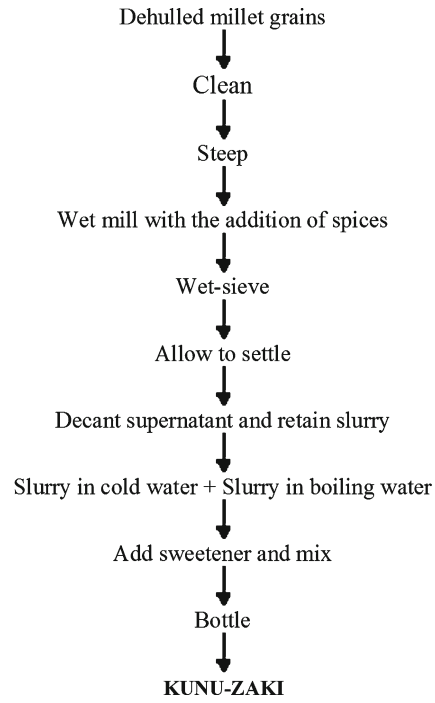

Fig. 6.2 Flow chart for the traditional processing of Kunun-zaki (*Source*: Haard et al., 1999)

Nasha is the traditional Sudanese porridge for weaning babies [38]. It is made from sorghum and millet. Fermentation is both lactic and alcoholic. Suckling infants are also given *Furesa* (butter) obtained by churning *kit rob*. It is very soft and is given in small quantities to suckling infants [47].

Beverages Used in Africa for Complementary Feeding In Africa, a number of beverages are used in complementary feeding. These include *Kunun zaki*, a millet-based non-alcoholic beverage widely consumed in the Northern parts of Nigeria. The traditional process [48] for the manufacture of *kunun-zaki* involves the steeping of millet grains, wet milling with spices (ginger, cloves, pepper), wet sieving and partial gelatinization of the slurry, followed by the addition of sugar, and bottling (Fig. 6.2). *Um gufufu* is used in Sudan and is prepared by milking cow directly into a bowl containing *rob* (milk from which fat has been removed) to give a foamy product appreciated by children [47].

Asian Complementary Foods

Local complementary foods in Asia are mainly cereal-based [49] but the following are also used [50]:

(a) Fruits (mashed bananas, boiled and mashed apples and other seasonal fruits such as papaya, *chikoo*, apples, bananas). They are mashed and given as such or mixed with *malai* (cream) or milk
(b) Vegetables are started as weaning foods after fruits. Vegetables are boiled, mashed in a blender and then strained. After the baby is 7 months, straining is not required because vegetable fiber is very desirable. Dark green leafy vegetables, carrots and pumpkin are very healthy. Ghee, butter, or cooking oil can also be added for flavour as well as for calories

(c) The first or introductory solid foods for infants and toddlers are gruels made from staple flours such as rice, wheat (*Triticum aestivum*), *bajra* (*Pennisetum typhoideum*), maize (*Zea mays*) and sorghum (*Sorghum vulgare*) [51, 52]. Cereals are introduced in the baby's diet gradually after proper cooking with vegetables to enhance the nutritive value. The cereal complementary foods include *Suji Upma* (*rava upma) and Suji kheer* made from suji, *Dalia* (from broken wheat) and rice preparations

Rice preparations include (i) *Khichri* (*moong dal*) in which the rice is cooked well till tender. To make it a very nutritious and filling full meal, vegetables and pulses are added. When the baby is still young, the entire mixture is mashed in a blender so that it is easy for the baby to swallow. The consistency can gradually be increased to a semi-solid state so that the child's palate starts getting used to regular foods; and (ii) *Pulav* which is prepared with vegetables. Other preparations include Pumpkin *Malagutal* and Spinach *Malagutal* which can be served with rice, and are very nutritious for an expectant mother as well as the baby.

Home-made baby foods used in diarrhoeal situations include: rice *kanji* and sugar, salt and water solutions. Orange juice may be added depending on the child's preferences.

In China, congee is used to feed young infants. It is a thick porridge or soup of rice which has disintegrated after prolonged cooking in copious amounts of water. The congee is not seasoned with salt or any other flavouring. Often it is mixed with steamed and deboned fish. Congee made from other grains, such as corn meal, millet, barley and sorghum are common in the north of China where rice does not grow as well as other grains suited for a colder climate. Multigrain congee mixes are used as health foods. Congee with mung beans is usually eaten with sugar.

In Nepal, Vaidya [53] reported that *kheer*, a special rice meal with milk and sugar is served to the infant at 5–6 months of age as a first solid food. After this, the infants are fed with *lito*, a traditional bland rice porridge made with clarified butter (*ghee*) and sugar (if these are available). Rice *lito* is deficient in protein and vitamins. *Jaulo* is a traditional complementary food made from rice, lentils and green vegetables for convalescing young children. *Sattu* is an instant food made from roast cereals and legumes, ground into a powder and mixed with water to make a thin gruel or cake.

In other East Asian countries and China, babies are started on rice porridge called *xifan*, then moved on to mashed fruits, soft vegetables, *tofu* and fish which are usually added to the porridge babies eat. In Indonesia, combinations of semi-solids and solids are offered to increase the energy intake of six- to 12-month-old infants [54]. In Bangladesh, a complementary food called *chop-chop* is made from a mixture of wheat flour, oil and brown sugar [55].

In the Palestinian homelands, majority of mothers provide their children with some types of fluids such as herbal tea, *sage*, water and other liquids in addition to breast-feeding. Majority of mothers (95%) prefer homemade over commercial complementary food because it is cleaner, free of preservatives, fresher and more economical. Rice, vegetables, fruits and soups are introduced at 1–6 months. At 7–12 month, milk, meat and eggs are used more frequently. When the child reaches 1 year of age, all the foods have already being introduced.

Latin American Complementary Foods

Foods most often used to complement breastmilk include locally produced cereal-based gruels and porridges (*atols*), coffee with sugar, tortillas and bread dipped in coffee, bananas and broths. *Atole*, a high-energy moderate protein, micronutrient-fortified drink is a preferred weaning drink [56]. Atole is prepared from boiled fresh maize ground into nixtamal and boiled with a variety of ingredients including sugar, milk and water to produce *atole*. In Mexico, when *atole* is mixed with chocolate it is called *champurrado*.

Maize-based non-alcoholic beverages and porridges include *acupe* from Venezuela; *cachiri* and *fubá* from Brazil; *champuz* and *napú* from Colombia and Peru; and *pozol*, *sendechó* and *atole* from Mexico. When producing *pozol*, water and lime are mixed in a suitable container to which maize is added and boiled. Once nixtamal has been prepared, the by-product is washed and ground into maize dough, which is then shaped into small balls and covered with banana leaves to ferment. The production of pozol lasts from one to fourteen days.

In Guatemala, mothers prefer thinner complementary foods (*atolls*) for children less than one year old and thicker foods (*masa de maiz)* for children more than one year old. When the child has a cough or fever, most mothers prefer thin, liquid complementary foods. When the child had diarrhoea, about half of the mothers believe thinner complementary foods would replace the water the child lost with diarrhoea, whereas other mothers believe that thicker complementary foods would harden the stool or stop diarrhoea [23]. Foods most often used to complement breastmilk include locally produced cereal-based gruels and porridges (*atols*), coffee with sugar, tortillas and bread dipped in coffee, bananas and broths. Mothers gave their children mostly soft, smooth complementary foods, such as soups or puddings, because they were easy to swallow. Simple herbal infusions, thin gruels or sweetened water are given to infants and toddlers. Early introduction (within first 2 month) of *agüitas* was strongly associated with more reported instances of diarrhea and respiratory infections irrespective of ethnicity.

In Peru, mothers prefer to give children with diarrhoea mashed rather than fried potatoes, toasted or roasted cereals and legumes rather than the coarser fresh, dried, or whole-grain forms and hard foods that had been peeled or ground [57].

Nutritional Quality of Complementary Local Foods in Developing Countries

Home-prepared complementary foods available in low-income countries frequently lack sufficient quantities of selected essential nutrients (iron, zinc and calcium) which have been designated by the World Health Organisation as problem nutrients. Deficiencies of these minerals can lead to adverse health consequences and restricted child growth and development. Inadequate intake of these nutrients occur most commonly when the local complementary foods are based primarily or exclusively on plant-derived products. This is because plant-based complementary foods usually have low mineral contents relative to young children's physiological requirements, and these foods often have high levels of inhibitors of mineral absorption, such as phytic acid (phytate).

The indigenous complementary food recipes based on starchy roots and tubers or rice contain very low amounts of iron, zinc and calcium unless they also include animal source foods. By contrast, the recipes prepared from maize and legumes or other cereal mixtures and legumes have higher iron and zinc content. But they also have considerably greater phytate content. Only those recipes enriched with liver, eggs, powdered fish (with bones) or milk powder have adequate (or near adequate) mineral contents [58]. Energy density in these foods are usually low because of the absence of a significant fat content, thus contributing to early growth faltering [40].

Improvement of Complementary Local Foods in Developing Countries

Most of the habitually used complementary foods in developing countries are unfortified cereal-based gruels characterised by low energy and nutrient density. They are often inadequate in iron, zinc and pyridoxine and in some populations, may be deficient in riboflavin, niacin, calcium, thiamin, folate, ascorbic acid and vitamin A [59–61] even in cases where strategies to improve their bioavailability are employed [29]. Incidentally, multiple micronutrient deficiencies have been reported in developing

countries; the most important "problem nutrients" are iron and zinc, which requirements are difficult to satisfy without the incorporation of animal foods into the diet or by fortification [62].

The main responses in the control of these micronutrient deficiencies are dietary diversification and modification approaches that optimise trace element bioavailability and increase trace element and vitamin density to enhance the nutrient intake from plant-based local complementary foods. The options to improve trace element (iron and zinc) bioavailability [63] include:

1. Addition of animal source foods (muscle tissue) and ascorbic acid sources (fruits, fruit juices) to complementary foods.
2. Increasing dietary diversity which is often constrained by a lack of resources for producing and purchasing higher quality foods in resource poor settings.
3. Degradation of phytic acid by adding exogenous phytase or by fermentation, germination and soaking to activate native phytase. Malting generates hydrolytic activity which is used to predigest and hence reduce the viscosity of food products, thus increasing the energy and nutrient density of weaning foods [31, 64]. It also aids easy dehulling [65].

It is necessary, however, to ensure that growth of mycotoxin-producing microorganisms does not occur. Contamination of grains with pathogenic bacteria like *Bacillus cereus* and *Staphylococcus aureus* can lead to multiplication of both species in kidney beans and of only *B. cereus* in finger millet during germination.

Fermentation enhances bioavailability of iron and zinc by reducing the content of phytic acid [29, 66] to below 1:1 and preferably below 0.4:1 to achieve a twofold increase in iron absorption [67]. For zinc, dietary phytate:zinc molar ratios below 18:1 are desired to markedly improve zinc absorption [68]. Phenolic compounds are also strong inhibitors of trace element absorption [69–71] which are affected by fermentation. Besides, the associated probiotic properties, increased vitamin content, diversity of flavours, aromas and textures and preservative effects may promote infant health especially in the high risk ones

4. Fortification

Fortification is especially important to meet the infants' needs for energy, protein and the problem micronutrients [72] especially for non-breastfed infants after the first 6 months of life [14]. The impact of fortification is, however, doubtful as the experience with commercially available, cereal-based manufactured complementary foods from Indonesia, the Philippines, Thailand, China and Mongolia [30] has shown. Complementary foods have, however, been fortified by using food wastes such as cattle bones and foods rich in certain micronutrients [73] but no bioavailability studies were conducted.

5. Supplementation

Higher intakes of foods from animal sources are usually associated with greater nutrient intake and higher dietary quality; it is therefore recommended that meat, poultry, fish, or eggs should be eaten daily, or as often as possible [74–76]. An unidentified component of muscle tissue from meat, poultry or fish significantly enhances non-heme iron bioavailability, especially from phytate-containing cereal- and legume-based meals fed infants and adults [77–79]. In addition, meat (in particular red meat) provides highly bioavailable heme iron and zinc.

Ascorbic acid is a good enhancer and may be added in the home as fruit/fruit juices. Ascorbic acid substantially enhances iron absorption, primarily by reducing ferric iron to the ferrous state and thus preventing its reaction with inhibitors [80, 81]. Human milk can be an alternative source of ascorbic acid for breastfed children in settings where fruits and fruit juices are rarely included in the young child's diet due to limited availability, affordability or tradition. Vitamin A intake could potentially be increased by regular consumption of B-carotene-rich fruits and vegetables.

Micronutrient supplementation may also provide a low-cost method to improving the consumption of the problem micronutrients [59].

6. A combination of approaches, e.g. dephytinisation of grains or legumes combined with enrichment with animal source foods or ascorbic acid-rich foods and/or fortification with appropriate levels and forms of mineral fortificants [57] might be necessary to increase the likelihood of overcoming the low micronutrient content of plant-based complementary foods used in low-income countries. The absorption and metabolism of vitamin A, iron and zinc are interconnected and the effect of poor status of one micronutrient on absorption and utilisation of other micronutrients should also be considered [82, 83].

   The approach(es) taken should be cost-effective if it must meet the needs of the majority of the rural and urban poor in developing countries.

Strategic Thrusts in Improving Complementary Feeding Practices

Indicators to assess complementary feeding practices were not available until recently when the WHO together with other partners developed a set of new and updated indicators for Infant and Young Child Feeding Practices [84, 85]. The main indicators are:

- Introduction of solid, semi-solid, or soft foods: proportion of infants 6–8 months of age who receive solid, semi-solid, or soft foods.
- Minimum dietary diversity: proportion of children 6–23 months of age who receive foods from four or more food groups of the seven food groups.
- Minimum meal frequency: proportion of breastfed and non-breastfed children 6–23 months of age who receive solid, semi-solid, or soft foods (but also including milk feeds for non-breastfed children) the minimum number of times or more.
- Minimum acceptable diet: proportion of children 6–23 months of age who receive a minimum acceptable diet. This composite indicator is calculated from the following two fractions: breastfed children 6–23 months of age who had at least the minimum dietary diversity and the minimum meal frequency during the previous day, and non-breastfed children 6–23 months of age who received at least two milk feedings and had at least the minimum dietary diversity not including milk feeds and the minimum meal frequency during the previous day.

  To achieve these, certain steps need to be taken to improve complementary feeding practices.

Improvement of Maternal Welfare and Empowerment

The importance of maternal nutritional status during pregnancy and during lactation must not be underestimated; good nutritional status ensures not only the adequacy of lactation, but also appropriate timing of weaning [86]. Poor policies and lack of support for mothers have also led to undernutrition and infant deaths. In 33 countries analysed, maternal characteristics such as education and socio-economic status have been identified as integral components of care-giving in relation to nutrition of young children [87]. There should also be provision of different complementary foods to breastfeeding and non-breastfeeding mothers as a deliberate Government Policy.

Women as change agents should be encouraged to be self-reliant in the homes, so that they would have a say in the choice of complementary foods fed to their infants. The change in women's role and behaviour will be sustainable if it is supported by male community leaders and family members [88]. Improvement of the socio-economic status of the principal child caregivers, who are mostly mothers,

could go a long way towards improving the nutritional status of children. Any intervention that seeks to improve income levels, particularly those of female-headed households, is likely to have a beneficial effect on child health and nutrition [89].

Complementary Feeding Practices

The first approach for improving complementary feeding is to increase the nutritional adequacy of locally available complementary foods containing probiotics and prebiotics, dietary diversification (production, availability and consumption of foods rich in micronutrients) and modification approaches that optimise trace element bioavailability, increase trace element and vitamin density.

Optimal timing for the introduction of complementary foods will depend on the infant's physiological and developmental status [90]. Small, frequent meals of easily digestible, smooth, semi-solid, nutrient- and energy-dense complementary foods should initially be offered while gradually increasing variety in both the type and texture of food. Protein and carbohydrate intake should increase with the infant's age while preference should be given to foods rich in micronutrients.

Time and when the food is administered: The untimely and inappropriate introduction of complementary foods has been shown to be risk factors for both under- and over-nutrition with resultant under- or overweight, stunting and micronutrient deficiencies [24]. In addition, if complementary foods are given too early or too frequently, they displace breast milk, which is of higher nutritional value than other foods.

Other factors that may compromise optimal complementary feeding are: (a) care aspects such as food safety issues and the need to educate caregivers [62] and (b) urbanisation which changes eating habits and limits the availability of home gardens and thus the prospects of dietary diversification.

Education for improved feeding practices is another essential consideration. Evidence shows that mothers are willing to prepare enriched complementary foods if they are culturally acceptable, and that improving maternal knowledge and feeding practices can lead to improved dietary intake and growth of infants.

Feeding interventions (provision of complementary food with and without nutritional counselling and nutritional counselling alone) have a positive significant impact on both weight and height in children aged less than 24 months. The impact of complementary food provision interventions is particularly large in settings with food insecurity [91].

Dissemination and Adoption of Improved Technologies and Practices

The traditional set-up in developing countries particularly in the rural areas requires that strategies for dissemination and adoption of improved technologies and practices in complementary feeding be tailored to the cultural lifestyle of the population. This is because majority of the poor live in rural areas where the facilities for mass media education is limited. The approaches would therefore need to make use of personalised methods, most likely using community health workers (CHWs) and extension personnel with the active involvement of the community [92]. The approaches include:

1. Education on the use of local resources as a sustainable strategy for the poor. Education should centre on the use of household technologies to prepare safe and nutritious complementary foods from local products
2. Education on improved infant and young children feeding practices which should emphasise the importance of:
    - Proper sanitation, hygiene practices, refrigeration and re-heating
    - Proper feeding during illness and after illness

- Increased food diversity based on local foods
- Breaking of cultural barriers to offering food that are rich in micronutrients
- Increased availability and accessibility to nutritious complementary foods
- The influence of breastfeeding for up to 6 months on complementary feeding

3. The goals of international and local organisations should aim at improving infant and young child nutrition (IYCN) along with maternal nutrition in a way that complements each other. Advocacy work should be geared towards raising issues on the political and developmental agenda by international organisations, multi-sector alliances such as GAIN and BF advocacy groups and all stakeholders [93]
4. Community involvement in disseminating the knowledge base [94] improves impact by providing the neighbourhood-level supervision and social approval that motivates regular application

Conclusion

In this chapter, local complementary foods across the developing world, aspects of their processing, nutritional quality and strategies to improve complementary feeding have been considered. The carbohydrate nature of the cereal grain base, their contents of anitinutritional factors and absence of good postharvest storage facilities mean that the cost of complementary infant food products and their nutritional quality are probably more important than products for any other groups of consumers.
Although ample research efforts to improve the quality of these local complementary foods have been undertaken, practical interventions for disseminating the technical details have to be made if these efforts are to have the desired impact. The technologies developed are easily adaptable household types and will therefore be economically viable for interested parties, especially women. In this way, complementary food processing can be a spur to rural development.

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Chapter 7
Introduction of Complementary Foods to Infants and Ultimate Risk of Allergies

Bright Ibeabughichi Nwaru

Key Points

- For the prevention of allergies in children, expert bodies recommend that the child should be exclusively breastfed for the first 4–6 months; afterwards complementary foods can be given alongside the breast milk.
- These recommendations have been on the basis of the hypothesis that the gut mucosal immune system of the infant is immature; hence introduction of solids early may trigger allergic sensitization.
- Recent findings from observational epidemiological studies question these recommendations by showing that early introduction of solids may, in fact, be protective against allergies.
- It is impossible to confirm these findings in a randomized trial setting, since it is not feasible to randomize breastfeeding, making observational studies the major source to judge the role of the timing of introduction of complementary foods in the development of allergies in childhood.
- The hypothesized immaturity of the infant's gut mucosal immune system has been suggested not to be clearly elucidated.
- In view of current evidence, the current recommendations on the timing of introduction of complementary foods as a strategy for the prevention of allergies in children may need further attention.

Keywords Allergies • Asthma • Children • Complementary foods • Gut mucosal immune system

Introduction

The prevalence of childhood allergies has been increasing in recent times, particularly in western countries, ranking one of the leading chronic diseases in children [1, 2]. Evidence also suggests that several low-income countries are already witnessing similar increase, although the reliability of the data is not clear [3–5]. As the prevalence increases, so also the associated cost burdens on families, the health care system, and the economy at large [1, 6–9]. Consequently, understanding and identifying the potential risk factors causing the increase will help in initiating early preventive strategies [10].

The etiology of allergies involves an induced shift in the balance between the T helper cells 1 (Th1) and Th2 cytokines, which usually favors Th2 dominance [11, 12]. For asthma, oxidative free radicals

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R.R. Watson et al. (eds.), *Nutrition in Infancy: Volume 1*, Nutrition and Health,
DOI 10.1007/978-1-62703-224-7_7,

are believed to be released in this process, with a consequence of inflammatory damages to the lung [12, 13]. Usually, an important feature of allergic subjects is the accumulation of immunoglobulin E (IgE)-mediated immune responses to allergen exposures, resulting in allergic sensitization [14, 15]. There is strong evidence that the sensitization of the IgE and subsequent development of allergies are initiated very early in life, possibly in utero [16, 17]. The etiology of allergies indicates that they are ailments with strong genetic predisposition, which usually manifests through familial lines [16, 17].

The genetic predisposition of allergies, however, has only been able to explain a portion of the current increase [13, 18]. Other factors currently under intense scientific investigations have been proposed to explain a portion of the increasing trend. Prominent among these are the noted changes in exogenous environmental factors; the so-called "hygiene hypothesis" (i.e., decreased or absence of microbial exposures in early life); and diet [10, 13, 18–20]. The hypothesized role of exogenous environmental factors and the "hygiene hypothesis" are not discussed here. For diet, it is hypothesized that prenatal and early life dietary exposures may play a role in the development of allergies in childhood [10, 13, 20]. Because diet is a modifiable exposure, identifying its role in the etiology of the diseases will constitute a major milestone in initiating strategies to early prevention of the disease [10]. Although a great work is currently being done to investigate the role of maternal dietary intake during pregnancy and the postpartum, as well as the dietary intake of the child during infancy, this chapter concentrates on the effect of the introduction of complementary foods during infancy on subsequent development of allergies during childhood. For the prevention of allergies, world expert bodies recommend that the child be exclusively breastfed for at least 4–6 months, thereafter other foods should be introduced to the diet, alongside the breast milk [21–25]. However, current evidence suggests that this proposition may lack strong scientific support.

This chapter starts with a presentation of the current recommendations on the introduction of complementary foods as a preventive strategy for allergies in children. Following this, a brief presentation of the mucosal immune system as the center of the biological premise for the role of age at introduction of new foods in the development of allergies will be given. After this, the chapter presents a summary of the recent findings from prospective epidemiologic birth cohort studies which have been investigating the effect of the age at introduction of new foods during infancy on the ultimate risk of allergies in childhood. The chapter ends with a discussion of issues arising from these studies and a look at the future prospects in this area of research.

Recognizing the heterogeneity of allergic diseases in children, for simplicity, the term "allergies" will be used throughout this chapter to represent all allergic disorders and hypersensitivity (i.e., wheeze, atopic dermatitis, eczema, allergic rhinitis, food allergies, IgE sensitization, and asthma). In addition, bearing in mind the inseparable link between breastfeeding and the introduction of complementary foods in terms of discussion, the focus of the discussion in this chapter will be on the introduction of new foods. In describing the introduction of new foods, most studies in the literature have used the term "solid foods" to indicate the addition of complementary foods to the diet of the infant. That term is ambiguous, because it does not differentiate whether "solid foods" include liquids such as water or entail only other complementary foods. As a result of this limitation, the term "new foods" or "complementary foods" will be used interchangeably throughout this chapter to indicate all foods (including liquids and water) introduced to the infant's diet in addition to the breast milk.

Recommendations on Complementary Foods for the Prevention of Allergies in Children

Although the benefits of breastfeeding for preventing allergies have been examined since the 1930s, it was only recently that studies started investigating the independent effect of the age at introduction of complementary foods on the occurrence of allergies in childhood [22]. Consequently, it was only

until recently that expert bodies started developing recommendations to guide the introduction of complementary foods as a strategy for preventing allergies in children, basically based on the evidence from few studies in this area. In 2000, the American Academy of Pediatrics (AAP) Committee on Nutrition, when dealing with the issue of hypoallergenic infant formulas, gave the first recommendation regarding the age at introduction of complementary foods for preventing allergies in children [21]. That recommendation was restricted to children with high-risk of allergy (i.e., infants with at least one first-degree relative with known allergic disease) and stated that complementary foods should not be introduced until the age of 6 months. It further recommended that dairy products should be delayed until the age of 1 year, eggs until the age of 2 years, and peanuts, nuts, and fish should be delayed until the age of 3 years. In 2008, AAP replaced that recommendation with another policy statement [22]. Acknowledging the lack of sufficient evidence to allow a succinct conclusion on the association between the timing of introduction of complementary foods and the development of allergic diseases including the known allergenic foods, the reverse policy statement, nonetheless, recommended that complementary foods should not be introduced before 4–6 months [22].

Similarly, although acknowledging insufficient evidence, the Australian Society of Clinical Immunology and Allergy, in 2005, recommended that, for the prevention of allergies in children, introduction of complementary foods should be delayed for at least 4–6 months [23]. In 2006, after a critical review of the available evidence and publications of scientific societies, expert bodies, and institutions on the role of age at introduction of complementary foods in the development of food allergies, the American College of Allergy, Asthma and Immunology concluded that evidence suggests that early introduction of complementary foods may increase the risk of food allergies [24]. It also indicated that while the avoidance of complementary foods may prevent the development of specific food allergies, some foods may be more allergenic than others. It thus recommended that 6 months is the optimal age for the introduction of complementary foods, and like the reversed AAP policy statement, that dairy products should be delayed until the age of 12 months, hen's egg 24 months, and peanut, tree nuts, fish, and seafood at least 36 months. In a further step, it recommended that a cautious individualized introduction of the complementary foods into the infant's diet should be pursued. However, unlike the AAP statement, these recommendations were not restricted to high-risk infants [24].

Finally, in rather a more modest step, the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN), after a careful consideration of the available evidence in 2008, recommended that complementary foods should not be introduced before 17 weeks and not later than 26 weeks [25]. It further suggested that the introduction of complementary foods should be done one at a time so that potential reactions to individual components can be detected. The statement also noted that, both in high-risk infants and infants not at high risk, there is no convincing scientific evidence to show that avoidance or delayed introduction of allergenic foods, such as fish and eggs, may prevent the occurrence of allergies [25].

Biologically, these recommendations were based on the premise that the infants mucosal immune system is immature, thus early introduction of complementary foods is suspected to trigger allergic sensitization with subsequent adverse allergic reactions [23]. Two early studies [26, 27] supported this proposition and greatly influenced these recommendations, despite the insufficient evidence the studies provided. For instance, in a Finnish nonrandomized prospective study of high-risk infants, delayed introduction of complementary foods until 6 months compared with 3 months was associated with a reduced risk of atopic dermatitis and food allergy up to 1 year of age [26]. Although these effects were not seen by the age of 5 years, the number of subjects in that study was small ($n = 236$) and important confounding factors were not considered. The second study was a prospective longitudinal study from New Zealand and included 1,210 unselected children who were followed from birth until the age of 10 years [27]. The study showed that children who were introduced to four or more complementary

foods during the first 4 months were more likely to develop eczema than those who were fed no complementary foods both during the 2–4 years and by the age of 10 years. However, this finding was not seen with asthma.

The Infant Mucosal Immune System, Allergies, and Introduction of Complementary Foods

The mucosal immune system plays a key role for survival during infancy and beyond [28–30]. It is the largest part of the body that is in direct contact with the external environment; hence, most antigens (pathological as well as harmless antigens such as foods, airborne antigens, or commensal bacterial flora) that are encountered by the immune system enter through the mucosal surfaces [29]. Consequently, in its functions, the mucosal immune system plays a dual role: one, as a defense against potential pathogens entering vulnerable surfaces of the epithelial and two, to develop tolerance for harmless antigens [28–30]. As a result of these functions, the mucosal immune system has developed a complex anatomical and functional capabilities that allow it to mount immune responses to the pathological antigens and at the same time maintain an acceptable level of tolerance to the harmless ones [29]. It has been suggested that these dual abilities develop simultaneously [30]. However, difficulties arise when any part of these developmental processes occurs inappropriately, eventually leading to disease susceptibility [28, 30]. It is at this juncture of inappropriate reactions that the development of allergic disorders is believed to be initiated [28, 30].

From animal models, it has been suggested that the periods immediately after birth and at weaning represent critical points in the neonatal development of appropriate responses to the impending pathogens and harmless antigens [30]. It is proposed that, relative to adults, the mucosal immune system of the neonates is immature, thus have limited capacity to mount immunological host defense against direct stimulation from environmental signals [28, 30]. This is consequent upon the fact that, during early life, the immune system is undergoing some fine-tuning of a variety of important functions [28, 30]. However, the mechanisms underlying these maturational processes are not clearly elucidated [28]. Thus, it has been suggested that the hypothesized immune deficiencies of newborns have been, for the most part, overestimated [28]. Particularly, the ability to detect antigen-specific immunoglobulin E (IgE) in cord blood indicates that the neonate, through the T and B cells, has the capacity to mount antigen-specific responses already at birth [28].

Evidence indicate that the breast milk contains both nutritional and immuno-modulatory components that play critical roles in the development of the immune system during early life and has been shown to protect against infections and allergies [31]. Based on the speculated immature nature of the infant's mucosal immune system, it has been suggested that early introduction of new foods to the infant may trigger allergic sensitization, leading to allergic disorders [31]. However, the mechanisms surrounding these processes are poorly understood [28]. Although it has been suggested that current immunological ignorance may be responsible for this uncertainty [30], the ethical dilemmas regarding performing randomized controlled trials to assess the effect of age at introduction of complementary foods have also remained a major challenge [22]. So far, the main strategy employed has been the so-called oral tolerance, a process of demonstrating immunological tolerance to harmless antigen usually through food challenge experiments [30]. However, there is difficulty in interpreting the results from such experiments, which have been suggested to demonstrate mainly systemic tolerance rather than tolerance in the mucosal immune system [30]. Majority of these experiments have also been demonstrated in animal models, and their findings may not have direct application to humans. Therefore, whether the timing of introduction of complementary foods induces any allergy-associated defects on the maturing mucosal system of the infant and the mechanisms involved in the process have largely remained uncertain.

Summary of Evidence on the Effect of Age at Introduction of Complementary Foods on the Occurrence of Allergies in Children

Undoubtedly, except for babies born with some health conditions, the breast milk and its exclusivity remains the optimal dietary option for the infant for a healthy growth and development. Thus, it has been widely recommended that babies be exclusively breastfed for 4–6 months, thereafter new foods can be systematically introduced to complement the breast milk [32]. For this reason and for the fact that babies cannot be denied breastfeeding, carrying out a randomized controlled trial to assess the effect of age at introduction of new foods on the development of allergies in children seems not ethically feasible [22]. However, some trials have assessed the role of different dietary advice and restrictions during infancy and others have compared exclusive breastfeeding and formula feeding. Since these studies were not specifically designed to assess the effect of age at introduction of complementary foods on the occurrence of allergies, they are not the focus of this chapter, hence are not discussed here. The following discussion will be based on the review of the evidence from observational prospective epidemiologic cohort studies, which at present remain the only source to judge the evidence of the effect of introduction of complementary foods on the occurrence of allergies in children.

Search Strategy to Identify Studies

To identify these studies, a systematic search of the published literature was undertaken using the search engines, MEDLINE, EMBASE, and Google Scholar. The search was carried from beginning of March up to the end of June 2011. Using the combination of key search terms (solid foods, complementary foods, new foods, allergies, atopy, asthma, and children), all relevant studies were extracted. The titles and abstracts of identified studies were checked, and the full texts of all potentially eligible studies were assessed. The bibliographies of eligible papers were scrutinized to identify additional potential studies. Seventeen studies were identified [26, 27, 33–47]. However, two of these studies were carried out prior to the introduction of the recommendations on complementary foods for the prevention of allergies in children (Actually, the current recommendations were greatly influenced by the findings from these studies.) [26, 27]. For this reason, these studies were excluded, focusing the review on studies carried out after the introduction of the recommendations. A fourth study was performed only on infants born preterm [33], thus it is not included in this review since its results cannot be applied to children outside its preterm birth study population. Finally, a fifth and sixth study performed a cross-sectional [34] and case–control [35] analysis, respectively, and were also excluded in this review. Table 7.1 presents the features and summary of the results from the 12 remaining studies, organized in descending order of year of publication.

Assessment of Information on Introduction of Complementary Foods and Allergic Outcomes

In practice, information on complementary foods is usually obtained through interviews with parents, and in some cases, diaries or special forms are kept with parents to record the processes and patterns of introduction of complementary foods to the infant's diet. At least one of these procedures was applied in each of the studies reviewed here, indicating a seemingly standardized and comparative assessment of the dietary exposures across the studies. Assessment of allergies in children is challenging [48–50]. A good proportion of allergies at this time are a result of microbial infections, which

Table 7.1 Summary of evidence from prospective epidemiologic studies on the effect of age at introduction of complementary foods on the occurrence of al and asthma in childhood*

Study and country	Length of follow-up (years)	Subjects (*n*)	Complementary foods and definition in the analysis	Outcomes and assessment	Main findings
Joseph et al. [36] USA	3	594	Eggs, milk, and peanut (<4; ≥ 4months)	Food allergic sensitization as measured in serum	Early introduction of new foods inversely associated with allergic sensitization
Chuang et al. [37] Taiwan	1.5	18,733	Any food (<4, 4–6, >6months)	Doctor-diagnosed atopic dermatitis (AD)	Age at introduction of new foods was not associated with AD
Hesselmar et al. [38], Sweden	1.5	184	Cow's milk products, potatoes, root vegetables, vegetables, meat, fish, and egg (median month)	Clinical and serum examinations for allergic sensitization and symptoms of eczema and asthma	Early introduction of fish inversely associated with eczema
Nwaru et al. [39], Finland	5	994	Thirds-categorized age at introduction of cow's milk, potatoes, fruits and barriers, carrots, cabbages, cereals, meat, fish, and egg	Specific allergic sensitization (any food, any inhalant, wheat, egg, and milk allergens) from serum	Late introduction of potatoes, oats, wheat, fish, and egg was associated with increased risk of allergic sensitization
Virtanen et al. [40], Finland	5	1302	Thirds-categorized age at introduction of fruits and berries; roots; wheat, barley, rye, and oats; other cereals; cabbages; milk products; fish; meat; egg	ISAAC-based asthma, allergic rhinitis, and atopic eczema	Early introduction of oats associated with decreased risk of asthma and early introduction of fish with decreased risk of allergic rhinitis
Zutavern et al. [41], Germany	6	2,074	Any food (0–4; 4–6; >6months) and food diversity at 4 months (no foods; 1–2; 3–8 groups)	Parental-reported asthma, eczema, and allergic rhinitis. Specific allergic sensitization measured in serum	Neither late introduction of foods nor food diversity was associated with the outcomes
Snijders et al. [42], The Netherlands	2	2,558	Cow's milk products (0–3; 4–6; 7–9; >9 months); introduction of "other foods" (3; 4–6; >7 months)	Specific allergic sensitization from serum; parental reported eczema, AD, and wheeze	Late introduction of cow's milk products increased the risk for eczema and late introduction of "other foods" increased risk of allergic sensitization
Filipiak et al. [43], Germany	4	4,753	Vegetables, cereal, fruit, meat, dairy products, egg, fish, other food products (≤4 5–6, >6months), and food diversity	Parental report of doctor-diagnosed and symptomatic eczema	Introduction of new foods was not associated with the outcome

Mihrshahi et al. [44], Australia	5	516	"Yes" or "no" answer on whether any new food was given by 3 months	Skin-prick test for allergic sensitization and parental-reported eczema and asthma	Introduction of new foods by 3 months associated with decreased risk of allergic sensitization
Zutavern et al. [45], Germany	2	2,612	Any food, vegetables, fruit, cereal, meat products, and dairy products (0–4; 5–6; >6 months); egg, fish, and "others" (0–6; >6 months); and food diversity	Specific allergic sensitization measured in serum. Parental-reported AD	Introduction of foods >4 months was inversely associated with symptomatic AD
Poole et al. [46], USA	Mean 4.7	1,612	Cereal grains (wheat, barley, rye, oats) and rice cereal categorized as 0–6, ≥7 months	Wheat allergy: wheat-specific IgE in plasma	Late introduction of cereal grains associated with increased risk of wheat allergy
Zutavern et al. [47], UK	5.5	642	Any foods, rice (≤3, >3 months); fruit, vegetables, cereal (≤4, >4months); meat, fish (≤5, >5months); milk (≤6, >6months); egg (≤8, > 8months)	Parental-reported doctor-diagnosed asthma, eczema and wheeze; skin-prick test used for atopy	Late introduction of egg and milk associated with eczema

*Adapted from: Nwaru BI. The role of diet during pregnancy and infancy in the development of childhood allergies and asthma. National Institute for Health and Welfare, Helsinki, Finland, 2012.

usually disappear with time. Consequently, the criteria for defining allergic endpoints sometimes vary across studies. However, some standard procedures are available and currently being employed in studies. These methods include serum samples particularly used for food allergies and IgE sensitization; doctor's diagnosis; and the International Study on Allergies in Childhood (ISAAC) questionnaire [48–50]. Depending on the outcome assessed, at least one of these procedures was applied in the studies reviewed here.

Summary of Studies

The 12 studies summarized here cut across most developed regions, including three studies from Germany [41, 43, 45], two studies each from the United States [36, 46] and Finland [39, 40], and one study each from Taiwan [37], Sweden [38], The Netherlands [42], Australia [44], and United Kingdom [47]. The latest among these studies comes from the US, in which the authors assessed the effect of introducing eggs, milk, and peanut (<4 months vs. ≥4 months) on the risk of sensitization to milk, egg, and peanut allergens in 594 three-year old children [36]. At the ages of 1, 6, and 12 months, parents were interviewed about the infant's feeding practices. After taking into account potential confounding variables, introduction of complementary foods before the age of 4 months decreased the risk of sensitization to peanut and egg allergens. However, these associations were confined mainly to children who had parents with history of asthma or allergies. The second US study examined the association between the introduction of cereals (wheat, barley, rye, oats, and rice cereal) less than 7 months vs. ≥7 months and wheat allergic sensitization in 1,612 children with mean age of 4.7 years [46]. The subjects were originally recruited to investigate the natural history of diabetes and celiac disease autoimmunity in children. Although the number of subjects who were affected by wheat allergy in that study was small ($n = 16$), thus giving less precise estimates, the authors found that late introduction of cereal grains (≥ 7months) was associated with increased risk of wheat allergy after adjustment for potential confounders.

The Taiwanese study [37] constituted a large number of subjects ($n = 18{,}733$) without a history of atopic dermatitis by the age of 6 months. The infants were followed up to the age of 18 months to assess whether introduction of any complementary food at <4 months, 4–6 months, and >6 months was associated with doctor-diagnosed atopic dermatitis. The parents were interviewed at 6 and 18 months postpartum about the infant's diet and diagnosis of atopic dermatitis. In adjusted statistical models, there was no association found between the introduction of complementary foods and the risk of atopic dermatitis in the children. The analysis in that study was restricted to children who had no history of atopic dermatitis by the age of 6 months. No specific complementary food was studied, thus possible association between some specific foods and the risk of atopic dermatitis might have been concealed by the use of "any" complementary food [37].

In the Swedish study [38], 184 infants were followed up to the age of 18 months to assess the effect of age at introduction of new foods (median month of introduction of cow's milk products, potatoes, root vegetables, vegetables, meat, fish, and egg) on allergic sensitization and clinically assessed symptoms of eczema and asthma. The subjects were recruited at birth and the parents were given diaries to record the feeding patterns of the infants. A telephone interview was used to recall the diary data from the parents when the child was 6 and 12 months of age. The results showed that early introduction of fish (<10 months) was beneficially associated with eczema, with a dose–response association: for every 2 months of delayed introduction of fish, a 16 % increased prevalence of eczema was observed. The children in this study were young, thus it is unlikely that the asthma symptoms may not be a result of early infant infections, which usually are unrelated to allergy. The diagnosis of asthma is difficult at this age. It is also possible that the small sample size of the study limited the ability to detect apparent potential associations [38].

In the Finnish cohort, two studies have been reported on the association between the age at introduction of new foods and allergen-specific sensitization to food and inhalant allergens on one hand [39], and asthma, allergic rhinitis, and atopic eczema on the other hand [40], in children aged 5 years. The cohort is multidisciplinary and population-based, and the subjects were originally recruited based on their increased risk (human leukocyte antigen (HLA) susceptibility) to type 1 diabetes. Information on the introduction of complementary foods was gathered using a special form kept with parents up to the age of 2 years to record the pattern of the infant's feeding. The IgE-based specific allergens were measured in serum while the asthma, rhinitis, and eczema outcomes were assessed using the ISAAC questionnaire. In both analyses, age at introduction of a priori-defined foods (cow's milk, potatoes, fruits and barriers, carrots, cabbages, cereals, meat, fish, and eggs) was categorized using an ad hoc third categorization. In the first study, 994 children were studied, and after adjusting for confounding factors and simultaneous study of all the foods, late introduction of potatoes (> 4 months), oats (> 5 months), wheat (> 7 months), fish (> 8.2 months), and egg (> 10.5 months) were associated with increased risk of allergic sensitization [39]. In the second study ($n = 1{,}302$), with similar modeling strategies, early introduction of oats (< 5 months) was associated with a decreased risk of asthma, while early introduction of fish (≤ 6 months) was associated with a decreased risk of allergic rhinitis [40].

Of the three German studies, two came from the same cohort [41, 45]. In the first study of that cohort, the association between the age at introduction of several food products (any food, vegetables, fruit, cereals, meat, dairy products, egg, fish, and food diversity) and the risk of specific allergic sensitization and symptomatic and doctor-diagnosed atopic dermatitis was investigated in two-year old children ($n = 2{,}612$) [41]. Because of the young age of the subjects, other allergic outcomes were not included in the two-year old analysis. However, when the children turned 6 years old ($n = 2{,}074$), the authors studied the effect of introduction of the complementary foods (any food, food diversity) on allergic sensitization and parental-reported asthma, eczema, and allergic rhinitis [45]. Using questionnaire assessment, the authors collected detailed information about the outcomes, the child's feeding practices, and other environmental exposures at reasonable time intervals until the age of 6 years. At the age of 2 years, in models adjusted for other covariates, introduction of vegetables and meat products after 6 months was moderately positively associated with doctor-diagnosed atopic dermatitis [41]. At the age of 6 years, no putative effect of age at introduction of any complementary food or the diversity of foods on the allergic outcomes was observed [45].

The third German study [43] was based on a randomized, double-blind trial that was established to investigate the effect of hydrolyzed formulas compared with conventional cow's milk formula in preventing allergies. On the basis of this trial, the authors analyzed the data for 4,753 subjects (2,814 from the intervention group and 1,939 from the control group) who completed the four-year follow-up to investigate whether delaying the introduction of complementary foods past 4 months is protective against the development of eczema. The intervention group constituted children with family history of allergy and received dietary recommendations (parents advised to exclusively breastfeed for at least 4 months, to feed a randomized formula if breast milk was insufficient, to introduce only one new food item per week after 4 months, and to avoid potential allergenic foods during the first year). The control group had no family history of allergy and received no dietary advice. The analysis was done by the intervention groups. Overall, the authors reported no clear association between age at introduction of new foods (vegetables, cereal, fruit, meat dairy products, egg, fish, as well as food diversity) and the risk of eczema [43].

In the Dutch study [42], the authors focused on assessing whether the timing of introduction of cow's milk (≤ 3 months, 4–6 months, 7–9 months, > 9 months) and "other food products" (≤ 3 months, 4–6 months, > 7 months) is associated with the risk of specific allergic sensitization and parental-reported eczema, atopic dermatitis, and recurrent wheeze in 2,558 two-year old infants. The detail of the foods included in "other food products" was not given. A repeated questionnaire at 34 weeks gestation and when the child was 3, 7, 12, and 24 months was used to gather the information on the

study. In confounder-adjusted models, late introduction of cow's milk (> 9 months) increased the risk for eczema while late introduction of "other food products" (>7 months) was associated with eczema, atopic dermatitis, recurrent wheeze, and allergic sensitization [42]. In children ($n = 642$) followed up to the age of 5.5 years in the UK [47], the association between the introduction of new foods (rice, fruits, vegetables, cereal, meat, fish, milk, and egg) and doctor-diagnosed asthma, eczema, wheeze, and atopy assessed by skin-prick test was investigated. In adjusted models, late introduction of milk (> 6 months) and egg (> 8 months) was associated with increased risk of eczema [47].

Finally, the Australian study [44] was a follow-up from a randomized controlled trial that investigated the role of dietary supplementation with omega three fatty acids and avoidance of house dust mite in the incidence of asthma and atopy from birth to 5 years in children with family history of allergies. This follow-up analysis included all the subjects in the trial ($n = 516$) and examined whether introduction of complementary foods by 3 months (based on a "no" or "yes" answer) was associated with allergic sensitization, parental-reported eczema and asthma at the age of 5 years. After adjusting for potential confounding variables, introduction of new foods by 3 months was not associated with the allergic outcomes [44]. The restriction of the study to high-risk children may limit the application of the results to the general population.

Synthesis of the Evidence from the Summarized Studies

In synthesizing the findings from these studies, it can be deduced that, for the most part, the evidence points to a potential beneficial effect of early introduction of complementary foods as a preventive strategy for allergies in children. Interestingly, these studies cut across most developed regions, thus showing a consistency across different contexts. Against current hypothesis and recommendations, none of these studies has reported a beneficial effect of late introduction of complementary foods on the development of allergies. Rather, while few of the studies report no association between introduction of new foods and allergies, majority found a beneficial effect of early introduction of new foods. Furthermore, most of the findings suggest that the observed effect of age at introduction of complementary foods on allergies may not be restricted to high-risk children, but may be applicable to the general population.

However, it should be reminded that these results have only emanated from observational epidemiologic studies, which may be influenced by some level of bias, including limitation in accounting for all known important confounding variables. Mostly, the studies reviewed here made reasonable efforts to minimize substantial bias affecting their results and adjust for the major known confounders. Apart from the Swedish study [38], the majority of the reviewed studies had reasonably large sample sizes. The collection of the information on infant feeding patterns, as well as the outcomes, was adequately done in the studies. Because of ethical issues, using a randomized controlled trial to assess the effect of introduction of complementary foods on the development of allergies may not be feasible [22]. Consequently, the best and only evidence at present to judge the effect of introduction of complementary foods on allergic outcomes remains to come from observational studies.

Two important issues arise from the evidence presented from these studies. First, there is an indication that rather than the effect of introduction of any complementary foods, the findings suggest that specific single foods may be more important than others in relation to the occurrence of allergies in childhood. Particularly, the results suggest that the introduction of the known allergenic foods (egg, cereals, fish, and cow's milk) seem to be the most important consistent determinants of allergies in childhood, and protective for that matter. Second, the results also show that the use of a single cut-off (4–6 months) for the introduction of all complementary foods in some studies and in some of the committees' recommendations may be inadequate. Usually, complementary foods are introduced consecutively, and not at the same time. Therefore, using the same cut-off for all foods will fail to

capture the consecutive and varied timing of introduction. This may result in underestimation or overestimation of the effect of introduction of complementary foods on the risk of allergies. For instance, in the Finnish studies [39, 40], the age at introduction of new foods was determined using thirds categorization, and it was clear that the introduction of each food was done systematically (potatoes introduced first and eggs introduced last). Accordingly, late introduction in those studies referred to a different time-points for each food. For instance, the observed effect of late introduction of potatoes on allergic sensitization was seen at the introduction of potatoes after 4 months, while the effect of late introduction of fish was seen at the introduction of fish after 8 months [39]. This point indicates that subsequent studies should use cut-off times that are specific to each complementary food, and that recommendations should not be based on the same cut-off for all foods but specific to timing of introduction of each food.

At the revival of the debate on the effect of age at introduction of complementary foods on the development of allergies in children, it was pointed out that studies should take into account the issue of reverse causality in their analyses [51]. It was suggested that the findings seen in current studies may be explained by reverse causality. In epidemiology, the concept of reverse causality describes a situation where, though there may be a potential association between an exposure and an outcome, the cause and effect actually occur in a reverse direction. In the context of the association between age at introduction of complementary foods and the risk of allergies, reverse causality implies that, due to increased information on the potential role of dietary interventions in decreasing the risk of allergies, atopic families or mothers whose babies show early signs of allergies may take steps aimed at reducing the probability of their child developing allergies [51]. Thus, rather than the age of introduction of new foods showing association with the risk of allergies, it may be the alteration or modification of the child's diet early in life that may be causing the observed effect. Apart from two studies [46, 47] that failed to take into account reverse causality, most of the reviewed studies either restricted the analysis to children who had early allergic symptoms or performed a stratified analysis by early allergic symptoms or family history of allergy. Apart from three [36, 41, 45] of these studies that found evidence for reverse causality, the majority of studies reported no evidence to show that reverse causality explained their findings.

Conclusions

Current evidence from prospective observational epidemiological studies indicates that the current recommendation of introduction of complementary foods after 4–6 months for the prevention of allergies in children may lack strong scientific backing. Although these recommendations were based on the speculation that the gut-mucosa of the infant is immature, thus may trigger the development of allergies if complementary foods are introduced early, the mechanisms underlying the maturational processes of the gut-mucosa are not clear.

Mostly, independent of several confounding factors and reverse causality, the available evidence points to a beneficial effect of early introduction of solid foods on the development of allergies, contrary to the hypothesized harmful effect. Interestingly, the specific important foods with a more consistent effect include egg, cereals (oats and wheat), fish, and cow's milk.

For ethical reasons, it may not be feasible to carry out a randomized controlled trial in order to confirm these findings. Consequently, the best evidence at present to judge the role of age at introduction of complementary foods in the development of allergies remains to come from observational epidemiological studies, despite their potential for bias. Mostly, the avenues of bias in the available studies were minimized.

Because new foods are usually introduced consecutively, and not at the same time, the use of the absolute cut-off of 4–6 months to categorize the age at introduction of complementary foods may be

inadequate, since it fails to account for the varied time points at which complementary foods are introduced. Overall, the current evidence demonstrates that the current recommendations on the introduction of complementary foods as a strategy for preventing allergies in children need further attention. Such attention must consider the possibility of recommending specific timing of introduction for the major complementary foods.

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Part II
Premature Infant Feeding

Chapter 8
The Role of Nutrition in Health and Disease in Premature Infants: Current Knowledge Gaps and Defining the Research Agenda

Margaret G. Parker, Liza Konnikova, and Camilia R. Martin

Key Points

- The influences of growth and nutrition in the neonate are multi-factorial requiring observational studies with careful control of confounding variables and randomized control trials of nutritional practices when feasible.
- Neonatal growth and nutrition have short- and long-term consequences necessitating assessment of positive and negative health effects along the continuum of development from infancy to adulthood.
- Reference growth charts should represent diverse, well-nourished populations with longitudinal, prospective measurements; growth charts should be specific to the population of interest (fetus, preterm, and term infant).
- Mechanisms that may contribute to long-term health outcomes during fetal development include epigenetic alterations, the formation of the microbiome, and immunomodulation.
- Epigenetic modifications that regulate gene expression are influenced by the nutritional state of the pregnant mother and infant.
- A stable microbiome is essential for both the development of the GI tract and initial programming of innate immunity.
- Immunonutrients such as long chain polyunsaturated fatty acids, glutamine, arginine, and oligosaccharides are necessary for proper neonatal development and their deficiency can lead to neonatal disease.

Keywords Fetus • Preterm • Infant • Growth • Nutrition • Growth charts • Measurement tools • Research • Epigenetics • Microbiome • Immunomodulation

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R.R. Watson et al. (eds.), *Nutrition in Infancy: Volume 1*, Nutrition and Health,
DOI 10.1007/978-1-62703-224-7_8, © Springer Science+Business Media New York 2013

Intoduction: Life Course Approach to Neonatal Nutrition and Growth

Mounting evidence demonstrates that nutrition and growth in early life has long-lasting effects, particularly for premature infants. The life course approach to neonatal nutrition and growth incorporates several key concepts that shape our current understanding of the role of nutrition and growth in the neonatal period and identify gaps in knowledge (Fig. 8.1).

The influences of growth and nutrition in the newborn period are multi-factorial. Fetal and neonatal (term and preterm) growth and nutrition is dependent on maternal pregnancy conditions, breast milk production, genetic contributions, socioeconomic factors, and maternal beliefs about nutrition for herself and her infant (Fig. 8.1). Gene-environment interactions (epigenetics) and access to placental nutrients that occur during fetal life may impact growth in both preterm and term infants, while the unique medical vulnerabilities, immunomodulation, and altered development of the microbiome among preterm infants impact growth when these infants reach term (Fig. 8.1). Many of these factors are associated with each other, making it difficult to study individual contributions of each and consequently develop effective strategies that promote optimal neonatal growth.

At times these factors may have opposing effects on optimal neonatal growth. For instance, maternal obesity is associated with gestational diabetes, which leads to macrosomia at birth in response to higher concentrations of fetal insulin growth factors [1, 2]. After birth, many macrosomic infants experience "catch down" or *slower* compensatory growth in the first months of life [3]. In contrast, obese mothers have more difficulties with breastfeeding and often formula feed their infants [4]. Because formula-fed infants are less able to self-regulate feeding volumes via a bottle compared to breastfed infants, formula feeding is associated with *faster* infant weight gain during infancy [5]. Thus, maternal obesity has contrasting downstream effects on the neonatal growth. This exemplifies that the interplay between various contributors to infant growth are complex, may "compete" with one another with respect to downstream effects, making research that seeks to identify predictors of neonatal growth difficult.

Most epidemiologic studies that evaluate determinants of neonatal growth and nutrition are observational, with variable control for important confounding or mediating variables. Although randomized control trials that evaluate the effectiveness of well-established, accepted nutritional practices during pregnancy or early neonatal life may be difficult to perform, previous experience shows that randomized trials can provide meaningful answers. For instance, several systematic reviews and meta-analyzes of published observational studies report a protective effect of breastfeeding on the development of childhood obesity [6–9]. In contrast, a large, randomized, cluster-control, breastfeeding intervention trial in rural Belarus demonstrated no association between breastfeeding and later childhood body mass index [10]. These results have been surprising to many, and show that residual confounding and selection bias are always possible in observational studies. Compared to observational studies, randomized trials can demonstrate causal pathways and are powerful in developing strategies to optimize neonatal growth and nutrition. However, they are often infeasible because they are extremely costly and impossible to perform in the absence of equipoise.

Neonatal growth and nutrition have both short- and long-term consequences. These consequences are also multi-factorial and interrelated (Fig. 8.1). The medical vulnerability, gut immaturity and immaturity feeding ability of preterm infants, the ability to regulate feedings in term infants and the gene-environment interactions, development of the microbiome and immunomodulation at play in both preterm and term infants have both immediate effects and long-term consequences on the development of child- and adult-onset diseases (Fig. 8.1). Nutrients are needed for short-term daily cell function, glucose control, and removal of wastes. For example, short-term effects of neonatal nutrition are closely monitored in preterm infants by measuring urine output, glucose, and triglyceride levels.

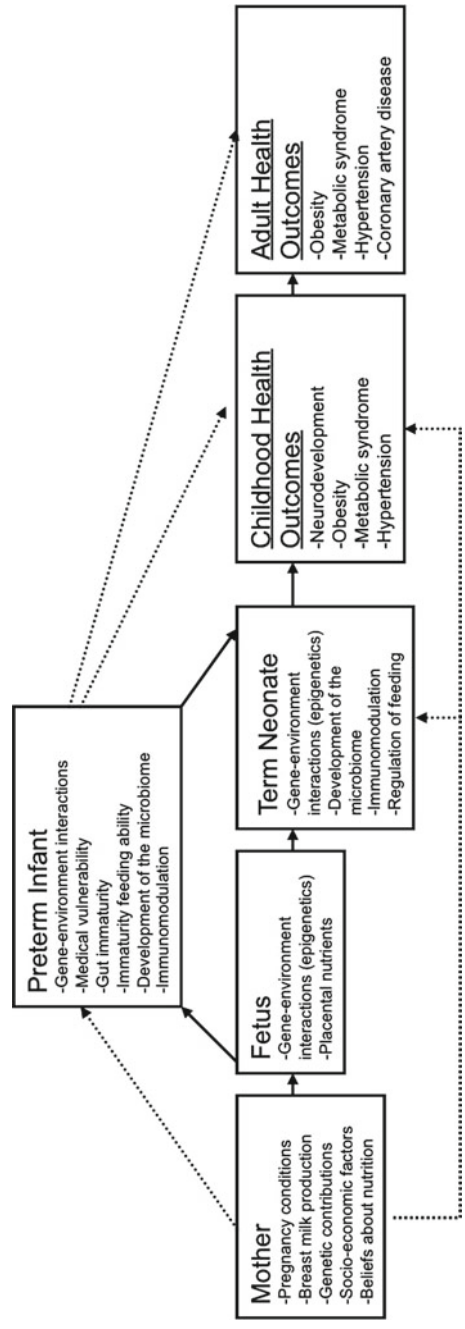

Fig. 8.1 Lifecourse model of nutrition

In addition, evidence demonstrates that growth and nutrition in the neonatal period have long-lasting effects. For instance, it is well known that more rapid neonatal growth is associated with obesity and poor cardiometabolic outcomes in later childhood and adulthood [11–16]. Problems arise when "optimal" nutrition strategies differ with respect to short- and long-term outcomes. Among extremely ill preterm infants, early nutritional support improves short-term weight gain and reduces time to achieve full feedings [17] and faster attainment of mature feedings is associated with early discharge [18]. Faster weight gain is associated with long-term improved neurodevelopment in childhood [19–21]. However, studies also demonstrate that faster growth among preterm infants may be related to insulin resistance [22] and higher blood pressure in later childhood [19, 23]. Thus, strategies to support faster weight gain among preterm infants may have competing short- and long-term effects. Belfort et al., have described a "risk versus benefits" approach to interpreting results of neonatal nutrition studies [24]. One must weigh the benefits and risks of nutritional strategies. Going forward, studies should be designed to measure both positive and negative short- and long-term outcomes.

Finally, the life course model illustrates the concept *that timing of events is critical to disease outcomes*. The developmental origin of disease hypothesis suggests that programming events that occur in early life can have long-lasting impact [25, 26]. One of the first epidemiologic examples of this phenomenon was described by Barker et al. who noted that offspring of mothers who were pregnant during times of famine in the first half of the twentieth century had growth restricted infants that were more likely to develop high blood pressure, coronary artery disease, and metabolic syndrome, suggesting that stressful intrauterine environments impact the development of the endocrine and cardiovascular systems and lead to increased risk for future disease [27]. Thus, understanding the mechanisms and timing of maturation processes is extremely important. Some of these described mechanisms include the role of epigenetics, microbiome, and immunomodulation. We will discuss these phenomena in more detail later in the chapter.

Unique Aspects of Growth and Nutrition Among Infants

There are several notable unique aspects of growth and nutrition of the fetus and newborn, making research that aims to identify and describe optimal nutritional strategies challenging. *Neonatal growth is extremely rapid*. Fetuses increase their weight tenfold in the second and third trimester. Gains in height and head circumference are also exponential. Preterm growth grossly mimics the growth of fetuses of the same gestation, although it is often stunted due to variety of medical vulnerabilities. After term gestation is reached, infants triple their birth weight during the first year of life. Thus, in order to adequately characterize fetal and neonatal growth patterns and study these patterns with respect to short- and long-term disease outcomes, several growth measurement points are needed. Unfortunately, many studies attempt to draw conclusions based on single or few measurements. For example, birth weight less than the 10th percentile-for-gestational age is defined as small-for-gestational age (SGA). SGA has been associated with cardiovascular disease and diabetes in adulthood [28]. However, with only one measure of weight at birth, it is unclear if an SGA infant was constitutionally small versus growth restricted in the latter half of gestation. Growth restriction and constitutional slow growth represent two distinct processes that should be studied with respect to disease outcomes separately in order to develop strategies to prevent later-onset disease. Multiple measurements of growth enable researchers to describe *patterns* of growth that may be more informative of future disease risk.

Unfortunately, obtaining multiple anthropometric measures during infancy is difficult as it can be costly and require multiple follow-up visits. Accurate measurements of fetal growth are even more difficult to obtain, as anthropometrics are limited to ultrasound measures of pregnant women. We will describe the pros and cons of the available fetal and neonatal dynamic growth charts in more detail

later. Nonetheless, research that accurately captures rapid growth patterns in fetal and early neonatal life is crucial to understanding the role of growth and nutrition in early life.

Predictors of fetal and infant growth are difficult to measure. Maternal pregnancy conditions such as smoking and preeclampsia lead to fetal growth restriction, while gestational diabetes and excessive gestational weight gain lead to higher birth weight. Because we cannot easily measure nutrients or hormones in the placenta or fetal tissues, it is difficult to elucidate the mechanisms at play in altered fetal growth environments. Some of the current interpretations of early life programming are based on animal models. For instance, animal models of leptin-deficient mice and rats provide the basis for understanding the mechanisms of fetal programming of satiety and energy balance [29, 30]. It is important that epidemiologists and basic scientists work collaboratively to synthesize complex epidemiological and biological data that explore early mechanisms of fetal and neonatal growth.

However, in situations where nutrients *are* directly available for measurement, studies may be limited by costs and feasibility. These barriers are notable when studying the effects of breastfeeding. The content of breast milk varies considerably; colostrum has higher protein content than breast milk later in the postpartum period, hind milk has greater fat content than foremilk and the caloric content of breast milk is higher among mothers who deliver preterm infants compared to term infants [31, 32]. Finally, because many infants drink milk directly from the breast, rather than pumped breast milk from a bottle, directly measuring the quantity of milk consumed is difficult. Because the content and volume of human milk varies so dramatically, one should draw cautious conclusions regarding the role of breast milk and neonatal growth outcomes.

Finally, *growth and nutrition of preterm infants differ from that of fetuses and term infants. Therefore, patterns of growth and long-term disease outcomes should not be compared*. It is typical for preterm infants to lose more weight in a shorter period of time after birth than term infants. Preterm infants have different nutritional needs than term infants; they require greater protein and lipid administration as soon as the first postnatal day [33] and increased vitamin, mineral, and caloric supplementation throughout the first year of life [34]. Preterm infants have different modes of nutrition delivery, compared to fetuses of the same post-conceptual age. The absorption and bioavailability of nutrients received through the premature gut are much different than nutrients that cross the placenta. Furthermore, preterm infants have significant medical morbidities such as lung disease requiring ventilation and blood-stream and gut infections which require specific nutritional interventions that do not occur among fetuses or term infants. The development of the microbiome also differs among preterm infant due to gut immaturity and medical vulnerabilities and will be discussed in more detail later. After preterm infants reach term equivalent, patterns of growth continue to differ from infants born at term. After discharge from the neonatal intensive care unit, preterm infants undergo "catch-up growth" which lasts the first several months or years of life and has been associated with improved neurodevelopment [19–21]. This association has not been seen in term infants [35]. Thus, it is important to evaluate the role of growth and nutrition among preterm infants separately as this population represents a medically vulnerable population with unique immediate and long-term nutritional needs.

Challenges of Measurement Tools of Growth and Nutrition in the Neonatal Period

Accurate and frequent measures of neonatal growth are needed when studying the effects of nutrition and disease outcomes. *Ideal measurement tools should be accurate, readily available, and cost-effective*. Unfortunately, many tools available lack these important characteristics.

Static Measurement Tools

There are many tools that determine static measures of neonatal growth and energy expenditure. Simple measures of weight, length, and head circumference are obtained routinely in the neonatal intensive care unit. Unfortunately, measures of length and head circumference are often inaccurate. One study found that infant length measures performed at clinical office visits using the "paper and pencil" method differed significantly from values obtained by trained research staff using a stadiometer (recumbent length board) [36]. Head molding that occurs after active labor may also impact head circumference measurements. Thus, abstracted anthropometric measures from clinical records can be erroneous. Nonetheless, the use of simple bedside anthropometric measures in research can be useful because they are readily available and inexpensive. The use of stadiometers is preferred in clinical practice and research whenever possible.

There are several methods in use to measure total energy expenditure. Indirect calorimetry estimates energy expenditure by quantifying the composition of oxygen, and carbon dioxide flow through a hood. Although commercial devices are available, this method is laborious and has been shown to be less accurate when used among infants on ventilators or receiving oxygen. Many isotope labeling techniques have been described that measure individual nutrient substrates and total energy expenditure including glucose, lactose, lipids, and proteins. These methods are not readily available in most hospitals and are costly [37].

In older childhood and adulthood, it is well recognized that measures of body composition may be more informative of disease risk than simple measures of weight and height alone. Lean and fat mass can be measured by dual X-ray absorptiometry (DXA), bioelectrical impedance analysis, or air-displacement plethysmography [38]. These methods have not gained popularity because they are costly or are perceived as less feasible in neonates. Alternatively, weight-for-length measurements (kg/m, kg/m^2, or kg/m^3) are used to represent fat mass. The use of weight-for-length measurements is relatively easy to obtain, but may be less precise than the methods mentioned above to describe body composition in infants. Studies of body composition among fetuses and preterm infants are few. Among sick and fragile preterm infants, many of the methods described above may be infeasible. Weight-for-length measurements likely are the most practical way to study fat mass in preterm infants. Unfortunately, to our knowledge, there are no validated normative references of preterm infants for weight-for-length or other measures of body composition stated previously. Evidence suggests that alterations in growth may begin in fetal life and early infancy. Thus, determining accurate, feasible, and cost-effective strategies to measure body composition in the earliest stages of life are important.

Dynamic Measurement Tools: Growth Charts

Static measurement tools limit our ability to see trends in neonatal growth and may be less precise in predicting later disease states. Fetal and neonatal growth is extremely rapid, requiring frequent measurement and comparison to validated normative growth charts. Growth charts are used in research as well as in routine clinical practice to make decisions about nutritional interventions. Many of the growth charts currently in use may lack accuracy. *Clinicians and researchers should interpret growth data within the context of the known limitations of term, preterm, and fetal growth charts*.

Term Infants

To date, the growth of term infants has been characterized more robustly than preterm infants and fetuses. The most common growth charts used among term infants are those published by the US

Table 8.1 CDC and WHO growth charts

Study characteristics	CDC	WHO
Means of data collection	Descriptive- cross-sectional anthropometry	Prescriptive- longitudinal anthropometry over time
Years of data collection	1963–1994	1997–2003
Population composition	Multi-ethnic, US	Multi-ethnic, international
Measures during early infancy	Few	Many
Mode of infant feeding	Mostly formula	Nearly exclusive breastfeeding
Exclusion criteria	<1,500 g at birth	Multiple gestation, preterm birth, nutritional or environmental factors known to impact growth
Anthropometrics available		
Sex-specific	Yes	Yes
Weight-for-age	0–19 years	0–5 years
Length-for-age	0–19 years	0–5 years
Weight-for-length	0–19 years	0–5 years
BMI-for age	24 months to 19 years	0–5 years

Centers for Disease Control (CDC) in 2000 [39] and World Health Organization (WHO) in 2006 [40, 41] (Table 8.1). The CDC growth charts are based on cross-sectional measurements of a US nationally representative group of children participating in five surveys from 1963 to 1994 [39, 42]. A minority of these infants were breastfed beyond the first months of life (21% at 4 months) [43]. Because there were no survey data for infants less than 2 months of age, birth certificate anthropometric data were abstracted and statistical smoothing techniques were used to achieve percentiles for infants less than 2 months. Very low birth weight (VLBW) infants were excluded, while children with environmental exposures that are known to impact growth, such as maternal smoking, were included. The CDC growth charts exist for children from 0 to 19 years [39, 42].

Positive aspects of these growth charts include their multi-ethnic US representation and exclusion of VLBW infants who have different growth patterns from term infants. The cross-sectional or "descriptive" nature of the CDC charts may be less accurate because they represent a range of growth measures of individual subjects at a single point in time. In contrast, prospective, longitudinal measures of growth incorporate several data points on individual subjects that more closely represent growth trajectories. These "prescriptive" growth charts may represent how infants "should grow" rather than how they "did" grow. The inclusion of infants with known risk factors of altered growth and infants living in a 40-year time span, during which time nutritional practices and obesity rates significantly changed, increase variability of subjects and may decrease accuracy of the growth charts. It is also known that breastfed infants grow slower than formula fed infants [5]. Therefore, growth percentiles among breastfed infants may be lower than the formula fed infants used to compose the CDC growth chart. Finally, the lack of frequent measurements in the earliest weeks of life, when growth is most rapid, also reduces precision.

The WHO standards are based on prospective data collected between 1997 and 2003 among exclusively breastfed infants in Brazil, Ghana, India, Norway, Oman, and the United States. Infants 0–24 months were followed longitudinally with visits at 1, 2, 4, and 6 weeks, monthly from 2 to 12 months, and bimonthly in the 2nd year. The study population lived in socioeconomic favorable conditions and had no health or environmental constraints to growth. Term low birth weight infants were included and preterm and multiple births were excluded. The WHO growth charts exist from birth to age 5 [40, 41, 44]. The use of the WHO growth standards has significant advantages to those published by the CDC when studying infant growth, because the WHO growth standards represent a contemporary, diverse sample of healthy infants with more uniform nutrition practices. The curves are well suited to diagnose inappropriate growth among breastfed infants and more accurately represent growth in early infancy because they are "prescriptive" and incorporate multiple measurements on many subjects longitudinally.

When planning or interpreting a research study, it is important to understand the benefits and limitations of CDC and WHO growth charts. The differences are outlined in Table 8.1 below.

Preterm Infants

Growth among preterm infants differs from term infants and fetuses that continue to grow in utero. Several reference growth charts exist [45–50], but unlike term infants, no one or two growth charts are used predominantly in research. One of the oldest and commonly used preterm growth charts is that published by Lubchenco et al. in 1963 [50]. This chart is based on cross-sectional data of birth weight-for-gestational age from 26 to 42 weeks of infants predominantly born in Denver, Colorado, from the 1940s to1960s. Dating was based on maternal history of last menstrual period [50]. Since the publication of the Lubchenco growth charts, growth charts with length and head circumference, in addition to weight, among infants as young as 22 weeks gestation at birth, representing more diverse and contemporary cohorts of infants have been published [46, 48]. The Fenton growth charts, published in 2003, attempted to combine data from multiple large population studies to increase the sample size of infants measured. However, accuracy is limited by the varied methods of measuring gestational age and exclusion criteria [45]. It is interesting that the authors state that, "separate gender charts were not produced since the gender differences were considered not important enough to warrant separate charts," when the authors later reported statistically significant differences in weight by sex among all infants >23 weeks gestation at birth [45]. Sex-specific preterm growth charts are necessary, as it is evident that anthropometrics vary by gender among term infants [48, 49].

Olsen, et al. published sex-specific growth charts for preterm infants aged 22–42 weeks for weight, length, and head circumference in 2010 based on cross-sectional data of ~400,000 infants born in the US from 1998 to 2006 [49]. A benefit to these charts is that they list weight, length, and head circumference for the 3rd, 10th, 25th, 50th, 75th, 90th, and 97th percentile, allowing clinicians to compare trends in weight within more narrow growth percentiles [49]. In contrast, the Fenton growth charts list 3rd, 10th, 50th, 90th, and 97th percentile curves, only. However, even more refined continuous z-scores are preferred for statistical analysis of disease outcomes in research. Oken et al., published sex-specific weight, length, and head circumference continuous z-scores for preterm infants aged 22–44 weeks gestation based on cross-sectional US birth certificate data in 1999–2000 [48]. The use of continuous z-scores as described in the Oken growth charts are preferred in research. Research studies that use published percentiles are often limited by traditional classifications of small-for-gestational age (SGA), <10th percentile, and large-for-gestational age (LGA), >90th percentile. These cut-offs are arbitrary and associations with disease outcomes are not limited to infants in the bottom and top decile.

None of the growth charts mentioned for preterm infants are "prescriptive" or measure longitudinal measurements on "healthy" preterm infants to represent optimal preterm growth over time. Thus, the cross-sectional charts mentioned above may not represent the actual growth of preterm infants. For instance, a typical infant born at 28 weeks gestation, weighing 1.2 kg at birth, may lose weight initially, and regain birth weight by 2 weeks of life. Despite the fact that most clinicians would deem this a normal expectant pattern of growth, the Fenton growth charts would interpret this infant as starting just above the 50th percentile and dropping to slightly above the 10th, where the Oken growth charts would define this infant as having a 0.24 z-score for weight at birth and −0.79 z-score for weight at 2 weeks of age. Currently, the International Fetal and Newborn Growth Consortium (INTERGROWTH-21st), a multi-national research study that aims to create prescriptive growth charts for fetuses and preterm infants, is in progress and data collection will be completed in 2012 [51]. The goal of this study is to follow healthy, well-nourished mothers with serial fetal ultrasounds and postnatal anthropometrics. Dating will be established by early ultrasound to assure accurate gestational age. Healthy mothers with singleton infants without conditions that impact fetal growth and preterm infants without significant NICU morbidities such as necrotizing enterocolitis, sepsis,

Table 8.2 Characteristics of the INTERGROWTH-21st study prescriptive standards for monitoring

Multiethnic, population-based, prospective data
Maternal inclusion criteria:
– Healthy, well-nourished mothers
– Gestational age confirmed by ultrasound examination <14 weeks
Infant inclusion criteria:
– Preterm infants (low birth weight infants will not serve as a proxy)
– No major neonatal complications or neonatal surgery
– No congenital malformations
– Death does not occur in the complete follow-up period
Measurements of growth:
– Prospective ultrasound measures of fetal growth (fetuses with evidence of impaired fetal growth will be excluded)
– Standardization of anthropometric measurements including use of the same equipment and techniques
– Frequent anthropometric measurements during periods of rapid growth (e.g., every 2 weeks during the first 2 months)
Standardization of feeding practices and newborn care among study centers
Follow-up period during infancy to allow interface with WHO child growth standards
Adequate sample size for each range of gestational ages to allow presentation by Z scores and centiles

Modified from [51]

and bronchopulmonary dysplasia will be included. Feeding practices will be standardized across centers. Finally, the sample size for each gestational age will allow continuous percentiles or z-scores that will be ideal for research use [51].

Use of prescriptive growth charts which represent the natural and optimal growth patterns of preterm infants is necessary for clinical practice as well as in preterm growth and nutrition research. Based on the methodology described by the INTERGROWTH-21st study team, these proposed growth charts will become the preferred growth charts of preterm infants (Table 8.2) (http://www.intergrowth21.org.uk).

Fetuses

The reference growth charts in use for fetuses vary even more considerably than term and preterm infants. One of the main reasons for this is that fetal weight is estimated by common fetal biometry measures such as biparietal diameter, femur length, and abdominal diameter. The accuracy of these measurements is limited by intra- and inter-observer variability, which some contend could be minimized with improvements in ultrasound image quality, averaging of multiple biometry measures, and frequent audits of measurement [52]. Other factors that limit accuracy of fetal biometry include maternal size, placental location, and multiple gestation [52]. There are dozens of published formulas which estimate fetal weight, yet systematic reviews reveal no superior formula [52]. Validation studies report errors of up to 10–20% of estimated fetal weight prediction of birth weight, [52] mainly because these formulas incorporate the variability of several biometry measurements which substantially increase imprecision. Unfortunately, ultrasound prediction of estimated fetal weight is most inaccurate among the smallest and largest fetuses, [52] the fetal population most "at-risk" of adverse outcomes where knowledge of estimated fetal weight may inform clinical decisions.

Researchers conducting longitudinal studies of fetal growth and childhood outcomes have "arbitrarily" chosen one of the many estimated fetal weight formulas and created internal growth percentiles or z-scores using data from their own study populations [53, 54]. There are several problems with this method. First, these internal z-scores only reflect the population of reference, making it difficult to generalize findings to other groups. For instance, it would not be appropriate to use published z-scores of a primarily Japanese cohort to study fetal growth in a Dutch population as it is well known

that mean birth weights, and likely patterns of fetal growth, differ among these groups. Secondly, most fetal growth charts are not prescriptive, but are based on cross-sectional data [55–58]. Thirdly, most published fetal growth charts are not sex-specific. Growth charts of term and preterm infants demonstrate differences in growth by gender, thus differences likely exist in fetal life as well. Finally, many existing fetal growth charts have been derived using measurements from fetuses at risk for abnormal fetal growth, in addition to "healthy" fetuses. As described in the context of the CDC growth charts among term infants, this practice introduces more heterogeneity and may decrease the accuracy of growth curves representing "optimal growth."

Because of these issues, emerging literature supports the use of customized fetal growth charts, which use certain fetal and maternal characteristics to predict fetal growth, in conjunction with fetal biometry [59, 60]. Optimal birth weight is modeled by linear regression taking into account characteristics which are known to impact fetal growth including fetal sex, maternal height, weight, parity, and ethnic origin [60]. Then percentiles during gestation are extrapolated backward from birth. Customized fetal growth curves have been shown to be superior to "traditional" ones in reducing false-positive diagnoses of fetal growth restriction and may be more accurate to follow growth of smaller infants [59]. Customized fetal growth charts are beneficial because they take into account fetal sex, ethnicity, and maternal characteristics. However, prospective longitudinal measures of "healthy" fetuses throughout gestation, rather than backward extrapolation from birth, may still prove to be a more accurate means to characterize fetal growth. Further validation of the use of customized versus traditional fetal growth charts are needed.

In summary, there are a multitude of measurement tools available for studying fetal growth, but none are predominantly used. Prospective, longitudinal, fetal biometry measures of a diverse group of normally growing singleton fetuses are needed to obtain accurate prescriptive fetal growth standards. Measurement should be performed among women where early trimester ultrasound dating aligns with maternal history of last menstrual period. The Altman and Chitty fetal growth charts published in 1994 based on a UK cohort [55–58] are better than others at the current time because they incorporated pregnant women with certain last menstrual periods, that were not taking medications and without conditions known to impact fetal growth, and fetuses without known congenital or chromosomal anomalies [55]. However, these references are not sex specific and based on cross-sectional measures of singleton fetuses with only a single ultrasound.

Finally, more evaluation of fetal growth in relation to later disease states is needed. Most existing data are based on the Raine cohort in Western Australia and Generation R of the Netherlands [53, 54]. Data from these cohorts have been used to examine associations of static and dynamic measures of fetal growth with childhood obesity and blood pressure [53, 54, 61]. Both of these cohorts created internal z-scores of their participants to follow fetal growth over time [53, 54]. Again, generalizability may be difficult as the fetal growth of these populations may differ from others. A more representative fetal growth chart, similar to the WHO standard is necessary to better study important changes that occur in fetal life with respect to later outcomes.

Mechanisms of Fetal and Neonatal Growth: Research Gaps and Controversies

Barker Hypothesis

In the late1980s, Barker and colleagues published a sentinel paper on the origins of cardiovascular disease. They noted that lower birth weight infants born to malnourished pregnant mothers had higher rates of death from ischemic heart disease. The authors proposed that the altered intrauterine environment of these infants led to lifelong changes in cardiovascular health [27]. These remarkable

observations gave rise to what is now known as the "Barker Hypothesis," or the "developmental origins of disease hypothesis," that adult-onset diseases have fetal origins. Since the original publication, a number of studies from the US, England, India, Finland, Sweden, and Denmark have replicated these observations [62–66]. Low birth weight has also been associated with a variety of other child-onset diseases including asthma, leukemia, and chronic kidney disease [67–69] and adult-onset chronic conditions including hypertension, cancer, obesity, and metabolic syndrome [70]. In contrast, higher birth weight has also been associated with cancer and cardiovascular disease [71]. This suggests that an ideal intrauterine environment that promotes "optimal" fetal growth and a subsequent "optimal" birth weight may minimize risks of chronic diseases, while deviations from this ideal fetal growth trajectory lead to changes in developmental programming that increase risk for later disease.

How is fetal programming established? Over the past decade it has become increasingly clear that multiple mechanisms occur during fetal and early neonatal life that lead to developmental programming that can be linked to future disease. These mechanisms are influenced by the micronutrient environment and include gene-environment interactions (epigenetics), the establishment of the gastrointestinal tract microbiome, and immunomodulation. We will explore current evidence, gaps in knowledge of each of these concepts separately.

Epigenetics

Definitions

Recently, it has become clear that developmental programming of adult-onset disease may be partly regulated by a phenomenon known as epigenetics, or the modification of gene expression without alteration in the original DNA sequences. Epigenetic alterations include DNA methylation, histone modifications, and altered expression of non-coding micro-RNAs that regulate transcription of coding genes. Briefly, DNA is methylated by the DNA methyltransferase family of enzymes (DNMTs) on CpG dinucleotide motifs at the C position, in a process that is cell and organ specific. These motifs can be found anywhere in the genome, but are highly concentrated in the promoter regions of genes, allowing for careful regulation of transcription at a given promoter [72].

Histone modifications are another mechanism of epigenetical change. Histones are proteins that help fold the DNA into chromatin. The smallest one of these units is known as a nucleosome and is comprised of DNA and eight histone molecules. The tail ends of histones can be modified by the addition of a number of subunits that include methylation, acetylation, phosphorylation, citrullination, ubiquitination, SUMOylation, and ADP-ribosylation. Though the function of these histone modifiers is diverse, they generally either increase or decrease transcriptional activity at a given promoter region. In combination, these modifications lead to changes in the three-dimensional structure of the chromatin, which in turn leads to alterations in the interaction between the chromatin and the transcription machinery. Although classical epigenetics was thought to be an on/off event, it is now understood to be much more plastic and believed to act in fine-tuning gene expression in a manner similar to a thermostat [72].

Classically, it was believed that the majority of DNA methylation was lost during gametogenesis, [73] with well-known exceptions such as imprinted and X-inactivated genes, both of which retain their original methylation pattern. New evidence suggests that epigenetic modifications of many genes are retained from one generation to the other, implying that the epigenetic changes acquired in one generation can have profound consequences not only for that fetus but also for generations to come [73]. However, it is not well understood how it is determined which epigenetic signatures are propagated and which ones are erased.

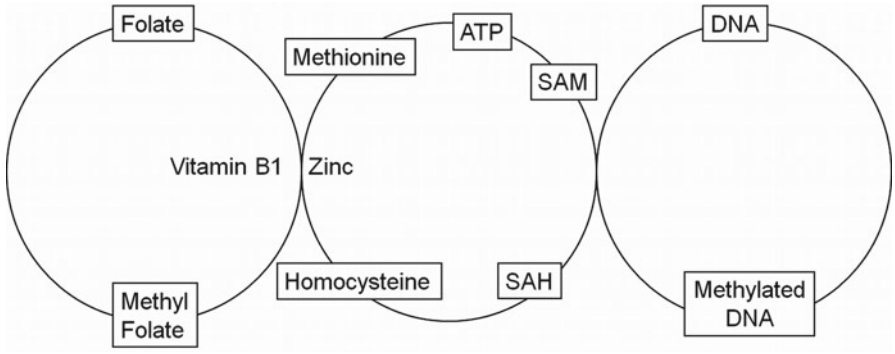

Fig. 8.2 1-carbon metabolism. Modified from [73]

What are the signals that govern DNA methylation? The first of these is "epimutations," or mutations to the previously established epigenetic code in a particular cell [73]. These mutations are much more common than somatic mutations due to a lack of proofreading activity and the innate error rate associated with the enzymes that maintain DNA methylation. Since epigenetics relies on the transfer of a modification group (e.g., methyl group) from a donor moiety to the accepting DNA, mutations in the enzymes that are responsible for either the actual transfer of the moiety or its creation can affect the rate of chromatin modification and lead to changes in gene expression. An example of this is the enzymes involved in 1-carbon cycle (Fig. 8.2), needed for the generation of the methyl donor group. A genetic variant of the MTHFR (methylenetetrahydrofolate reductase) gene that has a C-T substitution at nucleotide 677 produces an unstable enzyme. Individuals that carry this allele have lower rates of DNA methylation than those with the wild type allele [73].

Epigenetic Changes in Fetal Life

The micronutrient environment has well-known epigenetic effects that take place in fetal life. A number of micronutrients are involved in the 1-carbon metabolism and therefore are required for proper function of DNA methylation (Fig. 8.2) [73]. Both human and animal studies have elegantly demonstrated that alterations in the availability of micronutrients in the diet can change the degree of gene methylation. For instance, in a murine model, dietary folate intake correlated with the amount of methylated DNA in a number of genes [74]. Other micronutrients that are involved in the 1-carbon cycle, such as vitamin B12, choline, and betaine, have also been shown to affect methylation and regulate the expression of the agouti variable yellow (Avy) gene that causes a yellow fur color in mice [74]. This gene is expressed when unmethylated, causing yellow fur color in mice and silenced by methylation, causing brown fur color. In one study, mice whose diets were supplemented with folate, vitamin B12, choline, or betaine during gestation had offspring with increased methylation of DNA and silencing of the Avy gene, leading to brown fur color. Epidemiologic data in humans demonstrated that folate supplementation of pregnant women led to increased methylation of the insulin-like growth factor 2 (IFG2) gene in infants [75]. This study was powerful, because it was one of the first to demonstrate that maternal dietary intake may alter offspring gene expression. Furthermore, recent evidence demonstrated that the association between folate deficiency and neural tube defects may be epigenetically regulated [76].

A growing body of evidence suggests that the epigenetic modifications acquired in utero may last beyond infancy. In one study, offspring of sheep who were fed a low-folate diet were more likely to develop cardiovascular diseases than those whose mothers were fed a normal diet [77]. In these

animals, 4% of the methylated DNA regions were altered [77]. Similarly, in a rat model of intrauterine growth restriction (IUGR), investigators demonstrated that IUGR induces a histone modification of the insulin-like growth factor 1 (IGF-1) gene that persisted into adulthood [78]. Furthermore, individuals born to mothers who were malnourished in pregnancy due to the Dutch famine in the 1940s with greater risks of cardiovascular disease as adults, had increased hypomethylation at the IGF2 gene in adulthood compared to their same-sex siblings born at other times [79].

Is there a "window" *period during development in which epigenetic acquired modifications persist throughout life*? If so, how long is this period? Are these changes irreversible? Or can they be corrected with nutrient administration later in life? Are epigenetic changes gene dependent, where some in utero epigenetic modifications are permanent and others are reversible throughout our lives? Further research is needed to answer these next questions.

Postnatal Epigenetic Changes

Both animal and human data also suggest that epigenetic modification may occur in postnatal life in both full-term and preterm infants [72]. Faga et al. showed that DNA methylation and histone acetylation patterns of monozygotic twins were identical at birth and then diverged significantly as the twins became older, demonstrating that epigenetic modifications continue throughout the life course [80]. Animal studies have shown that epigenetic modifications occur to genes expressed in the brain after enriched dietary intake in the postnatal period [81]. Researchers have therefore proposed that epigenetic changes may explain the association between administration of nutrient-enriched preterm formulas and improved neurodevelopment in preterm infants [72]. These results are promising because they suggest that nutrition strategies may play a role in altering epigenetic changes postnatally. It may be possible to utilize nutrition strategies reverse detrimental effects of a stressful, nutrient poor intrauterine environment.

In summary, the field of nutritional regulation of epigenetics is an exciting and evolving area of research where it has become evident that the nutritional state of pregnant mother and infant may impact gene expression. Future research should further explore epigenetic mechanisms in both animal and human models and determine how nutrient strategies may minimize future health risks. Particular attentions should be paid to interventions that may improve the health of preterm infants as this population is most susceptible to adverse intrauterine environments and medical morbidities which impact long-term growth and nutrition.

Recent evidence shows that in addition to nutritional influences, environmental factors such as stress and placental insufficiency can have a profound influence on the epigenetic state of the fetus [82].

Microbiome

Definitions

The term mirobiome was originally coined by Nobel laureate Joshua Lederberg to mean the total number of microbes such as bacteria, viruses, and helminthes, along with their genomes, that reside in a particular ecosystem (skin, mouth, gastrointestinal tract) [83]. However, "microbiome" is often used to describe the genomic composition of the commensal flora and "microbiota" refers to the actual organisms. Confusion persists with definitions of these terms in the literature. The composition of the bacteria, the predominant member of the microbiota, differs from one ecosystem to another [84]. There is extensive evidence that even within a single organ such as the gastrointestinal (GI) tract

there are "sub ecosystems" that differ from one another. For example, the microbial content and metabolic activity differ significantly in the mouth, stomach, and small intestines [84].

Previous research on the human microbiota has been hampered by our inability to culture the majority of bacteria that make up the commensal flora. However, with the advent of culture-free methods, such as 16S ribosomal RNA gene sequencing to identify the bacteria present, the characterization of the human microbiota is now greatly improved. We now know that the adult human gastrointestinal tract is host to an order of magnitude more bacterial cells (10^4) than there are cells comprising the human body (10^3). The human intestine is the host to over 400 different bacterial species, the majority of which can be subdivided into two broad bacterial phyla, Bacteroides and the Firmicutes [84]. The composition of commensal bacteria varies from individual to individual, but remains remarkably stable in a particular host [84]. More studies are needed to further elucidate how the stability of the microbiota in a given host is established.

Microbiome of the Neonate

The microbiota of the neonate contains many fewer species than adults and varies between and within infants [85]. The acquisition of a stable GI microbiota reaches the adult levels by about 1 year of age [85]. It has long been postulated that the fetal environment is sterile and that the colonization of the infant GI tract is initiated at birth during contact with maternal vaginal flora or the environment depending on the mode of delivery. However, there are data that suggest that the colonization of the GI tract is initiated prior to delivery. Jeminez et al. detected bacteria in the blood of healthy neonates and found that meconium obtained from healthy neonates was colonized by bacteria mainly belonging to the Enterococcus and Staphylococcus genuses [86, 87]. Other researchers identified bacteria in the amniotic fluid of mice pups delivered by caesarian section and that genetically labeled bacteria fed to pregnant mice could be isolated from the meconium of pups delivered by caesarean section prior to induction of labor [86, 87]. Finally, Satokari et al. demonstrated the presence of Bifidobacterium and Lactobacillus DNA in human placentas of both vaginal and caesarean delivered infants [88]. These collective data are intriguing and more experiments are needed to determine both the timing and the route of the initial colonization. Are specific bacteria able to colonize the fetus better than others? If bacteria pass hematogenously, as some preliminary data suggest, what mechanisms are involved in protecting the body from developing inflammatory reactions seen in early-onset bacterial sepsis?

The process of bacterial colonization is dependent on numerous factors that include genetic background of the host, mode of delivery, type of feeding, and antibiotic use [84]. However, the extent to which each one of these factors influences the colonization pattern of neonates is not completely understood and varies from study to study. It is important to further delineate how these processes contribute individually and in concert to the establishment of the GI microbiota in neonates.

The microbiota of the GI tract and its metabolic activity are influenced by host dietary intake. For example, multiple studies have demonstrated that there are differences in the microbiota of the GI tract of breastfed versus formula-fed infants. Koenig et al. showed that the microbiome of breastfed infants is enriched for genes that control lactate utilization while solid food intake is associated with increased amount of genes involved in carbohydrate metabolism and vitamin biosynthesis [89]. In a similar set of experiments, Poroyko et al. demonstrated that the microbiome of breastfed versus formula-fed sheep differed in the expression of genes involved in protein metabolism and oxidative stress response [90]. Recent evidence suggests that particular components of dietary intake can stimulate bacterial growth; researchers found that the oligosaccharides in human milk stimulated specific commensal bacteria to grow [84]. Finally, direct injection of microorganisms also contributes to the "dietary" contribution of the establishment of GI tract microbiota. For instance, breast milk is a source of bacteria [84]. As demonstrated by the collective research mentioned, the process by which host diet determines the composition and metabolic activity of the microbiota of the GI tract is multi-factorial. Further research is needed to describe the regulatory mechanisms at work in this process.

Microbiome in Preterm Infants

Preliminary data suggest that the colonization patterns of the GI microbiota differ in preterm compared to term infants [91, 92]. The diversity of the premature GI tract microbiota is limited compared to full term healthy neonates and nearly all identified species are known neonatal pathogens [91, 92]. There is also a shift in the predominant flora, with Fermicutes increasing over Bacteroides, and a delay in bifidobacterial colonization [93].

Functions of the Microbiome

What function do the commensal bacteria serve? Some of the well-established functions include: facilitating digestion, increasing bioavailability and absorption of nutrients, and limiting pathogen colonization [94]. However, there is now increasing evidence that the colonization of the GI tract and the formation of a stable microbiome are essential for both the proper development and function of the GI tract and initial programming of the innate immunity. The microbiota of the GI tract and host works symbiotically to regulate diverse functions such as angiogenesis [95], proliferation, and proper crypt formation [96]. In addition, studies published in the past decade indicate that GI tract microflora regulates the development and function of gut-associated lymphoid tissue (GALT) [97]. GALT is required for the formation of germinal centers in the spleen and lymph nodes and systemic antibody production, [98, 99] and it aids with pathogen clearance during times of GI tract and systemic infections [100]. Recent data also demonstrate that GI tract colonization is required for prevention of intestinal inflammation. It has been shown that mice reared in germ-free environments develop intestinal inflammation much more frequently than mice reared in normal environments. Furthermore, mice that were colonized with Bacteroides fragilis had less colitis [101]. There is a need for further experiments to understand the functions of the microbiota to determine which specific types or groups of commensal microbiota are involved in the aforementioned developmental processes that are known to be associated with later disease outcomes.

The Role of the Microbiome in Host Disease

Which diseases are influenced by the microbiome? The rearing of mice in germ-free conditions and later exposing the mice to microbiota of other animals through fecal transplantation has enabled researchers to answer this question more systematically. Although this field is still in its infancy, early data suggest that both obesity and malnutrition can be modified by altering the host microbiota. Further characterization of these diseases and identification of others that are affected by the microflora is needed [102]. Can diseases be prevented by administration of commensal bacteria? Are some commensal bacteria "more" protective then others?

Probiotics are microorganisms that confer health benefits to the host. The first characterization of probiotics dates back to early 1900s when Metchnikoff proposed that "the dependence of the intestinal microbes on the food makes it possible to adopt measures to modify the flora in our bodies and to replace the harmful microbes by useful microbes [103]. The use of ingested microbes to modify gut flora has drastically increased over the past decade. For instance, probiotics have been shown to be beneficial in preventing and treating diarrheal illness in infants and children [84]. There are promising data that probiotics can be used to treat several other diverse conditions including, atopy, eczema, allergy, and inflammatory bowel disease [104]. Some studies show that probiotics may prevent childhood colic [105] and necrotizing enterocolitis (NEC) [106]. However, meta-analysis of such studies have failed to demonstrate benefit [107], which may be because of the vast differences in the strains and doses of probiotics administered. Thus, there is an urgent need for research to determine if there are specific strains or doses that are more beneficial than others.

Immunomodulation

Immunomodulators are substances that regulate the activity of the immune system. A number of dietary components such as vitamins and micronutrients, oligosaccharides, fatty acids, and amino acids can act as immunomodulators. The discussion of all immunomodulators is beyond the scope of this chapter. Here, we will focus on the contribution of long chain polyunsaturated fatty acids, arginine, glutamate, and oligosaccharides to neonatal health and disease.

Long Chain Polyunsaturated Fatty Acids

The long chain polyunsaturated fatty acids (LCPUFA), especially the omega-3, docosahexaenoic acid (DHA), and the omega-6, arachidonic acid (AA), are essential fatty acids that are required for proper development of the brain and retina as well as regulation of the immune system. Majority of prenatal accumulation of these substances occurs through placental transfer in the third trimester of pregnancy. For the full term infant, breast milk is an excellent source of LCPUFA. Autopsy studies show that infants who were fed breast milk had much higher levels of DHA in their brains and retina than those that were fed formula [108–110].

In contrast to the full term neonate, premature infants are born with a deficiency in LCPUFA as the placental transfer is interrupted and the enzymes that are needed to digest PUFA precursors do not work as efficiently [111]. Lapillonne et al. have demonstrated that our current supplementation recommendations result in a daily LCPUFA deficit that amounts to almost 50% by 1 month of age. Furthermore, neither breast milk nor current preterm formulas can compensate for this deficit [111, 112]. There is evidence that improper balance of LCPUFA is related to neonatal diseases such as NEC, retinopathy of prematurity (ROP), chronic lung disease (CLD), and late onset sepsis LOS [113]. Consistent with these observations, recent data have shown that low blood levels of LCPUFA in premature infants are correlated with increased risk for chronic disease such as CLD and LOS [114].

Blood levels of LCPUFA are very similar in the preterm infants fed PUFA supplemented formula and those fed breast milk [115]. However, the results on neurodevelopment are mixed; the majority of preliminary data show that premature infants whose diet was supplemented with n-3 LCPUFA had improvement in neurodevelopment [116]. Further studies are need to determine supplementary strategies in the preterm infant that reduces the postnatal deficit of the LCPUFAs and long-term follow-up studies are needed to determine if benefit from supplementation is sustained.

Amino Acids

Arginine is an essential amino acid that serves as a precursor for nitric oxide (NO), polyamines, [117] and many other biologically active substances (Table 8.3). NO is known to be a potent vasodilator and smooth muscle relaxant and to play an important role in inflammation. It is also critical in maintaining GI epithelial integrity [117]. Thus, researchers postulate that NO may be involved in the pathophysiology leading to NEC. Interestingly, several studies have demonstrated an association between NEC and plasma arginine levels [118]. Animal models suggest that arginine is protective against endotoxin-mediated intestinal damage [119] and reduces the incidence of NEC [120]. Similar results were obtained in a small randomized human trial, where infants that were supplemented with arginine had a substantial reduction in all stages of NEC as compared to those who received a placebo [121]. The modification of arginine by methylation, known as asymmetric dimethylarginine (ADMA) and symmetric dimethylarginine (SDMA), has been shown to be a potent endogenous NO inhibitor and may reduce inflammation which occurs in NEC. Richir et al. showed that both arginine and ADMA levels, as well as the arginine: ADMA ratio, were reduced in subjects who developed NEC and were associated

Table 8.3 Biologic functions of arginine and glutamine

Arginine
Enhanced synthesis of polyamines
Stimulation of growth hormone release
Creatinine synthesis
Nitric oxide production
Decreased hyperammonemia
Glutamine
Metabolic fuel
Nucleotide biosynthesis
Hexosamine synthesis
Ammonia scavenger
Glucose/glycogen biosynthesis
Protein synthesis
Modulation of pro-inflammatory response
Urea synthesis
Amino acid pools
Glutathione biosynthesis
Signaling molecule

Modified from [123]

with increased mortality [122]. A large randomized clinical trial is needed to determine if arginine supplementation in premature infants is protective against NEC.

Glutamate is a critical amino acid that serves a wide variety of functions including carbon and nitrogen metabolism, as an antioxidant through glutathione biosynthesis, in neurodevelopment by functioning as a neurotransmitter, decreasing gut permeability by inducing hexosamine synthesis and regulating immune function through modulation of pro- and anti-inflammatory cytokines (Table 8.3) [123]. Although glutamate can be synthesized by the body, its supply becomes very limited under "stressful" condition, and is likely an essential amino acid in the preterm infant [124].

Glutamate plays a key role in the developing intestine. Extensive evidence from animal models suggests that dietary glutamate is almost exclusively metabolized in enterocytes [125]. There is some controversy to the exact function of glutamate in the intestine, but it is thought to act as oxidative fuel as well a neurotransmitter for the enteric nervous system [126]. Multiple glutamate receptors have been described that localize to the enteric nervous system [126]. Some of these receptors are localized to the stomach. Recent animal studies have indicated that even super therapeutic administration of glutamate does not result in an increased blood level of glutamate and is metabolized in the intestine [125]. It would be interesting to determine if dietary supplementation with glutamate can increase gastric motility of the premature neonate through stimulating the enteric nervous system.

There is evidence that glutamate regulates the immune system in a number of ways. First, it is likely that glutamate is involved in maintaining mucosal integrity and preventing bacterial translocation. Substantial data from a variety of studies suggest that glutamate can decrease mortality and morbidity from bacterial sepsis [125]. Data are mixed in the neonatal population [127]. A randomized control trial of VLBW infants showed that those that received glutamate supplementation had significantly lower rates of sepsis [128]. However, a larger trial failed to show a decrease in sepsis, but did show improvement in intestinal function and a decrease in high grade intraventricular hemorrhage (IVH) and periventricular leukomalacia (PVL) [129]. The second role for glutamate in regulating the immune system might be in its ability to control expression of pro and anti-inflammatory cytokines. Both human and animal data show that enteral supplementation with glutamate increases anti-inflammatory cytokines and decreases pro-inflammatory cytokines [123]. Infants that develop NEC have lower plasma levels of glutamate [27]. Although meta-analysis of previous trials using glutamine supplementation failed to show a reduction in the incidence of NEC [130], a recent randomized trial showed a decrease in incidence of NEC in the glutamine supplemented arm when compared to control

and a trend toward reduction of sepsis [131]. It is critical to determine if glutamate supplementation can improve premature gut integrity.

Although numerous studies have shown that glutamate supplementation is safe [132], premature neonates continue to receive very little glutamate supplementation. Their enteral nutrition is frequently delayed or not optimized and parenteral solutions contain very little if any extra glutamate [132]. It is also important to evaluate if enteral and parenteral glutamate supplementation are similar.

Oligosaccharides

Oligosaccharides are a diverse group of substances thought to be non-digestible by humans and exert their biological function in the colon. These substances are abundant in human milk and are known as human milk oligosaccharides (HMO). Although we are only beginning to understand how these molecules function, a large part of their effect is exerted on the intestinal bacteria itself. HMOs have been shown to not only directly stimulate growth of commensal bacterial such as Bifidobacteria and Lactobacilli but also bind pathogenic bacteria and serve as decoy receptors [84]. When oligosaccharides have been given to formula-fed infants, their microflora became more similar to that of breast milk fed infants [133]. Although previously thought to be undigestable, there is some evidence HMOs can be absorbed, as they have been found in urine [134], and so can also directly regulate the immune system. They have been shown to bind directly to immune cells and inhibit leukocyte recruitment and adhesion [135]. Clinical trials of oligosaccharide supplementations have yielded promising results, suggesting that they might be able to reduce atopy [136] as well as overall infections in children [137]. More data are needed to determine if there is specificity of oligosaccharides. Are there certain ones that act to bind pathogens, where others stimulate the commensal bacterial growth, and yet others are absorbed and interact with the immune system? Or can a single oligosaccharide exert all of these functions? Are there other additional functions?

Summary

This chapter focused on the unique aspects of fetal, term, and premature neonatal growth. In addition, we summarized recent advances in the fields of epigenetics, microbiome, and immunomodulators that might be able to alter both the fetal and neonatal development and growth as well as control their susceptibility to disease later in life.

As can be seen in Table 8.1, influences on fetal and neonatal growth are multi-factorial. Thus, when studying infant nutrition, special attention must be paid toward avoidance of confounding variables. It would be optimal to have direct measurement of nutrients in human subjects compared using randomized controlled trials (RCT) whenever possible. When this is not possible, better animal models are needed. Fetal and neonatal growth is much more rapid than at any other point and future research is needed to establish frequent anthropometric measurements both during fetal and postnatal life. It is also important to use validated growth charts for research purposes. It has become clear that growth patterns and nutritional needs of preterm infants are unique and vary from that of the fetus and term infants. As such, better growth charts are needed that are specific to preterm infants. Animal models are needed for better understanding of predictors of fetal and postnatal growth. As nutrient sources are variable, better and more direct measures of the intake of both macro- and micronutrients are needed in order to determine their effect on disease outcomes.

With regard to static measuring tools for fetal, preterm, and term growth, these should be accurate, readily available and cost-effective. To ease this process, more frequent use of the stadiometer is recommended. In order to facilitate research, there should be increased availability and improved

techniques to measure total energy expenditure and body composition of term and preterm infants. Dynamic tools should represent diverse, well-nourished populations with longitudinal, prospective measurements. One needs to use continuous sex-specific reference z-scores among fetuses, preterm, and term infants for weight, length, head circumference, and weight-for-length.

Future research in the field of epigenetics should focus on determining how epigenetic signatures are propagated, whether or not epigenetic modifications are reversible throughout life, as well as to determine the "window" in which nutrient administration can alter the epigenetic code. As can be seen from the discussion in the chapter, the influences of the microbiome on the health and development of neonates are vast. There is a need to further characterize how the microbiome is established and maintained in the fetuses, preterm, and term infants. It is also important to determine which strains and doses of probiotics are protective against neonatal diseases. Finally, the chapter discusses the importance of immunomodulators to neonatal health. It would be important to determine the associations of LCPUFA supplementation in pregnant women, preterm, and term infants and long-term neurodevelopmental outcomes. Large RCT are needed to determine if arginine and glutamate supplementation can protect preterm infants from neonatal morbidities and mortality. With regard to oligosaccharides, there is a need to uncover mechanisms behind their ability to regulate the immune system.

Recent observations in the field of epigenetics, microbiome, and immunomodulators suggest that both pre- and postnatal nutritional status have profound consequences later in life and affect one's risk of a large number of childhood and adult on set diseases. In the future, it is essential to optimize both pre- and postnatal nutrition to prevent both under- and over-nutrition and to reduce the lifelong risk of chronic disease.

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Chapter 9
Intestinal Development and Permeability: Role in Nutrition of Preterm Infants

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Key Points

- Preterm infants exhibit intestinal wall immaturity which is measured as increased intestinal permeability.
- Human milk feeds are associated with decreased intestinal permeability and, therefore, increased intestinal maturation.
- The effect of components of human milk such as insulin-like growth factor, glutamine, prebiotics, and probiotics on preterm infant intestinal permeability have been studied, but no specific agent has been identified.
- Most likely, the human milk support of preterm infant intestinal maturation is multi-factorial.
- Determining the effect of preterm infant feeding practices such as donor human milk and bovine versus human milk fortifier is a critical next step to optimize preterm infant intestinal health.

Keywords Preterm infants • Intestinal permeability • Human milk • Intestinal maturation • Intestinal development

Introduction

Preterm birth necessitates that fetal organ development occur in the extra-uterine environment. This circumstance poses significant risk for gastrointestinal (GI) system development as this system doubles in length from 25 to 40 weeks' gestation. The most severe consequence of preterm intestinal development is necrotizing enterocolitis (NEC)—an inflammatory cascade that leads to ischemia/necrosis of the intestines. This disease is found in 7–10% of very low birth weight (VLBW) infants and is associated with 33% mortality and 33% long-term GI and/or neurodevelopmental morbidity. The two protective factors consistently identified to decrease risk for NEC are prolonged gestation and human milk feeds. Investigation into the mechanism of NEC has dominated the study of preterm infant intestinal development. Within this context, intestinal maturation and specifically intestinal permeability have been studied for 20 years.

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R.R. Watson et al. (eds.), *Nutrition in Infancy: Volume 1*, Nutrition and Health,
DOI 10.1007/978-1-62703-224-7_9,

Intestinal maturation begins in fetal development and continues into early childhood. A mature intestine is considered a "closed" intestine with optimal tight junction function with decreased permeability and selective absorptive capabilities. Tight junctions comprise over 50 proteins and seal the paracellular space between epithelial cells. They are not a static barrier but are regularly remodeled as a result of interactions with intestinal lumen contents. These functions are critically important for survival as the gastrointestinal system must master absorption of nutrients for growth and blockage of pathogens and toxins. To this end, the gastrointestinal tract is constantly performing a precarious balance that relies on intestinal permeability.

Intestinal Permeability Measurement

Decreasing intestinal permeability is considered a sign of intestinal maturation. Intestinal permeability is reliably measured by sugar absorption tests (SAT) [1–4]. SAT measure intestinal permeability by a ratio of two sugars—one absorbed by intracellular diffusion and the other by paracellular diffusion. Commonly used for tests are monosaccharides such as mannitol, L-rhamnose, and xylose (intracellular diffusion) and disaccharides such as lactulose (paracellular diffusion). The lactulose/mannitol ratio is the most commonly used SAT. Both lactulose and mannitol are absorbed as whole molecules by the human small intestine. Mannitol is small with a molecular radius of 0.4 nm, and lactulose is larger with a radius of 0.52 nm. Mannitol easily diffuses through the small intestine membrane while lactulose is too large and relies on paracellular diffusion for absorption [5]. The intestinal capacity to absorb lactulose is a direct measure of the tightness of junctional complexes and thereby a measure of intestinal permeability [4–6]. The absorption of mannitol is not dependent on tight junction mechanics. The enteral intake of lactulose and mannitol simultaneously controls for fluctuations in gastric emptying, intestinal fluid volume, and intestinal transit time. Additionally, both lactulose and mannitol have similar volumes of distribution within the body and similar renal clearance with excretion in the urine within a 5-h period after enteral administration [1, 2, 5]. Therefore, lactulose and mannitol standard-dose ingestion followed by urine collection allows direct measurement of the paracellular absorptive capacity of the GI tract [7]. The paracellular absorptive capacity is commonly referred to as intestinal permeability. Decreased intestinal permeability is appreciated with intestinal maturity. Additionally, increased intestinal permeability is thought to represent intestinal damage and/or disease, intestinal inflammation, and a point of entry for systemic infection [8]. In adults and older children, increased intestinal permeability is associated with inflammatory bowel disease, celiac disease, type I diabetes, IgA nephropathy, and multiple sclerosis [9–14].

Preterm Infant Intestinal Development

High intestinal permeability as a marker of intestinal immaturity is best described in the context of other factors associated with preterm birth and the premature end to fetal development. The fetal intestine is nurtured not only through the placenta but also by the amniotic fluid. In fact, 15% of fetal nutrition is delivered by amniotic fluid proteins, carbohydrates, lipids and phospholipids, and electrolytes [15–17]. Additionally, amniotic fluid is a source of growth factors and immune-modulating factors for the fetus and specifically the fetal gut [15]. Several cytokines have been evaluated for trophic and potentially maturing effects on the developing intestine [15, 18]. Possible factors such as insulin-like growth factor (IGF-1) and glutamine have been studied by randomized, controlled trial [19–21]. Additionally, clinical trials of an artificial amniotic fluid containing recombinant erythropoietin and

recombinant granulocyte colony stimulating factor (GCSF) and its effect on preterm infant feeding tolerance are promising [22]. Factors that are present in *both* amniotic fluid and human milk are likely candidates as important intestinal development factors as human milk is known to protect from NEC [18].

The potential candidates are numerous as human milk and amniotic fluid share bioactive factors such as epidermal growth factor, nerve growth factor, hepatocyte growth factor, insulin, IGF-1, interleukins, transforming growth factor-alpha and beta, vascular endothelial growth factor, erythropoietin, GCSF [15]. These factors are likely key players in intestinal epithelium development, but, unlike amniotic fluid, human milk also must contain factors to promote healthy development of the intestinal microbiome. The role of these human milk components and the role of the developing intestinal mucous and microflora in intestinal permeability is critical to understanding preterm infant gastrointestinal maturation.

An important constituent of gastrointestinal maturity is the mucous layer [23, 24]. The mucous layer is a complex gel containing immune-functioning factors and binding sites for the intestinal microflora. Mucin is a major component of the mucous layer that coats the epithelial surface and serves as a protective interface between the intestinal epithelium and the enteral contents. Factors in the mucous layer, including glycoprotein bacteria-binding sites, interact with both commensal and pathogenic microbes. The commensal bacteria, or intestinal microbe, are critical for extra-uterine survival.

The exact role of the intestinal microflora in intestinal maturation and, specifically, intestinal permeability is a key area of investigation especially for preterm infant intestinal health [25–27]. Both intestinal bacteria and dietary intake have been shown to target intracellular pathways and change the expression and distribution of tight junctions [9, 28, 29]. Preterm infants have abnormal development of the intestinal mucous layer and microflora when compared to term infants and adults [23]. Not only are the effects of these abnormalities being investigated in preterm infant feeding intolerance and NEC but the causes of these abnormalities, absence of feeding, feeding types, and decreased exposure to amniotic fluid growth factors, have been evaluated in the context of intestinal permeability.

Preterm Infant Intestinal Permeability and Postnatal Age

Realization of the natural progression of preterm infant intestinal maturation and specifically intestinal permeability is limited by the small number of studies and the diversity in population, feeding practice, and postnatal day of evaluation. Studies agree that intestinal permeability is higher in preterm infants than term infants in the first postnatal days [3, 5, 6, 19, 30]. Most studies did not find a difference in intestinal permeability based on degree of prematurity for infants born <34 weeks' gestation [3, 5, 6, 30–32].

One study by Rouwet et al. [33] compared infants born before or after 28 weeks' gestation. They had similar intestinal permeability at birth, but infants born <28 weeks demonstrated higher intestinal permeability at postnatal day 7. Of importance to the results of this study is that enteral feeds were held until postnatal day 8 and, therefore, this study represents intestinal permeability progression in the absence of enteral nutrition [33]. In the Rouwet et al. study and others, preterm infant intestinal permeability decreases in the first postnatal week [6, 19, 25, 32–34]. A similar postnatal age-related decline in intestinal permeability is described in term infants [4].

In description of preterm infant intestinal permeability past the first postnatal week, most studies demonstrate an increase in intestinal permeability followed by a decrease, but studies vary in the time period at which these fluctuations occur (Table 9.1). Part of the variation is due to differences in the postnatal day of intestinal permeability measurement, but likely is partly due to variation in

Table 9.1 Comparison of postnatal intestinal permeability measurements in preterm infants

Study	Study characteristics	Postnatal measurement	Intestinal permeability changes
Rouwet et al. [33]	All infants had feeds initiated at day 8	Day 1, 4, 7, 14	Increased day 7 compared to other 3 measurements
Beach et al. [30]	26–29 weeks' gestation only	Weekly intervals	Increased weeks 3–4 compared to weeks 1–2 and weeks 4–6
Shulman et al. [3]	Feeding regimen, antenatal steroids, diet	Day 10, 28, 50	Peak at day 28 but day 50 higher than day 10
Taylor et al. [31]	Formula vs. human milk-feeds	Day 7, 14, 30	Peak at day 14

feeding practice (timing and/or type), also. This increase and then decrease in preterm infant intestinal permeability in the first postnatal weeks was at one time thought to be advantageous. Investigators theorized that a period of increased intestinal permeability promoted absorption of large compounds with growth-promoting or immunological benefit [5, 30, 35]. However, a study by Taylor et al. [31] described how human milk feedings blunt the increase in intestinal permeability observed in formula-fed infants. The results of this study negate the theory of a health advantage with increased intestinal permeability and instead raise concern that formula-fed infants demonstrate intestinal disease in the first postnatal weeks. Increased intestinal permeability as a marker of disease state is seen in inflammatory bowel disease and celiac disease. For preterm infants, the increase in permeability after the first postnatal week may mark loss of an in-utero protective mechanism or exposure to an extra-uterine toxicity associated with formula feeding.

Preterm Infant Intestinal Permeability and Feeding

In preterm infant nutrition, experts agree that human milk feeding affords the best protection of gut health. However, if human milk is not available, then distinguishing the best option between no enteral feeds or formula feeds is unclear. Two studies demonstrate improved intestinal maturity with enteral feeds versus no feeds [3, 33]. Shulman et al. [3] in a large study to determine the effects of postnatal age, feeding regimen (including time of initiation), antenatal steroids, and diet (human milk versus formula) found a significantly lower intestinal permeability at postnatal day 10 for infants with feed initiation at postnatal day 4 versus postnatal day 15 [3]. As presented earlier, Rouwet et al. [33] demonstrated decrease in intestinal permeability with feed initiation on day 8, but results are limited by the absence of a comparison group.

A 2003 publication by Van Elburg et al. [34] presents a randomized controlled trial of minimal enteral nutrition versus no enteral nutrition in preterm intrauterine growth restricted (IUGR) infants. Intestinal permeability was measured pre and post 5 days of minimal enteral nutrition or no enteral nutrition. Both groups demonstrated decrease in intestinal permeability with time and this decrease was not significantly different between groups. Additionally, feeding tolerance, growth, and incidence of NEC were not significantly different between the two groups [34]. The results potentially are influenced by the IUGR status of the population. From a different perspective, the studies performed do not show increased intestinal permeability with feeding versus not feeding, and support the growing body of evidence that early feeding is not associated with harm and, in some studies, is associated with decreased time to full feeds, improved feeding tolerance, and decreased length of hospital stay [36–39].

Preterm Infant Intestinal Permeability and Feeding Type

For a preterm infant who no longer has the growth-stimulating amniotic fluid available, mother's milk serves as the best substitute. Human milk is associated with improved preterm infant gut health—most notably, in decreasing the risk of NEC, but also improved feed tolerance and decreased infection [40–42]. For term infants, Catassi et al. [4] and Weaver et al. [5] both demonstrated improved intestinal maturation with breastfeeding versus formula feeding in the first postnatal week. For preterm infants, Shulman et al. [3], in their study of feeding regimen, antenatal steroids and feeding type, demonstrated decreased intestinal permeability at postnatal day 28, but not day 10 or 50 with human milk feeding when compared to formula feeding. Taylor et al. [31] specifically evaluated the effect of feeding type (mother's milk versus formula) and found that infants who received the majority of feeding as human milk (>75%) had significantly lower intestinal permeability when compared to infants receiving minimal or no human milk (<25% or none) throughout the first postnatal month (days 7, 14, and 30). The predominantly mother's milk-fed infants had a 3.8-fold lower composite lactulose/mannitol ratio than infants receiving minimal or no human milk. When evaluating the relationship of increased intestinal permeability and formula exposure over the month, they found exclusively formula-fed infants had a 2.8-fold higher composite lactulose/mannitol ratio when compared to infants who received any mother's milk [31].

To add to the comparison of human milk versus formula, Westerbeek et al. [25] in their randomized controlled trial of the effect of a prebiotic formulation on intestinal permeability found significantly decreased lactulose/mannitol ratio with exclusive breast milk feeding and mixed breast milk/formula feeding in the first postnatal week. These studies provide insight into the physiology of human milk protection from NEC. In this way, they promote study of the human milk intestinal maturity factors as agents to reduce the incidence of NEC and improved intestinal health.

Potential Agents to Decrease Intestinal Permeability

In investigation of how human milk may improve gut maturation and thereby decrease risk for NEC, factors to directly promote intestinal maturation and barrier function as well as factors to promote healthy gut microflora have been studied in recent randomized, controlled trials. One such study was performed by Stratiki et al. [32] and involved administration of a probiotic (*Bifidobacterium lactis*) supplemented formula compared to a control formula with no probiotic. *Bifidobacterium* is a commensal organism that dominates the intestinal tract of breast-fed term infants. Although found in the intestine of formula-fed term infants, *bifidobacteria* species are less dominant and *lactobacillus* species are more common [43, 44]. Preterm infants also have less colonization with *bifidobacteria* and instead have high colony counts of pathogenic bacteria such as *enterobacteriaceae, staphylococcus, streptococcus, clostridia, and bacteroides* [45, 46]. Multiple randomized, controlled trials of probiotic administration demonstrate significantly decreased risk of NEC [47]. In this one evaluation of the probiotic effect on intestinal permeability, Stratiki et al. [32] found that preterm infants receiving formula supplemented with *Bifidobacterium lactis* had significantly decreased intestinal permeability at postnatal day 30 but not at day 7. This study provides clues as to how probiotics may improve and protect preterm infant intestinal health.

A second agent studied in evaluation of how human milk may improve intestinal maturation is a prebiotic mixture of short-chain galacto-oligosaccharides/long-chain fructo-oligosaccharides and acidic oligosaccharides. Human milk, especially colostrum, is loaded with oligosaccharides known to promote commensal microflora. In the only evaluation of the effect of prebiotics on preterm infant intestinal permeability, Westerbeek et al. [25] performed a randomized, controlled trial of a prebiotic

supplement versus placebo. Preterm infants received the prebiotic mixture from postnatal day 3–30 and had intestinal permeability measured on day 4 and 7. In both groups, the intestinal permeability decreased from day 4–7 and the decrease was not significantly different between groups. Of note, this study demonstrated improved intestinal maturation with exclusive breast milk feeding and mixed breast milk/formula feeding when compared to exclusive formula feeding [25]. Possibly, the predominance of breast milk feeding (>60%) in the study diluted any prebiotic supplement effect. Also, the authors present that high antibiotic exposure for the preterm infant population may counteract any probiotic effect. With the high risk of infection as the cause of preterm labor, many preterm infants receive at least 48 h of antibiotic therapy at birth. The prospect that this therapy may have a significant effect on intestinal colonization and thereby intestinal permeability deserves further evaluation.

Other investigations of the effect of human milk factors on preterm infant intestinal permeability include evaluation of IGF-1. IGF-1 is a growth factor found in amniotic fluid and human milk and, therefore, has potential as a potent factor in intestinal development and maturation. To evaluate the effect of IGF-1 on preterm infant growth and intestinal health, Corpelijn et al. [21] performed a double-blinded randomized, controlled trial to assess the effects of IGF-1 on infant growth and gut maturation and permeability.

In this study of preterm infants in the first postnatal month, infants were randomized to receive standard formula or standard formula with IGF-1 in a concentration twice that of human colostrum. Intestinal permeability was measured weekly through the month. Intestinal permeability decreased in both groups with time. At day 14, gut permeability was significantly decreased in the IGF-1 group compared with the control group. At day 21, this difference was no longer apparent. No difference was found in infant growth throughout the study. With these results, the authors postulate that IGF-1 may not act alone in promoting infant growth and intestinal health, but likely synergistic work between a combination of growth factors and hormones in human milk provides the optimal stimulation for growth and health [21].

Another agent known to protect the intestinal mucosa is glutamine. Glutamine is an amino acid with known function in intestinal mucosa maintenance, modulation of inflammation, and energy metabolism [48, 49]. With involvement in the synthesis of amino acids required for tight junctions, it is likely involved in human milk's promotion of intestinal development and maturation [50, 51]. Glutamine is not provided in parenteral nutrition which means an important building block for gut health is not available to parenteral nutrition-dependent patients who need it most. In adults, a study of patients with multiple gastroenterologic diseases receiving parenteral nutrition demonstrated that glutamine supplementation prevented an increase in intestinal permeability associated with intestinal barrier failure [52]. In preterm infants, studies of glutamine supplementation to improve health outcomes, including gastrointestinal health, have led to equivocal results. A Cochrane Review published in 2008 appraised the preterm infant glutamine trials and concluded that VLBW intake of glutamine is not related to NEC or to time to full feed establishment [53].

Two randomized, controlled trials have evaluated the effect of glutamine supplementation on intestinal permeability in preterm infants. In both trials, infants received oral glutamine supplementation daily from day 3–30 versus placebo. In Van Den Berg et al.'s study published in 2006 [19], glutamine-enriched enteral nutrition had no effect on the decrease in the lactulose/mannitol ratio found to occur in both groups through the 1-month study period. The authors concluded that enteral glutamine does not enhance the VLBW infant postnatal decrease in intestinal permeability. Conversely, Sevastiadou et al. published in 2011 [20] their trial of enteral glutamine to preterm infants with evaluation of intestinal permeability pre-intervention and then at day 7 and 30. They found lactulose/mannitol ratio to be decreased in the glutamine group when compared to the control group at day 7 and 30. They also demonstrated less NEC and septicemia in the glutamine supplemented group.

In exploration of the dissimilar study results, one confounding factor is the high intake of human milk to both groups in the Van Den Berg et al. study. Unlike previous studies of feeding type and intestinal permeability, the Van Den Berg et al. study did not show significantly lower intestinal

permeability with increased human milk intake [19]. Perhaps the glutamine supplementation promoted intestinal permeability in formula-fed infants and, with the high intake of human milk in both groups, no significant difference in intestinal permeability was apparent. Therefore, the role of human milk glutamine in intestinal maturity and the potential for glutamine supplementation of formula-fed infants to improve the intestinal barrier remains relevant.

In the same way as glutamine appeared on the forefront of research as an intestinal maturity stimulator over the past 20 years, research involving nitric oxide (NO) and its role in intestinal health and NEC is growing. NO and its derivative, peroxynitritie, may affect intestinal permeability by inducing enterocyte apoptosis and necrosis or by disruption of the tight junctions [54]. Laboratory evidence demonstrates that NO plays a key role in the breakdown of the intestinal barrier as seen in the pathogenesis of NEC [55]. Further evaluation of the role of NO in intestinal permeability is anticipated as investigators continue to study the role of intestinal permeability breakdown in development of NEC.

Other Factors Related to Preterm Infant Intestinal Permeability

With prematurity and absence of human milk intake as risk factors for NEC, the development of NEC appears related to the immature intestinal mucosa and the absence of human milk growth and/or immune-functioning factors. Clinical studies of preterm infant intestinal permeability have shown that preterm infants have higher intestinal permeability than term infants at least through the first postnatal week [3, 5, 6, 19, 30]. Additionally, preterm infants appear to have a time of heightened intestinal permeability between one and six postnatal weeks followed by a decrease in permeability [3, 30, 31, 33]. Furthermore, human milk feedings appear to decrease intestinal permeability [3, 25, 31]. Evaluation of the human milk factors that may be responsible for this improved intestinal barrier function is inconclusive.

Other parameters that have been demonstrated to have a significant association with intestinal barrier function are low arterial umbilical pH at birth [6] and antenatal steroid exposure [3]. Of note, the association of antenatal steroids and improved intestinal permeability has been evident at the end of the postnatal month, but not earlier [3, 32]. No correlation has been seen between Apgar score, dopamine infusion, or patent ductus arteriosus and intestinal permeability [32].

Questions Remaining in Preterm Infant Intestinal Permeability

Human milk feeding appears to decrease intestinal permeability and thereby promote intestinal maturation [3, 25, 31]. However, natural mother's milk feeds are rare in preterm infant care. Preterm infants can avoid formula feeding, but, to do so with adequate growth, they receive parenteral nutrition and bovine- and/or human-based human milk fortifiers [36]. Additionally, donor human milk is often used to avoid formula when mother's milk supply is inadequate or contraindicated [56]. Evaluation of the effect of these nutrition practices on preterm infant intestinal permeability is the required next step to optimize nutritional practices for anthropometrical growth, neurodevelopment, and intestinal maturation. Previous studies of intestinal permeability by feeding type include human milk with bovine fortification and donor human milk but without regard to effect of these supplements [3, 25, 31]. Recent report of decreased NEC with intake of human-based human milk fortifier when compared to bovine-based human milk fortifier suggests a difference in intestinal health dependent on fortifier exposure [57]. For donor human milk, the pasteurization process may decrease the activity of crucial growth factors and immune modulators and, thereby, afford less gut protection than mother's

milk [56]. In regard to parenteral nutrition, animal studies demonstrate that colostrum feeds are not as protective against NEC when also receiving parenteral nutrition [58]. Evaluation of gastrointestinal health with these common nutritional practices is warranted and represents the next stage of preterm infant intestinal permeability science.

Conclusion

As evidence grows in regard to the importance of the gastrointestinal barrier in numerous health outcomes, understanding how the preterm infant's gastrointestinal system matures without the natural amniotic environment is essential to understanding the infant's health. Studies point to increased intestinal permeability for preterm infants compared to term infants, but not necessarily related to degree of prematurity. Human milk feeding improves intestinal permeability measurements. Early feedings may or may not lead to earlier gut maturation, but at least do not appear associated with gastrointestinal damage. Evaluation of human milk growth factors such as glutamine and IGF-1, and evaluation of commensal organism stimulators such as prebiotics and probiotics demonstrate equivocal results and require further study. Additionally, as new factors in intestinal barrier function, such as NO, are revealed, randomized, controlled trials of intestinal permeability provide an opportunity to measure clinical outcomes. Similarly, current nutritional practices such as parenteral nutrition, donor human milk, and bovine- and human-based human milk fortifier warrant evaluation of their role in intestinal maturation. Intestinal permeability research demonstrates that, despite the importance of in utero intestinal growth, the majority of preterm infants develop an adequate intestinal barrier. As commonly found in preterm infant health, human milk as a substitute for amniotic fluid provides the best opportunity for normal development and avoidance of disease.

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Chapter 10
Colostrum as a Therapeutic for Premature Infants

Nancy A. Rodriguez

Key Points

- Human colostrum may have potential immunomodulatory effects.
- Preterm colostrum is a potential immune therapy for extremely premature infants.
- The costs of prematurity-associated morbidities may be reduced with early administration of colostrum to extremely premature infants.
- The oropharyngeal administration of colostrum is feasible, easy, and cost-effective.

Keywords Human colostrum • Breastmilk • Prematurity • Immunomodulation • Oropharyngeal administration

Introduction

Extremely low birth weight (ELBW: birthweight <1,000 g) infants represent the smallest and sickest of the premature population. Despite dramatic advances in neonatal medicine and technology which have significantly decreased mortality, survivors are burdened with significant morbidity associated with prematurity-related diseases [1–3]. Of particular concern are nosocomial infections such as bacteremia, ventilator-associated pneumonia (VAP), and a potentially lethal gastrointestinal infectious and inflammatory disorder known as necrotizing enterocolitis (NEC). These morbidities are highly prevalent, costly, increase the length of hospitalization, and are associated with a potential for adverse neurodevelopmental outcomes in survivors [4–6].

Human milk, particularly colostrum (early milk) contains a multitude of immunologically derived factors [7–29] that protect against nosocomial infections. Colostrum expressed by mothers who deliver ELBW infants, (preterm colostrum) is more highly concentrated in protective factors when compared to colostrum expressed at a later gestation [30–38]. As such, preterm colostrum is potentially an "immune therapy" for the immunodeficient ELBW infant, especially in the first days post-birth. Unfortunately, clinical instability typically precludes enteral feeds in the first days of life and the administration of colostrum is delayed several days until enteral feeds can be safely introduced. An alternative method of administering colostrum, as a potential immune therapy, is needed. Oropharyngeal administration is a feasible alternative [39–44]. This chapter is organized into the following sections: (1) Extremely

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R.R. Watson et al. (eds.), *Nutrition in Infancy: Volume 1*, Nutrition and Health,
DOI 10.1007/978-1-62703-224-7_10,

Premature Infants and Nosocomial Infections, (2) Protection against Infection with Human Milk, (3) Preterm Colostrum: Implications for the Extremely Premature Infant, (4) Preterm Colostrum as a Potential Immune Therapy, (5) Oropharyngeal Administration of Colostrum.

Extremely Premature Infants and Nosocomial Infections

Nosocomial infections, including bacteremia and VAP, are highly common in the ELBW population and associated with poor growth, adverse long-term neurological sequelae, increased length of hospital stay, and a substantial cost to families, hospitals, and society [4–6]. The risk for acquiring a nosocomial infection is directly related to the severity of illness at birth and inversely related to gestational age and birth weight [45]. Therefore, ELBW infants have the highest risk and up to 65% will have at least one nosocomial infection during their hospitalization [4].

ELBW infants are at high risk for nosocomial infection because they are functionally immunodeficient at birth, in both innate and adaptive components of the immune system [46, 47]. They also have an immature, intestinal mucosal barrier that is highly vulnerable to injury, allowing for pathogenic bacteria to translocate across the intestinal epithelium and gain access to the bloodstream [48–50].

Compared to larger premature infants, ELBW infants are more frequently exposed to invasive, life-saving procedures and remain in the pathogen-laden NICU environment for a prolonged duration, with an average length of stay between 12 and 17 weeks. The presence of pathogenic organisms, overuse of antibiotics that generate pathogenic strains, long-term presence of indwelling catheters and tubes, overcrowded NICU conditions, prolonged mechanical ventilation and intravenous parenteral nutrition, function singly or in combination to increase the risk for nosocomial infections such as bacteremia and VAP, in addition to NEC.

Bacteremia, a nosocomial infection of the blood-stream, is highly common primarily as a result of long-term vascular access for parenteral nutrition because of *inability to tolerate enteral feedings*. A single case of bacteremia extends the length of hospital stay by 7 days for ELBW infants, and costs an additional $5,875 for infants weighing 401–750 g and $12,480 for infant weighing 751–1,000 g [5].

VAP is costly, associated with a significantly prolonged length of stay and high mortality rate [51]. The etiology of VAP is related to the long-term presence of an endotracheal (breathing) tube and prolonged mechanical ventilation. The ELBW infant's immunodeficiencies coupled with the rapid colonization of the endotracheal tube with pathogenic NICU organisms quickly lead to VAP.

NEC, a particularly lethal gastrointestinal infection and inflammatory disorder, is another source of morbidity. Because the risk of NEC is inversely related to birthweight, ELBW infants have the highest incidence, most severe course of the disease, and the greatest NEC-associated mortality rates [52, 53]. Despite many years of research, the multi-factorial etiology is not fully understood. The pathogenesis appears to be triggered by an initial injury to the intestinal mucosa with resultant ischemia and loss of mucosal integrity. Substrate from enteral feedings and a paucity of beneficial intestinal bacteria facilitate the local proliferation of pathogenic gas-producing bacteria which invade the intestinal mucosa, causing inflammation of the bowel wall (pneumatosis intestinalis) which is diagnostic of NEC. The release of inflammatory mediators leads to the rapid progression of this deadly disease, with areas of necrotic tissue potentially leading to perforation of the bowel and subsequent peritonitis [52–55]. In severe cases, NEC leads to multisystem organ failure and death. NEC costs an additional $73,700 and extended the hospital stay by 22 days if managed medically; or $186,200 and 60 days if managed surgically [56]. At present, successful preventative therapies are still not available, despite many years of research, and the only existing preventative strategy against NEC is the provision of human milk, especially colostrum, to these high risk infants.

Extreme prematurity is the greatest risk factor for acquiring bacteremia, VAP, and NEC. The risk for acquiring each of these morbidities is modifiable through the provision of human milk and particularly colostrum in the first days post-birth.

Protection Against Nosocomial Infection with Human Milk

Epidemiologic studies over recent decades have consistently linked human milk feedings with enhanced health outcomes including decreased risk for acquiring infections, particularly of the respiratory and gastrointestinal tracts [57, 58]. Human milk feedings have also been linked with a lower incidence and severity of several *prematurity-specific morbidities* including bacteremia [59–65], enteral feed intolerance [66–69], and NEC [70–73] in premature infants when compared with formula-fed cohorts.

Protection against bacteremia is provided through a multitude of protective factors, including nutritional components, hormones, soluble CD14, growth factors, immunoglobulins, glycoproteins, oligosaccharides, and cytokines which have overlapping functions and work synergistically [7–29, 74–78]. The mechanisms of protection include antimicrobial, anti-inflammatory, and immunomodulatory functions and the creation of a gastrointestinal microflora milieu that prevents the proliferation of pathogenic organisms [7]. Other protective functions include mucosal membrane healing functions, enzymatic, anti-oxidant, and intestinal growth/motility promoting properties which (indirectly) protect against bacteremia [79–86]. The majority of these protective components survive freezing, thawing, and storage practices that are routinely used in the NICU [87].

Protection against VAP is afforded by human milk oligosaccharides, secretory immunoglobulin A (sIgA), and lactoferrin among others [18–28]. Oligosaccharides and secretory immunoglobulin A (sIgA) provide barrier protection and inhibit the adhesion of respiratory pathogens to epithelial cell surface receptors in the mucosa of the oropharynx. This may lessen the ability of the pathogens to colonize the upper respiratory tract where they could translocate and cause VAP. Lactoferrin and oligosaccharides also provide antimicrobial, anti-inflammatory, and mucosal-healing properties which serve to protect against VAP.

The protection against NEC afforded by human milk is attributed to the presence of numerous growth factors, including transforming growth factor-beta (TGF-beta), epidermal growth factor (EGF), heparin-binding EGF-like growth factor (HB-EGF), polyunsaturated fatty acids (PUFAs), erythropoietin, lactoferrin, and anti-inflammatory cytokines; which are not found in commercial formula [14–17, 80–85]. Many of these protective factors are more highly concentrated in colostrum. For example, interleukin-10 (IL-10), an anti-inflammatory cytokine is highly concentrated in colostrum and appears to be protective against NEC. Animal models have shown that IL-10-deficient mice spontaneously develop enterocolitis upon weaning, while administration of IL-10 prevents this condition [86]. Additionally, a correlation between lower IL-10 concentrations in human milk and a higher risk of NEC in premature infants has also been demonstrated [88]. Finally, more recent evidence suggest that oligosaccharides contained in human milk also protect against NEC because they promote the presence of commensal bacteria, provide antimicrobial protection, maintain the integrity of the intestinal epithelial barrier, decrease inflammation, repair injured areas, promote intestinal maturation, and regulate the ELBW infant's immune response [18–22].

Preterm Colostrum: Implications for the Extremely Premature Infant

Evidence from biochemical and immunological studies suggest an inverse relationship between the duration of pregnancy and the concentration of human milk protective factors, meaning that the milk produced by mothers of the least mature ELBW infants contains the highest concentrations of protective factors, particularly during the colostral phase [30–38]. The gestation-specific trends in the immune

composition of colostrum suggest a biological function for protecting the ELBW infant from infection during the critical exposure period post-birth. However, the ELBW infant's immature gastrointestinal tract and the presence of co-morbidities that cause bowel hypoperfusion usually preclude enteral feedings during this time. Prolonged "nil per os" (NPO) status and the use of antibiotics leads to intestinal atrophy [89], and an abnormal pattern of intestinal colonization [90]; factors which significantly increase the risk of feeding intolerance, bacteremia, and NEC. Currently, the only method to administer colostrum is via a gavage tube when the infant is clinically stable and ready to accept enteral feedings; an alternative administration method does not exist.

In utero, during the last trimester of pregnancy, the fetus swallows up to 150 mL/kg/day of bacteriostatic amniotic fluid [89], which is rich in many protective factors including cytokines, antibodies, and growth factors [89, 91], and the weight of the intestinal mucosa more than doubles during this period [89, 91, 92]. This rapid growth and development of the intestine is partly attributed to the abundance of growth factors in the amniotic fluid. In addition to growth factors, amniotic fluid also contains cytokines and other immune factors such as sIgA and lactoferrin [93]. ELBW infants are born before the last trimester of pregnancy and experience an abrupt cessation of these "continuous feedings" of amniotic fluid which places the infants at risk for intestinal atrophy [89]; significantly increasing the risk for feeding intolerance, bacteremia, and NEC. With current standard NICU care, ELBW infants never have colostrum placed in their mouth because all colostrum is administered via a nasogastric tube in the first weeks of life, as a minimal volume or "trophic" enteral feeding. Milk is not placed in their mouths until at least 2 months post-birth, until "per oral" feeds can be safely introduced, at (a minimum) of 32 corrected weeks of gestation; mature milk-never colostrum. The absence of protective factors in the infant's oropharynx facilitates pathogen colonization which can lead to VAP. The composition of amniotic fluid and human colostrum are very similar [93–95], which suggests that colostrum has an important biological function in facilitating the infant's transition to the extrauterine environment. In addition, the inability to administer colostrum in the first days post-birth may have detrimental effects on intestinal maturation [96] and may increase the risk for subsequent feeding intolerance. Research has shown that whereas the fetal (human) intestine has an immature epithelium, delayed enterocyte proliferation and few lymphoid cells, examination of the same intestinal segment once exposed to human milk shows a proliferating epithelium with all subclasses of enterocytes present as well as abundant lymphoid tissues [97]. Thus, early provision of colostrum post-birth appears to be an urgent clinical priority. Administering colostrum via an alternative route and as a biological therapeutic may be a feasible alternative.

Preterm Colostrum as a Potential Immune Therapy

The study of the immunology of human milk is a relatively new but rapidly expanding area of research. Many immune factors have been identified [7–29], but their biological functions are not yet fully described. The concept of utilizing colostrum as a potential immune therapy is based largely on evidence supporting the efficacy of oropharyngeally administered cytokines [43, 44, 98–108], studies of immune factors in human milk and colostrum [8–26, 29–38, 74–78, 81–86, 109], and research involving bovine colostrum as a biological therapeutic [110–114].

Oropharyngeal administration is different than oral administration. Oral administration involves swallowing a substance with passage into the stomach and gastrointestinal absorption. Oropharyngeal administration involves placing small amounts of a substance directly onto the oral mucosa such that the solution or any of its components is absorbed by the mucous membranes and/or interacts with immune cells within oropharyngeal mucosal tissues [44, 108]. Studies have shown that the oropharyngeal route can be used to effectively and safely administer interferon-alpha (IFN-alpha), an immune cell-derived cytokine, to adult human subjects who are unable to tolerate its parenteral administration

[98–101]. The oropharyngeally administered cytokine is thought to have a stimulatory effect on the oropharyngeal associated lymphoid tissue (OFALT) system [44, 108], resulting in T-cell activation and dissemination throughout the systemic circulation leading to a variety of end-organ immune responses [115]. Theoretically, providing colostrum to ELBW infants via the oropharyngeal route during the first days post-birth would similarly influence the OFALT system providing an immunostimulatory effect.

Substantial evidence derived from animal and human studies suggest that components in OMC, particularly cytokines, may provide immunomodulation for the recipient infant. For example, animal research has demonstrated that cytokines, interleukins (IL) -2, -12, -15, and -18, administered onto the oral mucosa of mice, interact with immune cells in the lymphoid or epithelial tissue of the oropharyngeal cavity, resulting in a systemic immunostimulation response as a result of cell to cell signaling [105]. It is plausible that oropharyngeally administered colostral cytokines may also potentially exert a similar cell-to-cell effect by interacting with the lymphoid cells in the infant's OFALT and GALT, potentially providing systemic immunostimulatory effects and protection against infection. While oropharyngeally administered colostrum is intended to remain in the oropharynx to be absorbed by the oral mucosa, it is possible that factors in colostrum may be swallowed and may travel to the gastrointestinal tract and provide local maturational effects at the mucosal surface. For example, immune agents such as oligosaccharides, secretory immunoglobulin A (sIgA), and lactoferrin may provide local barrier protection against the adhesion and translocation of pathogenic bacteria across the intestinal mucosa; thus protecting against NEC. Additionally, growth factors may also travel to the GI tract and provide local maturational effects, enhancing intestinal motility, and protecting against enteral feed intolerance. Research has shown that numerous colostral factors can be systemically absorbed including immunoglobulins (such as sIgA), glycoproteins (such as lactoferrin), cytokines, and fatty acids [116]. The fact that these macromolecules are absorbed intact into the circulation suggests an important biological function [116] for the recipient infant and possible protection against systemic infection including bacteremia and NEC.

The use of colostrum as an immune therapy is supported by evidence from animal studies, and research with adults, which demonstrates that colostrum is a powerful biological therapeutic and its administration has been linked to improved health outcomes [112, 117].

Whereas colostrum was originally considered simply a vehicle for passive immunity transfer, current thinking reflects its role as potential source of immunomodulation though cytokines, and other protein compounds of very low molecular weight, which impact many biological functions [110, 112, 117]. Bovine colostrum is highly protective against infection and inflammation [113, 114]. Additionally, recent studies in adults show that derivatives of bovine colostrum are efficacious in diseases such as rheumatoid arthritis, systemic lupus erythematosus, AIDs-related diarrhea among others. Because it has high concentrations of lactoferrin and therefore potent immunomodulatory effects, bovine colostrum has been shown to modulate immune activation cascades in human peripheral blood mononuclear cells in vitro, by either enhancing or suppressing a Th-1 type immune response [111].

Oropharyngeal Administration of Colostrum

The oropharyngeal administration of own mother's colostrum, as an immune therapy, is hypothesized to protect ELBW infants via three distinct mechanisms: (1) immunostimulatory effects of cytokine interaction with immune cells in the recipient infant's OFALT system [17, 39, 43, 44, 108], (2) passive mucosal absorption of protective antimicrobial and trophic factors [75, 76, 78, 81], and (3) barrier protection against pathogens in the oropharynx [18–22, 27, 28, 74, 109]. With oropharyngeal administration, cytokines are not likely to be degraded by proteases or diluted locally as occurs with enteral exposure [118–120]. They remain intact and may interact with OFALT immune cells potentially

resulting in an anti-inflammatory, protective immunostimulatory response. Mucosal absorption of growth factors among others, and beneficial effects of oligosaccharides may promote feeding tolerance and lead to an earlier achievement of full enteral feeds. Barrier protection, provided by oligosaccharides, lactoferrin, and sIgA, may prevent the adherence and penetration of respiratory pathogens; protecting against VAP.

The oropharyngeal administration of colostrum is a new intervention and to date, only two pilot studies and a small RCT have reported its use [40–42]. One pilot study [40] examined the feasibility, safety, and infant's response to the oropharyngeal administration of colostrum. In that study, five ELBW infants received 0.2 mL of colostrum administered oropharyngeally every 2 h for a treatment period of 48 consecutive hours starting before 48 h of life. The intervention was well tolerated by all of the infants. No adverse effects were noted and all infants began to suck on the breathing tube during the administration of the colostrum drops. Another pilot study [42], examined the feasibility of administering small volumes (0.2 mL) of colostrum every 3 h via oropharyngeal swabbing to very low birth weight infants for seven consecutive days. Results demonstrated that 80–90% of mothers were able to supply the colostrum, although the initial colostrum was typically not available until the infant's second day of life. Once started, approximately 75–80% of the planned swabbings were administered as planned [42]. A more recent study [41], a small blinded placebo-controlled randomized clinical trial, was designed to determine whether own mother's colostrum has an immunostimulatory effects when administered oropharyngeally to ELBW infants in the first days of life. Sixteen ELBW infants served as subjects and were randomly assigned to either the experimental group or the control group. Infants in the experimental group received 0.2 mL of colostrum administered oropharyngeally every 2 h for 48 consecutive hours starting within 48 h post-birth. Infants in the placebo group received sterile water, using the same dose and following the same protocol as those in the experimental group. Dependent measures were collected at baseline and at the completion of the 48-h treatment protocol. The most compelling finding was that colostrum-treated infants had a shorter time to full feedings. Infants in the colostrum group were smaller and younger (mean BW: 776.1g vs. 940.8g, mean GA 25.9 vs. 26.8) compared to those in the placebo group, yet they reached full enteral feedings (150 mL/kg/day) sooner, at an average of 14.3 ± 5.7 (range 9–25) days compared to 24.2 ± 8.7 (15–37) days for the placebo group. This was the only characteristic that was statistically significant ($p = 0.032$). The between group comparisons did not reveal any statistically significant differences in any of the immune markers; however, the sample size was small and may have lacked sufficient power to achieve a significant result. These studies were all limited by a very small sample size, but results will inform future studies. Further research is needed to fully investigate the health outcomes of this easy, inexpensive intervention using a natural immune therapy; own mother's colostrum.

Summary

The use of human preterm colostrum as a potential immune therapy for the ELBW infant is supported by the observation that in all mammals, maternal milk compensates for postnatal immune deficiencies by replacing defense agents that are lacking; enhancing survival of the offspring [121]. In human beings, the immune system is underdeveloped at birth; with immunocompetence being directly related to gestational age. ELBW infants are therefore at highest risk for acquiring nosocomial infections. However, the lactating mammary gland compensates for prematurity-associated immune deficiencies with enhanced production of immunologically derived protective factors to meet the specific needs of the ELBW recipient infant [121]. As such, preterm colostrum is a potential immune therapy for ELBW infants. However, because of clinical instability, ELBW infants do not typically receive colostrum during the first days post-birth; a potentially critical exposure period. The administration of colostrum via the oropharyngeal route serves to provide immunostimulation via OFALT, mucosal

absorption of protective factors, and barrier protection against pathogens; providing protection against bacteremia, VAP, and NEC. Preliminary research has demonstrated the feasibility of this intervention. Future research is warranted to investigate the health outcomes for ELBW infants who receive this intervention and mechanisms to maximize the use of human colostrum, as a potential immune therapy, for immunodeficient extremely premature infants.

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Chapter 11
Protein Nutrition for the Preterm Infant

Christina J. Valentine

Key Points

- The preterm infant has huge demands for dietary protein and requires early parenteral and enteral nutrition to avoid proteolysis.
- Human milk bioactives are life saving for the preterm infant but due to volume limitations requires nutritive supplementation.
- Growth is associated with adequate calorie and protein ratios and developmental sequela and therefore must be carefully determined.
- Further research is necessary to determine the quantity, quality of the protein, body composition of this growth, and whether relationships are associated with long term outcome.

Keywords Parenteral/enteral • Human milk • Preterm infants

Introduction

Protein nutrition is essential for the preterm infant's growth and development. The preterm infant misses fetal accretion which provides a large amount of daily protein over the last trimester. Unlike the adult, the preterm infant is quickly vulnerable to calorie and protein deficits that can lead to catabolism. Essential amino acids are required in order to avoid autophagy and facilitate adequate signaling events, growth factors, and enzymatic reactions. Early amino acid delivery with a minimum 3 g/kg per day parenteral nutrition is paramount to diminish growth failure. Enteral milk should begin within the first few days to provide trophic factors and to reduce proteolysis. Human milk is preferred for its essential amino acid blend and bioactive ingredients. If human milk is unavailable or when boosting the density of milk, a commercial fortifier, free amino acid product, or a blend of hydrolyzed protein to mimic the essential amino acid profile may be preferred. Preterm formulas and then post discharge formulas are recommended when human milk is unavailable. Growth velocity using weight, length, and head circumference remain the standard for measuring nutritional adequacy. Measuring such blood urea nitrogen (BUN) (mg/dL) is helpful during supplementation of human milk to target

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R.R. Watson et al. (eds.), *Nutrition in Infancy: Volume 1*, Nutrition and Health,
DOI 10.1007/978-1-62703-224-7_11,

protein needs. In the future, sophisticated tools such as air displacement technology to measure body composition may provide a more accurate insight as to goal standards to guide our dietary recommendations.

Protein Requirements

Protein nutrition is imperative for metabolism [1] and growth [2]. The human genome itself is composed of some 25,000 proteins and other nitrogenous compounds [3]. Protein balance and the use of their amino acid building blocks are highly regulated by the metabolic processes, gender, and activity of the individual [2]. In order to examine requirements, techniques for understanding this balance are necessary and often investigators utilize nitrogen balance [4] or a factorial approach to calculate human needs where allowances are made for nitrogen contents needed for growth [3, 5]. More sophisticated research methods often evaluate a stable isotope label N- or C-labeled essential amino acid to examine balance [6]. Term infants who are born with body stores of fat and glycogen that can preserve nitrogen losses have a recommendation for daily protein intake of 1.5 g/kg/day the first 6 months of life [3]. The demands for protein are much greater for the preterm infant who misses intrauterine accretion and has increased energy and protein needs for growth of new tissues [7]. Using a factorial calculation, the smallest infants <700 g require 4 g/kg/day whereas the infants >750–1,500 g require 3–3.5 g/kg/day [7] but may need more dietary protein if there are exogenous losses from chest tubes or ostomies. The preterm infant after delivery has a physiology that is different from their intrauterine counterpart that complicates the ability of the infant to utilize protein for anabolism [8]. Careful attention to detail is therefore required in calculating the dietary prescription to give enough total calories to ensure protein is used for anabolism [9] and not autophagy. Energy intake had a significant effect on the nitrogen used for protein synthesis in preterm infants, <1,600 g [9, 10]. The desired weight gain of 15–16 g/kg/day requires 80 parenteral calories with 3 g of protein [11]. On enteral feeding it has been indicated that 1 g of protein gain resulted in 10 kcal extra energy expenditure [12]. Total energy and protein needs for preterm enteral nutrition are therefore 120 kcal/kg with a minimum of 3 g/kg protein respectively [13]. Total body protein turnover evaluated by 15 N enrichment of urinary urea differs in the small for gestational age where 26% higher nitrogen flux was observed [14]. The lower birth weight babies examined (<1,500 g) had significantly higher protein break down calculated as 1.23 g/kg/day compared to the 0.5 g/kg day in the infants >1,500 g [14]. In addition, during the first year of life a tremendous amount of protein is required for normal growth [15] and thus makes reaching goals difficult. It has been described that the preterm infant has a deficit of 43 g/kg protein [16] by the time of discharge from the intensive care unit which translates to an adult equivalent of 18 oz of a meat source! In fact, most recently, Wemhoner described the risk of Bronchopulmonary dysplasia (BPD) was significantly associated with a cumulative protein intake <43 g/kg day in preterm infants <31 weeks gestation and <1,500 g [17]. The quality of protein and the quantity of amino acids are essential [18] for the preterm as the adult and include threonine, valine, tyrosine, tryptophan, isoleucine, lysine, leucine, phenylalanine, methionine—a pneumonic to help memorize the essentials is T.V. T.I.L.L. P.M.—Table 11.1.

The biological value of food sources are determined by the adequacy of the amount of essential amino acids in the sample diet [3]. Free amino acids (FAA) constitute 5% of the total amino acids and are more abundant in human milk than that of other mammals. They correlate with plasma levels of amino acids and provide an immediate source for gluconeogenesis (alanine), innate immunity, nitric oxide production (arginine), Krebs cycle substrates, intestinal cell integrity (glutamate), IgG and IgA (threonine), and protection against oxidant stress (cysteine), vital to the physiology of the immature neonate. Cysteine is also an important component of the tri-peptide antioxidant glutathione, often limiting in the preterm infant [19]. The preterm infant has immature cystathionase activity [20] the

Table 11.1 Essential amino acids in the preterm infant

Essential amino acids (FAO/WHO)
Tryptophan
Valine
Threonine
Isoleucine
Leucine
Lysine
Phenylalanine+tyrosine
Methionine
Histidine
Semi-cysteine, taurine

enzyme that enables the conversion of methionine to cysteine and therefore has a "semi-essential" requirement for the dietary inclusion of cysteine early on after delivery. Transsulfuration of methionine in healthy full term infants and nine stable preterm infants on parenteral nutrition has been recently demonstrated [21] however and at 1 month of age in stable enterally fed preterm infants synthesis of cysteine from methionine is apparent if the enteral intake is adequate [22]. What is not known is the ill, unstable preterm infant and most likely prudent need for cysteine.

The primary significance of protein and the adequacy of all the essential amino acids in the diet is for preterm growth [3]. Growth remains the gold standard for protein sufficiency in the diet [23]. The intake of milk protein [24] and in particular the adequacy of arginine and lysine are major determinants for stimulation of growth hormone and insulin–like growth factor [24, 25]. Goals then for the preterm infant are at best to mimic intrauterine accretion of weight gain—16–18 g/kg/day (AAP). Many growth charts have been developed over the years but the current chart recommended is the Fenton curves [26]—Fig. 11.1.

The design of the chart included numerous infants and statistically smoothed the lines to provide an avenue for the clinician to assess the preterm infants' growth [26]. Daily weights should be plotted and discussed in the unit and then weekly weight gain average (g/kg/day), linear growth (cm/week), and head circumference measurement of fronto-occipital circumference (FOC) (cm/week) should be determined and compared to goals. Poor growth velocity was defined as 12 g/kg/day in a large, multicenter cohort studied by the Neonatal Research Network of hospitals [27]. In reviewing 495 preterm infants at 18–22 months corrected age, they found that the lower weight velocity was significantly associated with low mental development indices Bayley II <70, psychomotor scores <70, and the incidence of cerebral palsy [27]. Slow postnatal weight gain can also identify infants at highest risk for retinopathy of prematurity [28]. In a prospective, double blind study, Dabydeen found that increased postnatal brain growth occurs in infants with a history of perinatal brain injury on higher calorie and protein diets [29]. Functional consequences can occur without adequate protein intake. It is imperative then that after the infant's airway is established that nutrition has the highest priority.

Parenteral Nutrition

Amino acid solutions were designed in the 1980s to provide a more appropriate essential amino acid profile to mimic the term breastfed infant [23]. Dr Zlotkin demonstrated that calories become important in combination with protein so that nitrogen balance is positive [11]. With the survival of infants with very immature gestational ages (<24 weeks) it remains to be determined if these calorie and concentrations of amino acids are able to meet their requirements. Amino acids should be included in

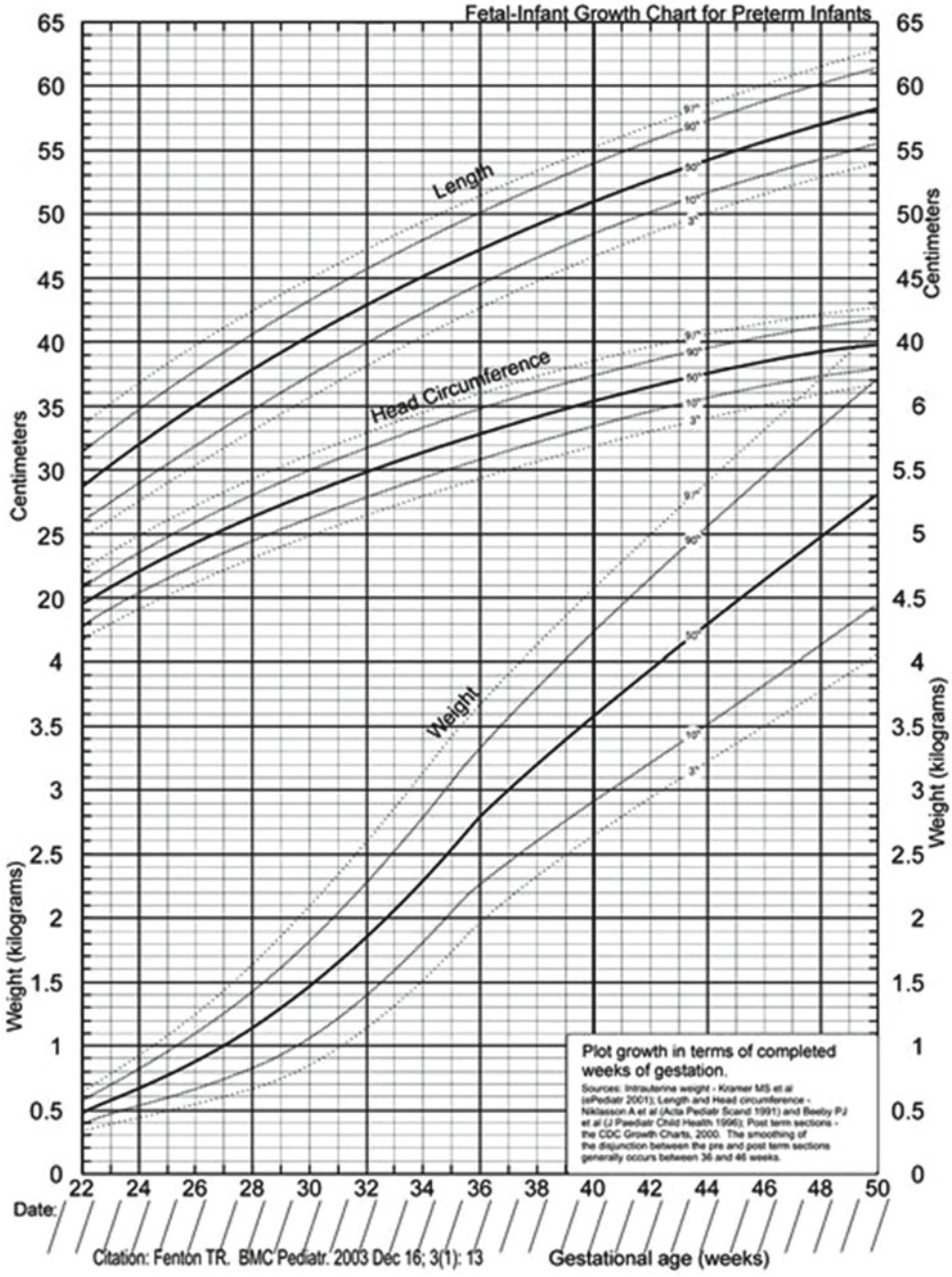

Fig. 11.1 Growth goals for the preterm infant

first fluids after delivery to improve nitrogen balance and decrease growth failure [30–35]. Many studies have convincingly demonstrated functional benefits for providing early amino acids to preterm infants of >24 weeks but the primary relationships were demonstrated in these early studies. Amino acids are known to stimulate insulin and insulin like growth factor [1] which helps with attenuating the hyperglycemic episodes previously demonstrated in glucose only solutions in the preterm infant. Most important is that such an early intervention with amino acids after delivery can reduce

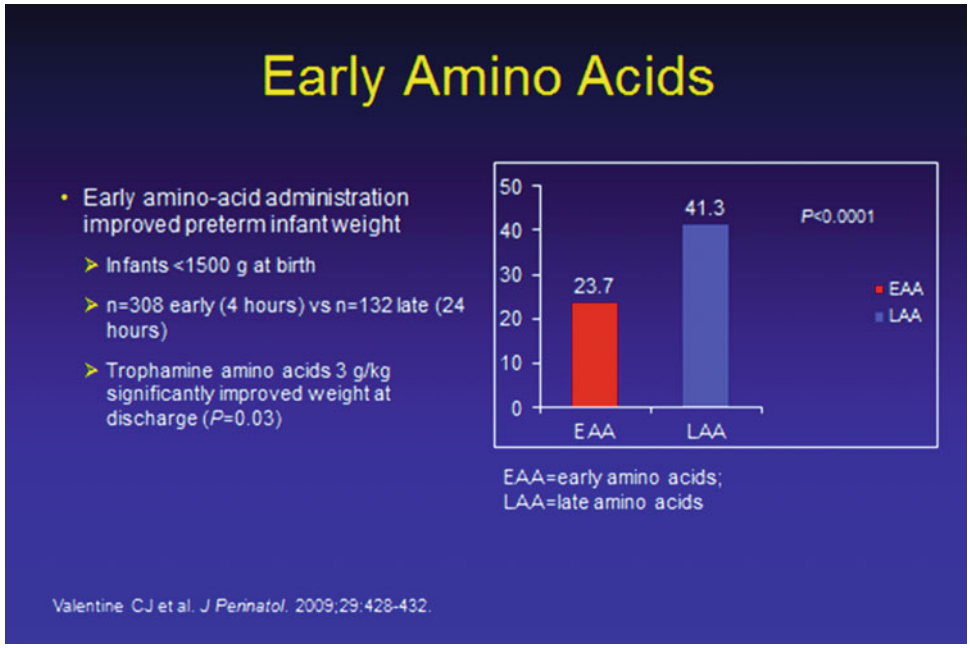

Fig. 11.2 Decreased growth failure with early amino acids, % percent <10th percentile for corrected age

growth failure significantly at discharge—Fig. 11.2. Utilization of the amino acids and tolerance has been explored and appears that the potential for toxic concentrations, uremia, and acidosis has not been well correlated with the current amino acid solutions [36]. What is concerning however is that even with adequate parenteral nutrition, proteolysis is not entirely suppressed [37, 38] and an enteral source of nutrition is necessary.

Enteral Milk Protein

Human Milk

Human milk is often the gold standard for enteral feeding, contains a significant amount of protein nitrogen and non-protein nitrogen [39, 40] which contain biologically important immunomodulatory peptides [41, 42] and lactoferrin [41] and prevents significant morbidities such as BPD [43], necrotizing Enterocolitis [44–46], and retinopathy of prematurity [47]. Early preterm milk can contain a total protein content of 2.5 g/dL week 1 [48, 49] but begins to have a significant fall in the concentration to <1.5 g/dL after 2 weeks [48, 50], and <1 g/dL after 4 months in term donor milk [34] compared to when reference protein needs are highest—Fig. 11.3. The term infant would begin solid foods by 4–6 months whereas the preterm infant due to immature suck and swallow mechanics is unable to ingest solid foods for many months and remains dependent on the protein intake from the milk source. When mother's own milk is not available, a pasteurized source of donor milk (PDM) is the next most reasonable alternative for the preterm infant [13]. The total protein in the PDM however can be very limiting for the preterm infant [34] because the lactational stage is often 4–12 months in the donor mothers and practice in the United States often limits volume of enteral feeding to <150 mL/kg/day. The later lactational stage milk's protein concentration can be 0.9 g/dL a 75% less than baseline estimates

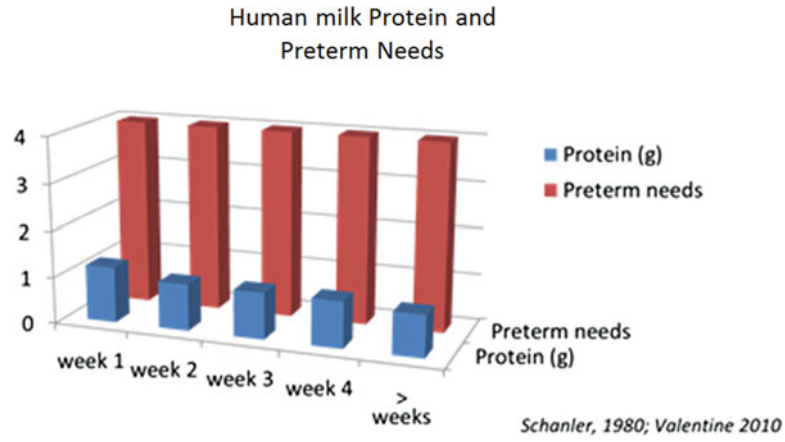

Fig. 11.3 Human milk protein (g/dL) compared to preterm infant protein requirements

often cited. Therefore feeding an infant <1,500 g 150 mL/kg of human milk would provide only at most 2.1 g/kg/day protein; whereas volumes >200 mL/kg could reach 3 g/kg [51] but this volume is typically not practiced particularly in our smaller, sickest neonates. Donor milk amino acids are not significantly affected quantitatively [34] but the absolute quantity of these amino acids are far less than what would be seen in early milk [52, 53]. Jackson found that postnatal retention was significantly less than intra uterine counterparts and that glycine may be limiting in plain human milk [54]. In addition, biological peptides may be diminished for pasteurized donor milk fed preterm infants [55] and protein conformational changes are of concern and have not been investigated. Despite the lower concentrations of anti-infective properties however; donor milk still comprises a higher concentration than formula [56, 57]. The immunobiology of human milk is unparalleled but the nutritional quality when fed at limiting volumes in the neonatal intensive care unit requires exogenous fortification with energy, protein, and additional multinutrients to avoid growth failure [44] and improved calcium balance [58, 59]. The concern however is at current fortification, human milk fed infants have slower weight gain and linear growth than their formula fed comparisons [43, 44]. Healthy human milk fed term infants often have slower weight velocities than a predominately formula fed group [60] so that is not concerning as long as intrauterine goals are achieved but what is different that the term breast fed infant is the slow linear growth which cannot be accepted.

Human Milk Supplementation Strategies

Commercial human milk fortifiers are available from cow or human sources because of the limits in volume a preterm can ingest to provide adequate protein. Preterm infants fed human milk fortified with commercial fortifiers grow significantly better and tolerate it well [61–63]. Despite in vitro concerns that commercial fortifier with iron may influence antimicrobial defenses [64, 65] this has not been shown in a randomized clinical trial [66]. The type and amount of protein is however up to debate. Current fortifiers contain either a human milk source or cow milk protein and recently it has been shown that NEC can be significantly reduced from 15 to 4% in an exclusive human milk fed diet [45]. In a clinical quality approach however we found that the use of cow milk fortifier along with human milk diets reduced NEC from 11 to 4% alone and did not seem diminished by the cow milk fortifier but rather effected primarily by the inclusion of human milk only for 30 days in the NICU [67]. Careful attention is important to ensure that baseline estimate for human milk is not estimated to

be too high—i.e., a fortifier has 2 g of protein in their formulation and they estimate human milk to be at 2 g/dL—so if mixed the combination would provide 4 g/dL—this is too high an estimate because as we have learned preterm human milk does not stay at 2 g/dL very long. It is more prudent to estimate baseline human milk at 1 g/dL with fortification—max 1.4 g/dL since predominately preterm infants are being fed with week 2–12 week milk. A registered dietitian is imperative in the NICU to help with these recipes and investigations. The monitoring of BUN has proven to be useful [68]. In former 600–1,750 g infants, at <21 days of life and at 90 mL/kg enteral feeds, using the cut-off of a BUN <9 mg/dL the authors supplemented protein at 0.3–0.6 g/100 mL human milk and found significantly improved weight gain [68]. If a human milk source is not available, preterm formulas should be chosen [13].

Commercial Formulas

In studies on preterm formulas it appears that the protein energy ratio becomes very important for nitrogen balance and weight gain [69, 70] and even up to a ratio of 3.6 g of protein to every 100 cal provided optimal weight gain without toxicity was found in preterm infants [71]. In infants with viral bronchiolitis it was also shown that an increased P:E ratio promoted anabolism [72]. Recently new "high Protein" preterm formulas have been marketed but in fact their label should state "adequate" protein as they more clearly provide what the current protein requirements suggest. What remains to be evaluated is a more accurate evaluation of the weight gain to ensure it will not be a metabolic disadvantage to the preterm infant. What is reassuring however is that in a study conducted with a P:E ratio of 3.2 g/100 kcal compared to 2.6 g per 100 cal in preterm infants the proportion of lean mass to fat mass both approached the estimation in the fetus [73].

The formula industry has taken cow milk and changes the ratio of casein to whey or a predominate whey solution that can provide a closer concentration to the goal amino acids [74]. Protein quality then in formulas can be provided as intact cow milk casein: whey protein or can have 100% whey hydrolysis, casein hydrolysis or FAA and the potential benefit for reduction in antigenic exposure or absorption in the intestine. In animal studies hydrolyzed casein does not accelerate bowel adaptation greater than an intact protein [75] but FAA in rat studies accelerates villus height [76] perhaps very important in our intestinal injured infants. Whey protein also has provocative effects on immune modulation in the enhancement of innate immune responses [77, 78]. What begs to be more understood is what effects intact cow protein compared to these hydrolyzed products and FAA has on the immature intestine and microbiome in the preterm infant. Intolerance to cow-milk protein has presented clinically with hematochezia and on colonoscopic examination, the mucosa has ulcerations and inflammation [79] .

Whey hydrolysis has been shown to improve gastric emptying rates in infants [80], and have nitrogen retention rates similar to the fetus [81]. Clinical evaluation of gastric emptying however in preterm infants that are stable and on enteral nutrition did not differ however when using a hydrolyzed versus intact protein product [82]. Hydrolyzed proteins to molecular weights <1,500 kDa as is contained in casein hydrolyzed products are less antigenic [13]. True cow milk allergy to cow milk occurs from 1.9 to 7.5% of infants [83]. But several studies now have documented less atopy if infants with a family history are fed a casein or whey hydrolyzed protein formula compared to an intact cow protein [84–86]. Free amino acid formulas are even more protective against antigenic response and are used if anaphylaxis occurs in rare occasions even with a protein hydrolysis [87, 88]. A retrospective study evaluated which milk type was most likely to be associated with an intestinal injured infants likelihood to get off parenteral nutrition found that after human milk, free amino acid formula feeds were the next most successful [89]. The mechanisms behind this are speculative but provocative. The free amino acid products for neonates are however not specifically designed for the preterm infant and contain less

calcium and phosphorus and care is suggested to fortify as needed if used. The discharge formulas should be considered when the infant reaches >35 weeks and >2 kg in order to continue to provide a special blend of nutrients and increased protein for the preterm infant and have demonstrated adequate growth and increased bone density after discharge [90]. Soy formulations should not be used because of effects the soy has on calcium and phosphorus balance in the preterm infant [91].

Nutrition Assessment

Daily intake of kcal/kg/day and protein g/kg/day with growth values in weight should always be discussed on rounds. Weekly, growth velocity-weight (g/kg/day), length (cm/week), and head circumference-FOC (cm/week) should be calculated and compared to goals. Weekly electrolytes with BUN concentration can help target supplemental strategies. Body composition of this growth will be important to investigate and currently DEXA scanning [92] or air displacement tools [93] are available but require cost and expertise and use in the research setting.

Conclusion

The preterm infant has huge demands for dietary protein and requires early parenteral and enteral nutrition to avoid proteolysis. Human milk bioactives are life saving for the preterm infant but due to volume limitations requires nutritive supplementation. Growth is associated with adequate calorie and protein ratios and developmental sequela and therefore must be carefully determined. Further research is necessary to determine the quantity, quality of the protein, body composition of this growth, and whether relationships are associated with long term outcome.

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Chapter 12
Parenteral Nutrition of Preterm Infants: Methods to Improve Safety and Prevent Disease

Pita Birch

Key Points

- Parenteral nutrition (PN) is an essential part of the care of preterm infants, but the delivery of PN is associated with significant complications.
- Non-infective complications associated with delivery of PN via an umbilical venous catheter (UVC) can be minimised by ensuring correct placement and by prompt removal within 14 days.
- PN delivery via a peripherally inserted central catheter (PICC) has benefits over delivery via a peripheral venous cannula.
- Non-infective complications associated with delivery of PN via a PICC can be minimised by ensuring correct position confirmed by instilling radio-opaque contrast prior to an appropriate radiograph.
- Central line associated bloodstream infections (CLABSI) are a serious problem in neonatal intensive care and are associated with increased mortality, morbidity and health care costs.
- CLABSI and the associated adverse outcomes can be minimised using heparin in the PN at 0.5 IU/mL, combining multiple risk reduction strategies into bundles and by prompt recognition, diagnosis and appropriate management.

Keywords Parenteral nutrition • Preterm infant • Prevention • Umbilical venous catheter • Peripherally inserted central venous catheters • Extravasation injury • Central line associated blood stream infections

Introduction

Parenteral nutrition (PN) is a mainstay of neonatal intensive care and is essential for providing adequate nutrition to preterm infants as there is a delay in establishing enteral feeding because of early respiratory and haemodynamic compromise, feed intolerance, concerns regarding links between necrotising enterocolitis and rapid advancement of enteral feeds and inadequate early breast milk supply. At birth, infants are in a catabolic state and early nutrition, particularly PN, may have a significant effect on growth and neurodevelopmental outcomes [1]. However, there are risks associated with PN

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R.R. Watson et al. (eds.), *Nutrition in Infancy: Volume 1*, Nutrition and Health,
DOI 10.1007/978-1-62703-224-7_12,

use and methods to reduce these risks, improve safety and prevent disease associated with the use of PN in preterm infants will be the focus of this chapter.

Improving the safety of parenteral nutrition use can be divided into methods that minimise the complications associated with the delivery of parental nutrition and methods to improve the safety of the PN solution itself. This chapter will concentrate on the former.

Minimising the Complications Associated with the Delivery of PN Via an Umbilical Venous Catheter, a Peripherally Inserted Central Catheter or a Peripheral Venous Cannula

PN, as the name suggests, is intravenous nutrition, usually made up of an amino acid/carbohydrate solution with electrolytes, minerals and trace elements and a lipid solution. Delivery of this solution can be into a central vein or via a peripheral vein. In newborn infants, there is a unique opportunity to access umbilical vessels and so PN delivered via a central vein can be through a central line, a peripherally inserted central catheter (PICC) or an umbilical venous catheter (UVC). In this first section, we will explore the non-infective complications associated with the delivery of PN via three main routes (peripheral vein, PICC or UVC) and methods to reduce these complications and improve safety (see Table 12.1).

Delivering PN Via an Umbilical Venous Catheter

In the first few days of life, PN is often delivered via a UVC, particularly in the extremely preterm or extremely low birth weight infants who also have an umbilical arterial catheter in situ. The main complications associated with UVC use are related to malposition of the catheter, extravasation, infection, thrombosis and there may be an association with necrotising enterocolitis (NEC).

One of the key points in improving safety with UVC use is ensuring correct placement. Pericardial extravasation and cardiac tamponade, hepatic venous thrombosis and necrosis, hepatic and intraperitoneal extravasation and portal vein thrombosis and subsequent portal venous hypertension are all reported serious complications of UVC use in preterm infants, and are often, although not always, associated with incorrect placement of the catheter [2–7, 13, 14, 40, 41].

It is important before inserting the UVC that an estimation of insertion length is made. A simple and commonly used calculation for insertion distance from the base of the umbilical stump is derived from birth weight – insertion distance (cm) = 1.5 × birth weight (kg) + 5.5 [8]. The website www.nicutools.org has tools to make the calculation of estimated UVC insertion length based on this formula [9].

Once inserted, it is then imported to ensure correct placement of the UVC, in the ductus venosus or inferior vena cava (IVC) and not in hepatic or portal veins or within the heart. Generally, the placement is checked using an antero-posterior (AP) chest radiograph (CXR); however, more accurate estimation of the tip of the UVC may be made if this is accompanied by a lateral CXR [10, 11] or using echocardiography [12].

The other important complication of UVC delivery of parenteral nutrition is serious invasive bacterial and fungal infections, including localised hepatic abscesses secondary to malposition of the catheter [16]. UVCs are central lines and as such are prone to central line associated blood stream infections (CLABSI). A more in-depth discussion of methods to prevent infection associated with the delivery of PN through a central line will take place later in this chapter.

Prompt removal of an UVC is important for the prevention of any complication; so one should always be cognisant of the ongoing need for the central line, but there is evidence to suggest than an appropriately placed catheter can be left in situ for 14 days without increasing complication rates [15].

Table 12.1 Summary of non-infective complications of PN delivery and methods to improve the safety of the delivery of PN

Route of delivery	Complications	Methods to improve safety
UVC	Pericardial effusion ± tamponade [2–5]	Estimate UVC insertion distance prior to insertion
	Hepatic venous thrombosis ± necrosis [6, 7]	Distance(cm) = 1.5 × birth weight (kg) + 5.5 [8, 9]
		Check correct UVC tip placement [10–12]
		In the umbilical vein or ductus venosus
	Hepatic extravasation [5, 13]	Not in portal or hepatic vessels and outside of cardiac silhouette
		Use antero-posterior chest radiograph in combination with lateral chest radiograph and/or echocardiography
	Portal vein thrombosis [6, 14]	Prompt removal of UVC as soon as no longer required, but not to remain in situ for >14 days [15]
	Hepatic abscess [16]	
Peripheral venous cannula	Compared to peripherally inserted central catheter (PICC) use	Delivery via a PICC confers some benefit with no evidence of increasing the risk of invasive bacterial or fungal infection [17]
	There is an increased incidence of painful procedures [17, 18]	
	There may be an increased incidence of extravasation injury [17]	
	There is inconsistent and reduced nutritional delivery [19]	
PICC	Pericardial effusion ± tamponade [20–23]	Always check the position of the PICC after insertion by instilling radio-opaque contrast into the catheter prior to performing a radiograph [24]
	Extravasation into	Ensure that the catheter tip is outside of the cardiac silhouette/pericardial reflection on chest radiograph [20, 22, 23]
	Epidural space [25–28]	Withdraw or remove any PICC where there is a "cobweb" sign suggesting tip is in a superficial tributary [29]
	Pleural space [30–33]	When using an upper limb vein ensure that correct placement taking into consideration tip movement of up to 1.5 cm [34]
	Kidneys [35, 36]	When using the lower limb calculate the insertion distance from the long saphenous at the medial malleolus (between 0.55 × birth weight (kg) − 4 and 0.44 × birth weight (kg) − 3) so as to ensure tip placement avoids right atrium and ascending lumbar veins (T9–L3) [9, 37]
	Peritoneum [38, 39]	Restrict PICC use to units that insert and manage PICCs frequently [21]

If it is envisaged that the PN is likely to be required beyond 14 days then the UVC may be removed earlier and other forms of delivery of PN, discussed next, should be utilised.

Delivery of PN Via a PICC Versus a Peripheral Venous Cannula

In infants who do not require umbilical lines or when PN is ongoing, beyond what clinicians feel is safe for the UVC to remain in situ, the question is whether to deliver PN through a peripherally inserted central venous catheter (PICC) or via a peripheral venous cannula. PICCs generally remain usable for longer than peripheral venous cannulae and are less likely to extravasate into superficial

tissues, but there are concerns that PICCs are associated with more complications including invasive bacterial and fungal infections and more serious extravasation injuries.

A Cochrane review of PICCs vs. peripheral cannulae for delivery of PN to neonates, including five small clinical trials with a combined total of 432 infants, found no significant difference in death or invasive bacterial or fungal infection [17].

Three of the five randomised controlled trials compared extravasation injuries in infants where PN was delivered via PICCs vs. peripheral venous cannulae and although the results were not statistically significant, there was a trend towards less extravasation with PICC use [17].

The advantage that PICC lines have over peripheral venous cannulae is that they are able to remain in situ for longer and thus reduce the number of painful procedures the infant has to undertake. The meta-analysis showed a significant reduction in peripheral intravenous cannulae replacement in those infants where PN was delivered through a PICC: mean difference −4.3 (95% confidence interval (CI): −5.24, −3.43) [17]. A cohort study not included in the Cochrane review also showed a reduction in peripherally inserted cannulae replacement when PICCs were used with no increase in bacterial infections [18].

It is possible that PICCs may confer another advantage in that nutritional delivery may be better when the PN is infused through a PICC compared to PN infused through a peripheral venous cannula. A small study of 49 infants showed a statistically significant difference in the deficit of delivered PN (from that actually prescribed) favouring PN delivered through a PICC compared with that through a peripheral venous cannula [19]. This was related to an increase in pauses in PN delivery when peripheral venous cannulae required resiting. The difference was a mean deficit of 3.2% in the PICC group vs. 10.3% in the peripheral cannula group. The mean difference in the percentage of the prescribed nutritional intake actually received was −7.1% (95% CI: −11.02, −3.2). This 7.1% difference over a week represents 12 h less nutrition in peripheral venous cannula group, a significant amount in a preterm infant where nutrition is very important for growth and development.

The evidence was not felt to be strong enough for the Cochrane review authors to recommend either PICC or peripheral venous cannula use for the delivery of PN, but the limited evidence suggests that delivery through a PICC confers benefits without increasing the risk of invasive infections [17]. Delivery through a PICC may reduce episodes of extravasation injury, reduce painful procedures through a reduction in peripheral venous cannulae replacement and deliver better nutrition more consistent with what is prescribed.

Delivering PN Via a PICC

PICC use is now widespread in neonatal intensive care for the delivery of PN and it is therefore important to minimise the risks involved. The two commonly reported and serious complications associated with PICC use are extravasation injuries and central line associated blood stream infections (CLABSI). This section will concentrate on minimising extravasation injury with the next section concentrating on CLABSI.

There are multiple reports in the literature of severe extravasation injuries secondary to the use of PICC lines used for the delivery of PN to preterm infants. The most serious of these is pericardial extravasation causing effusion and at times cardiac tamponade with a high associated mortality. An important report from the United Kingdom (UK), Department of Health publically highlighted four deaths in Manchester from cardiac tamponade as a result of extravasation of central lines inserted for the administration of PN (two PICCs, one surgically inserted central catheter and an UVC) [20]. There are three large series published on the use of PICCs for the delivery of PN and all report low rates of pericardial effusion and even lower rates of fatal cardiac tamponade. In a series of 2,186 PICCs in 1,862 infants in a large Australian perinatal centre, there was one case of non-lethal pericardial

effusion giving a rate of 0.05% [42]. In a series of 46,000 PICCs in 168 neonatal intensive care units (NICUs) across the UK over a 5-year period, there were 82 cases of pericardial effusion (0.18%) and 30 infants died as a result of cardiac tamponade (0.07%) [21]. In a survey of 92 NICUs in Japan where there was an estimated 5,000–7,500 PICCs inserted per year over a 5-year period, there were 28 cases of pericardial effusion (0.07–0.11%) [22].

The reported rates of pericardial effusion associated with the use of PICCs (0.05–0.11%) for the delivery of PN to preterm infants is low, but the mortality associated with this complication is very high and so it remains a real fear for neonatologists. It is therefore important to consider ways of avoiding this serious complication so as to safely delivery PN.

In the report out of Manchester, all four deaths occurred in infants where the position of the line was in the right atrium and the very strong and public recommendation of that report was that central lines should not be placed with the tip inside the heart [20]. This is backed up by a report from Texas reviewing 14 local cases and 47 case reports in the literature of pericardial effusion associated with PICC use for the delivery of PN to neonates which found that 92% of cases had the PICC tip located within the pericardial reflection on chest radiography [23]. Their recommendations were that CXRs should be performed to check the position of all PICCs and that the tip should be outside of the cardiac silhouette, but still within the vena cava. In the Japanese series, the rates of pericardial effusion associated with PICC tended to be higher in NICUs that allowed tip position in the right atrium ($p=0.09$) [22].

In the UK series, the tip position could not be verified, although the units surveyed claim the choice of tip position was within either the IVC or superior vena cava (SVC), and so conclusions about safe position of a PICC could not be made [21]. However, they did find a statistically significantly increase in pericardial effusion associated with PICCs in units that inserted fewer lines.

Thus to increase safety and minimise the risk of pericardial effusion, PICC insertion should be restricted to units that are familiar with their use and the tip position needs to be confirmed by CXR to be outside of the cardiac silhouette.

Serious injury from extravasation associated with PICC use is not restricted to pericardial effusion. There have been literature reports of extravasation of PN into the epidural space [25–28], the pleural space [30–33], the kidneys [35, 36] and the peritoneum [38, 39] all with serious consequences. In these anecdotal reports, there is a common thread of malposition of the PICC. Therefore, like reducing the risk of pericardial effusion, it is important that the tip position is confirmed. However, confirming tip position of a PICC can be difficult and interobserver and intraobserver reliability has been shown to be relatively poor [43]. Interobserver reliability is improved when radio-opaque contrast is instilled, not injected, into the PICC prior to performing the radiograph [24].

When a PICC is unable to be placed to the calculated full length, then it may be better to inject the radio-opaque contrast while the radiograph is being taken because a “cobweb sign” (multiple thin rays of radio-opaque contrast visible in different directions like a cobweb) indicates that the tip is a superficial tributary and is at a high risk of extravasation [29]. If this situation arises, then the PICC needs to be withdrawn and the position rechecked using the same radiological technique, or removed and resited.

Confirming the PICC tip position by radiography is essential in improving safety when delivering PN via a PICC, but the position of the tip at the time of the radiograph is not necessarily the position the tip will stay all the time. The SVC is considerably shorter than the IVC and there are concerns that when a PICC is inserted into the upper limb, arm movement may result in movement of the PICC tip and may result in the tip entering the right atrium and placing the infant at risk of pericardial effusion. Nadroo et al. compared 280 radiographs of 60 neonates with PICCs inserted into the upper limb and found that arm movements significantly affected the tip position of the PICC and that the migration towards or away from the heart differed with the same arm movement depending on which vein was used—basilic, axillary or cephalic [34]. Shoulder adduction will bring a basilic or axillary vein PICC closer to the heart, but a cephalic vein PICC will be displaced away. Flexion of the elbow moves a basilic or cephalic vein PICC towards the heart, but has no effect on an axillary vein PICC.

Combined shoulder adduction and elbow flexion causes a basilic vein PICC to have the greatest movement towards the heart (15.11 ± 1.22 mm). Therefore, the position of the arm when the radiograph is taken must be considered when deciding whether an upper limb PICC tip is in a safe position and while using the basilic vein, consideration must be given for a 1.5 cm movement of the tip during spontaneous arm movement.

Although upper limb PICC lines are more likely to be associated with pericardial effusions and lower limbs with epidural, renal and peritoneal extravasation, in a study comparing upper limb with lower limb PICC insertion, there was some evidence to suggest that there were less infective complications with lower limb insertion; however, there were no cases of significant extravasation in either group to make a comparison about safety from that aspect [44]. The most commonly used vein in the lower limb for PICC insertion is the long saphenous and a study of 46 PICCs inserted into the long saphenous vein at the medial malleolus resulted in a formula based on the infant's weight which will calculate a safe position for the PICC tip between the ninth thoracic vertebral body (T9) and the third lumbar body (L3) [37]. The position between T9 and L3 takes into consideration the movement of the PICC tip with leg movement to ensure the tip remains out of the right atrium and beyond the ascending lumbar veins. Insertion length (mm) should be between 0.55 × birth weight (kg) − 4 and 0.44 × birth weight (kg) − 3 and again the website www.nicutools.org has tools to make this calculation [9].

In summary, to reduce serious extravasation injury and improve the safety of PICCs used for the delivery of PN, the most important intervention is to ensure that there is clear radiographic confirmation of the PICC tip in a safe and appropriate position using radio-opaque contrast. If choosing the lower limb the PICC insertion length should be calculated to place the tip between T9 and L3 and confirmed radio-graphically using. When using the upper limb, the PICC tip should be outside the heart by up to 1.5 cm to take into consideration the full range of tip migration with arm movements. Should the line not be able to be inserted to the calculated distance, then injection of contrast during the radiograph may help to determine if the line is in a superficial tributary and therefore likely to extravasate. PICC use for the delivery of PN should be restricted to units that are familiar with PICC insertion and management.

Improving Safety by Minimising Central Line Associated Blood Stream Infections in the NICU

Preterm infants have comparatively low immunoglobulin concentrations, a lack of interleukins, immature immune responses such as phagocytosis, opsonisation and intracellular killing, poor skin and intestinal integrity and are exposed to pathogens in NICUs, all of which increase their risks of nosocomial infections [45–50].

The most common organisms causing nosocomial infections in preterm infants are coagulase-negative staphylococci (CoNS), especially *Staphylococcus epidermidis* [51–56]. Studies have shown that preterm infants are 1.7–3.7 times as likely to contract a blood stream infection with a central line in situ and up to four times as likely if that central line is used for the delivery of PN [52, 53, 55]. The risk is even greater if lipids are part of the PN delivered through the central line as there are concerns that not only does lipids provide a medium for bacteria growth, but also intravenous lipid may impair neutrophil and macrophage function [57]. In one study, the risk of nosocomial infection with CoNS in infants receiving intravenous lipid was increased 9.4 times [odds ratio (OR) 9.4, 95% CI: 1.2, 74.2] with 85% of blood stream infections attributed to intravenous lipid therapy [58].

Preterm infants are particularly susceptible to infection and the risk is greater when a central line is in situ, particularly for the delivery of PN, making CLABSI a significant issue in neonatal intensive care. Report rates of CLABSI in the literature vary greatly. In the large Australian cohort study described earlier in this chapter, 116 out of 2,182 PICCs (5.3%) in 1,862 infants were complicated by

CLABSI [42]. An earlier review found rates of up to 29% and up to 15.3 infections per 1,000 catheter days [59]. One of the most recent reports of CLABSI in preterm infants reported a rate of 8.3 infections per 1,000 catheter days [60]. The risk of CLABSI in infants receiving PN is increased with lower gestational age, lower weight and the longer the central line remains in situ [60–64].

Late onset or nosocomial septicaemia is associated with increased rates of death, severe intraventricular haemorrhage, periventricular leukomalacia, chronic lung disease and with increased time on respiratory support and increased hospital stay [65]. In a recent study of 514 preterm infants (24–27 weeks gestation) in Switzerland, proven sepsis was shown to independently increase the risk of cerebral palsy (OR 3.23, 95% CI: 1.23, 8.48, $p=0.017$) and increase the likelihood of neurodevelopmental impairment (OR 1.85, 95% CI: 1.12, 3.05, $p=0.016$) [66].

CoNS infections are sometimes regarded as minor illnesses, but CLABSI with CoNS are a significant problem in NICUs and result in prolonged hospital stay, increased hospital costs and increased mortality [55, 56, 67, 68]. There is also an association with CoNS CLABSI and NEC, although causality is unproven [56]. Thus CLABSI in preterm infants is a significant cause of death and neurodevelopmental disability and is a significant cause of increased time on respiratory support, increased time in intensive care and increased overall hospital stay and therefore increased health costs.

Infections associated with central lines can also be localised with phlebitis and local inflammation and it is postulated that local inflammation secondary to infection is a risk factor for extravasation, a serious complication we have already covered in this chapter [69].

Practices That Reduce CLABSI and Improve the Safety of Providing PN

Considering the significant morbidity, mortality and health costs associated with nosocomial infections and the increased use of central lines, it is critically important that all possible measures are taken to reduce CLABSI in NICUs in order to facilitate the safe delivery of PN to preterm infants (see Table 12.2).

In the literature there are many studies looking at the individual components of central line insertion, most often focussing on PICC insertion and management, to provide evidence to guide safe practice. Recently, there have been several collaborative studies combining all the evidence-based best practices from the literature into "bundles" and implementing these to demonstrate a reduction in CLABSI [103–105]. For the purposes of this review, we will look at the individual components shown to reduce CLABSI before dwelling on the impact that best practice "bundles" have on improving the safety of PN delivery via a central line.

Methods to reduce the risk of developing CLABSI can be divided into prevention during insertion and prevention during catheter maintenance. Although there is a paucity of evidence, it is important to consider that during central line use there are other procedures completely separate from central line insertion or maintenance that may introduce bacteria into the blood stream and contribute to the risk of developing CLABSI such as peripheral venous cannula insertion, blood sampling (venepuncture or heel prick), oral or nasal suctioning, gastric tube insertion and other procedures/conditions that result in a loss of skin integrity (tape removal, napkin dermatitis, pressure lesions, etc.). Due to a lack of evidence surrounding the risk these procedures pose in the development of CLABSI and the lack of preventative evidence, this will not be discussed any further, other than to recommend that any procedure likely to have an impact on skin integrity should be kept to a minimum and should be performed using aseptic techniques.

Central line insertion is a key moment in the development of CLABSI and so there needs to be appropriate preparation. In fact, preparation should be at a unit level before any individual patient has a central line inserted and this requires an emphasis on quality control. Achieving and maintaining

Table 12.2 Summary of strategies to reduce the incidence of CLABSI and so improve the safety of the delivery of PN to preterm infants

Unit level, quality interventions and policy	Developing a central line insertion and maintenance guideline or protocol [70–72]
	Continuous education around insertion and maintenance of central lines along with regular feedback of surveillance data [70, 72, 73]
	Creating a central line insertion kit or cart [72]
	Restricting staff who insert central lines to a highly trained team within the service [73, 74]
	Hand hygiene before and after any patient contact combined with policy and education around promoting and enforcing hand hygiene [75–83]
Central line insertion	Selecting lower limb if possible (evidence cannot recommend avoiding upper limb insertion) [44]
	Avoiding femoral line insertion [60]
	Maximal sterile barrier precautions during insertion (mask, hat, sterile hand wash, sterile gown, sterile gloves, large sterile drape) [70, 84, 85]
	Do not attempt insertion through incubator port holes [71]
	Disinfect skin with an appropriate antiseptic solution [70–72, 85]
	Avoid any iodine based antiseptic solutions [86, 87]
	Use a chlorhexidine-based antiseptic solution [88–91]
	Avoid concentrated chlorhexidine-based antiseptic solutions or solutions with alcohol in extremely preterm infants in the first few days [92–94]
	Combined with alcohol for more mature or older infants [91, 95]
	Do not use the same needle for several attempts at central line insertion ("one needle, one puncture") [71]
Central line management	Minimise any manipulation of the central line [96, 97]
	Avoid accessing the catheter for blood sampling
	Reduce the number of line changes—stretch out the time between PN changing to as long as recommended by the PN supplier
	Strict sterile precautions for any line changes or when accessing the line [98, 99]
	Use the same precautions as during insertion of the line
	Use concentrated chlorhexidine with alcohol to sterile the lines and hubs
	Promoting care of the catheter exit site [96, 100, 101]
	Changing the dressing and sterilising the site if soiled, wet or visibly dirty
	Regular cleaning and dressing changes even when visibly clean
	Use of heparin in the PN solution at a concentration of 0.5 IU/mL [102]
	Promoting enteral feed progression and actively assessing the ongoing need for the central line so as to promote prompt line removal [60–63]
Combining strategies	Use of "bundles" [103] of evidence-based risk reduction strategies (similar to those described in this table) combined with policy, education and promotion [76, 103–106]
Recognition, diagnosis and management of CLABSI	Emphasis, promotional and educational, on vigilance and awareness of the possibility of CLABSI to promote early recognition and diagnosis [70, 75, 76]
	Draw a single appropriate volume sample for blood culture, 0.5 mL likely to be adequate [107–109]
	Combine clinical judgement with measures of inflammatory mediators to differentiate between true CLABSI (whether culture negative or positive) and false positive and true negative blood culture results [110–113]
	Promote the judicious use of vancomycin as over use is associated with VRE [111, 114]
	Prompt removal of any central line where there is suspected or proven CLABSI with *Staphylococcus aureus* or gram-negative organisms or where ongoing CLABSI is suspected or proven despite appropriate treatment [115]

low rates of CLABSI require a central line insertion and maintenance policy associated with a continuing education programme and regular feedback of surveillance data [70–73]. A simple quality measure, the creation of a central line kit or cart where all the equipments required for insertion can be kept, thus reducing the number of steps and the amount of travel required to prepare for insertion,

reduces CLABSI [72]. Reducing the number of people who insert PICCs to create a highly trained team within a service will also reduce CLABSI [73, 74].

Hand hygiene is an extremely important quality issue within neonatal intensive care and in the prevention of CLABSI [75–83]. Before any patient contact, particularly before palpating for veins, one cannot stress enough the importance of thorough and effective hand washing or hand hygiene with an alcohol-based hand product.

The site of insertion of the central line may also have an impact on the safety of PN delivery. A study comparing upper limb insertion with lower limb insertion found that there were less complications when the PICC was inserted in the lower limb [44]. There were no cases of serious extravasation injury in either upper or lower limb PICCs in this study; so there is still no answer as to whether there is a difference in extravasation complications related to which limb the PICC is sited in, but rates of CLABSI with CoNS were higher (5.7% compared with 10%, $p<0.05$) and cholestasis were greater (30% compared with 21.5%, $p<0.05$) in the upper limb PICCs. This was a small study and there was no statistically significant difference in the overall rates of CLABSI (9.3% lower limb compared with 11.6%, not statistically significant) and the rates of cholestasis are extremely high suggesting that the definition may not be clinically relevant. However, if possible, preference should be for a lower limb PICC.

Central line insertion via the femoral vein, however, should be avoided as this is associated with a significant increase in CLABSI compared with non-femoral central catheters (risk ratio [RR] 1.76; 95% CI: 1.01, 3.07, $p=0.045$) [60].

Central line insertion is a strictly aseptic procedure and there needs to be a strong focus on sterility from the beginning to the end of the procedure. Maximal sterile barrier precautions during insertion, including wearing a mask and hat, performing a sterile hand wash, wearing a sterile gown and sterile gloves and covering the area with a large sterile drape reduces CLABSI [70, 84, 85]. Anything that hampers the ability to maintain sterility during the procedure needs to be avoided, including attempting insertion through incubator port holes [71].

Although it is clear that the infant's skin needs to be thoroughly disinfected with an appropriate antiseptic solution [70–72, 85], it is unclear as to what is the best solution for a preterm infant. In adult studies, chlorhexidine-based solutions are more effective than either povidone-iodine or alcohol-based solutions in reducing CLABSI [88–90]. In a meta-analysis comparing chlorhexidine, often with 70% alcohol, with povidone-iodine for the prevention of CLABSI the authors estimated that for every 1,000 catheter sites disinfected with chlorhexidine gluconate, 11 episodes of CLABSI would be prevented [88]. Two percent chlorhexidine gluconate in 70% alcohol is more effective at skin antisepsis than aqueous chlorhexidine gluconate without alcohol [95].

In preterm infants, the skin is fragile and in the first few days it is not fully keratinised and so is highly susceptible to chemical burns when concentrated chlorhexidine gluconate or chlorhexidine gluconate with alcohol is used as a skin disinfectant [92–94]. It is also important that iodine-based solutions are not used in preterm infants as these are easily absorbed and can result in iodine overload and significant hypothyroidism [86, 87]. For more mature or older infants, 0.5% chlorhexidine with 70% alcohol may be safe and effective and is more efficacious than povidone-iodine [91].

Thus chlorhexidine ± alcohol is the best solution for skin disinfectant, but the concentration and whether alcohol is used need to be a compromise between skin disinfectant and maintaining skin safety. It is therefore appropriate for each unit to develop a protocol for skin disinfection based on gestational age, days of life and weight of the infant (e.g. infants ≥1,000 g use chlorhexidine 0.5% in 70% alcohol, infants <1,000 g use aqueous chlorhexidine 0.1% in the first 2 weeks of life and then chlorhexidine 0.5% in 70% alcohol [116]).

Once preparation of skin disinfectant is over, the central line is ready for insertion. The procedure of inserting a PICC can be difficult and is not always successful on the first attempt, but to reduce CLABSI it is important that each attempt to insert the PICC uses a new introducing needle; "one needle, one puncture" [71].

Once the central line has been inserted, there needs to be constant vigilance and emphasis on sterility throughout the time the catheter is in situ. Although mentioned earlier, strict and thorough hand hygiene for *every* patient contact is an important aspect of neonatal care, but is of even more importance when there is a central line in situ [75–83, 117].

Organisms that cause CLABSI can gain entry to the blood stream through colonisation of the catheter hub and exit site and migration along the internal and external surface of a PICC [97, 100, 101]. It is therefore of utmost importance that catheter hub site colonisation is minimised. Any manipulation of the catheter can result in colonisation with evidence linking increased rates of CLABSI directly with catheter manipulation, particularly accessing the catheter for blood sampling and disconnecting the catheter for PN changes [96, 118]. Thus, PICC lines should not be used for blood sampling and this probably should be extended to sampling for a blood culture. PN should be hung for as long as the solution remains stable so that line changes are kept to a minimum. However, line changes do become necessary and thus any accessing of a PICC line should be treated as a strictly sterile procedure and all the same processes for line insertion should be followed with all connections thoroughly disinfected with a strong disinfectant such as 2% chlorhexidine and 70% alcohol [98, 99].

Care for the catheter exit site is also important. If the exit site is soiled, wet or dirty, then the site needs to be cleaned and the dressing changed antiseptically and even if visibly clean, regular disinfection of the site reduces CLABSI [96, 100, 101].

Prompt removal of the catheter is a key preventative measure. We have already discussed in this chapter how the risk of CLABSI is associated with the length of time the catheter is in situ [60–63]. Thus, regular assessment of the need for the central line to remain in situ needs to take place and there should be a concerted effort to advance enteral feeding so that as soon as the catheter is no longer required it can be immediately removed.

A simple measure that is effective in the prevention of CLABSI in infants with PICCs used for the delivery of PN is the use of heparin in the PN. Heparin as a continuous infusion in preterm infants prolongs the duration of PICC usability and reduces PICC obstruction without any adverse effects [119]. Heparin has been shown to reduce microthrombi formation that can act as foci for infection as well as reduce the ability of staphylococcal species from adhering to and colonising foreign surfaces [101, 120–123]. The use of heparin in adults receiving PN through a central venous catheter has been shown to reduce CLABSI [124]. In a study of 210 infants randomly assigned to PN with or without heparin at a concentration of 0.5 IU/mL, Birch et al. found a statistically significant reduction in all episodes of culture-positive CLABSI in those infants receiving heparin (RR 0.57, 95% CI 0.32, 0.98, $p=0.04$, number needed to treat 9, 95% CI 4.6, 212.4) [102]. We also found that in extremely low birth weight infants (<850 g) the reduction in CLABSI in the heparin group was protective against progression of intraventricular haemorrhage. There were no adverse effects associated with the use of heparin in preterm infants in this study or the study of Shah et al. [102, 119].

Combining Evidence-Based Risk Reduction Strategies into "Bundles" to Reduce Rates of CLABSI and Improve the Safety of PN Delivery to Preterm Infants

In the previous section, a large number of evidence-based risk reduction strategies have been discussed, all of which individually reduce the risk of CLABSI. There has been a recent publication showing that the combination of a number of these strategies into "a 'bundle' of evidence-based care elements for insertion and maintenance of central lines" [103] is extremely effective in reduced CLABSI [103].

The implementation of a number of quality improvement and risk reduction strategies rolled out collaboratively through several NICUs in California [104], in Connecticut [105] and among those

participating in the Vermont Oxford Network [76] all showed a reduction in CLABSI. Where most of these studies focused on a limited number of key quality improvement measures, the major referral NICUs in New York State collaborated to combine as many evidence-based risk reduction strategies to generate a central line insertion and maintenance "bundle" [106].

Having developed these "bundles", incorporating many of the measures discussed in the previous section of this chapter, all 18 NICUs in New York State adopted them along with educational and promotional programs and monitoring of "bundle-adherence" [103]. The prospective cohort study included more than 55,000 central-line days in both the pre-intervention ("bundle" implementation, education and promotion) and post-intervention periods. They were able to show an extremely promising clinical and statistically significant decrease in the rates of CLABSI, after adjusting for a change in definition of CLABSI between the two periods, of 40% state wide (RR 0.60, 95% CI 0.48, 0.75, $p<0.0005$).

Recognition, Diagnosis and Management of CLABSI

Prompt recognition, accurate diagnosis and appropriate management of CLABSI are as important in the reduction of adverse effects as the measures used to prevent the development of CLABSI. It is important that there is a strong ongoing educational emphasis within the unit so as to create a culture of vigilance and constant awareness of the possibility of CLABSI as early detection relies on recognition and then diagnosis [70, 75, 76]. Once there is a suspicion of CLABSI, then there needs to be prompt assessment and management including diagnosis and treatment.

The gold standard for the detection of CLABSI is the blood culture and although the adult literature would suggest that successful detection of bacteraemia increases with increases in blood volume drawn for culture [107], there is debate in the neonatal literature as to what volume is required for optimal detection. In the care of preterm infants, multiple blood tests are taken and often transfusions are required to replace the blood drawn. It is therefore important to be able to make an accurate diagnosis of CLABSI with the minimum volume of blood for culture. The lower the blood volume drawn, the higher the likelihood of false negative results; however a blood volume of 0.5 mL is likely to be adequate [109].

There is also no increase in detection when two blood cultures are drawn from separate sites compared with a single reasonable volume culture [108]. Although taking a culture from the PICC itself may increase the ability to make a diagnosis of CLABSI, accessing the line for blood sampling increases the risk of developing a CLABSI and should be avoided [96, 118].

Despite taking an adequate blood volume for culture, there is always the risk of false negative results and so it is important to use clinical judgement along with the measure of inflammatory mediators such as neutrophil count, immature to total neutrophil ratio, C-reactive protein and interleukin-6 [110, 111].

As we have discussed the most common organisms responsible for CLABSI in preterm infants are the CoNS. As common skin organisms it can at times be difficult to distinguish CoNS bacteraemia from contamination. This is important as over treatment is associated with an increase in multi-resistant bacteria within the NICU [112, 113]. Similar to the detection of CLABSI in the presence of a negative culture, the differentiation of positive culture from contamination relies on clinical judgement and the use of inflammatory mediators.

The management of CLABSI relies on antibiotic therapy and the judicious removal of infected PICCs. CoNS are the most common organisms associated with CLABSI and typically most hospital-acquired CoNS are methicillin resistant [111]. Thus empiric therapy should include either Vancomycin or Amikacin. Although most CoNS are sensitive to Amikacin, if CoNS is confirmed then Vancomycin should be the preferred antibiotic. Vancomycin use should be monitored as its use is associated with the development of vancomycin-resistant enterococci (VRE) [114]. We have already discussed the

importance of PICC lines in the delivery of PN to preterm infants and so when CLABSI develops a decision regarding whether to remove the line or not is required. Certainly, it may be possible to treat CLABSI for CoNS with the line in situ, but in certain instances it is safer to remove the line. If the blood culture is positive for *Staphylococcus aureus* or a gram-negative organism or where the culture remains positive for CoNS or any other organism despite appropriate treatment then it is safer to remove the line [115].

Summary

PN is essential for providing adequate nutrition to preterm infants, but there are significant risks associated with the delivery of PN and strategies to reduce these risks, improve safety and prevent disease associated with the use of PN in preterm infants are important components to provide effective neonatal care. In this chapter, we have discussed the non-infective complications arising from the delivery of PN to preterm infants and strategies to prevent or reduce the risks of these complications (see Table 12.1). We have also discussed the common and serious complications of CLABSI when delivering PN to preterm infants via umbilical catheters, central venous lines and PICCs and a number of strategies to reduce the rates of CLABSI (see Table 12.2). Promising results have come from combining strategies to prevent CLABSI into "bundles" [103] and one could expect that combining all the strategies, for both non-infective complications and CLABSI, discussed in this chapter will improve the safety and prevent disease associated with the delivery of PN to preterm infants.

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Chapter 13
Early Parenteral Nutrition and Subsequent Growth of Premature Infants

Kenneth Herrmann and Sean Woolen

Key Points

- Two cohorts of infants born before 30 weeks gestation received parenteral nutrition (PN) from birth. Both cohorts demonstrated successful postnatal growth. The second cohort ($n=53$) received 50–70 kcal/kg/day beginning 1 h after birth, 2 days earlier than the first cohort ($n=84$). The increase in PN did not change the weight lost after birth, the nadir weight day, or the time required to return to birth weight.
- An increase in the use of indomethacin for the treatment of a clinically significant PDA was observed in the second cohort, but no other common morbidities were changed significantly.
- The quality of postnatal growth at 36 weeks postmenstrual age was evaluated by three methods: the 10th percentile of the Alexander et al. reference for intrauterine weight; the exponential growth model of Patel et al. for weight; and the change in z scores (Δz) for weight, head circumference, and length, using the Fenton reference for intrauterine growth. The three methods were compared for their abilities to measure postnatal growth.
- Evaluation of the distribution of Δz growth for weight, head circumference, and length demonstrated a wide range. Infants with $\Delta z > 0$ growth were considered to have received nutrition adequate to support postnatal growth at the intrauterine growth rate.
- The first cohort was evaluated for catch-up growth by the change in z scores (Δz) for weight, head circumference, and length, using the CDC reference for infant growth at age 1 year. Complete catch-up was observed for the cohort for head circumference and length, but the weight catch-up for the cohort was minimal.
- Early growth gains by early PN did not result in later obesity.
- BSID-3 (Bayley) evaluations were in the normal range for a subset of infants born <28 weeks gestation. This observation supports the safety of early PN.

Keywords Growth • Growth and development • Infant • Premature • Parenteral nutrition

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R.R. Watson et al. (eds.), *Nutrition in Infancy: Volume 1*, Nutrition and Health,
DOI 10.1007/978-1-62703-224-7_13, © Springer Science+Business Media New York 2013

Background

This chapter concentrates on the importance of parenteral nutrition (PN) provided in the first days of life to premature infants born before 30 weeks gestation. The information presented in this chapter was collected in the context of quality improvement evaluations. The observational data has value for planning future research in clinical trials of early PN.

A retrospective cohort study recently evaluated infants born between 2003 and 2007. The emphasis of that study was early PN and the subsequent growth of these infants through 36 weeks postmenstrual age (PMA) [1]. The Eunice Kennedy Shriver National Institute of Child and Human Development (NICHD) Neonatal Network conducted a large study of premature infants' nutrition and postnatal growth in the mid-1990s. The NICHD study was selected to be a reference standard of postnatal growth.

The NICHD authors reported that 97% of infants with weights less than 1,500 g at birth had poor postnatal growth through 36 weeks PMA. Poor growth was defined as a weight less than the 10th percentile for intrauterine weight at 36 weeks gestation. Although postnatal and intrauterine physiologies are not equivalent, this weight was used to demonstrate restricted postnatal growth. NICHD authors suggested that improved postnatal nutrition may lead to improved postnatal growth [2–4].

Postnatal nutrition for infants born before 30 weeks gestation may be divided into three phases. The PN phase begins on the day of birth, when the majority of nutrition is provided parenterally. During this phase the infant's weight decreases by 6% or more due to water loss [5, 6]. A catabolic state caused by an inadequate nutrient supply may increase the weight loss in this phase. The transition phase occurs while the infant receives a combination of PN and enteral nutrition (EN). During this phase the infant's weight stabilizes and physiologic adaptations to extrauterine life continue. The EN phase occurs when EN provides the only source of nutrition. Limited nutrition in the PN phase and poor postnatal growth during the EN phase lead clinicians to provide EN supplements [7]. This chapter focuses on the PN phase for infants born before 30 weeks gestation and the consequences of PN on subsequent growth and development.

Early Parenteral Nutrition

Prior to birth, the placenta provides nutrition to the fetus from the mother's circulating nutritional resources. The goal of early PN is to provide nutrition similar to nutrition provided by the placenta. In clinical practice, PN is composed of macronutrients (glucose, amino acids, and lipids) and micronutrients (minerals and vitamins). There are few qualitative PN options commercially available for premature infants. Clinical PN solutions contain no potentially important biological factors (hormones or other modulators). Insulin provided for the treatment of hyperglycemia is an exception. Lacking qualitative options, early PN quality improvement is limited to quantitative adjustments of the macronutrient components.

Infants born before 30 weeks gestation receive little EN in the first days of life due to the risk of developing necrotizing enterocolitis (NEC). In past decades, PN in the first days of life consisted of glucose, minerals, and water. In recent years, premature infants have received PN solutions that contain all macronutrients and micronutrients beginning on the day of birth. The quantity of PN macronutrients used in clinical practice is variable [8, 9]. The variability of the clinical nutrition practice, observations of uniformly poor postnatal growth, and potential adverse consequences due to deficient nutrition create a need for observational studies of early PN.

Observational Study of Early PN and Postnatal Growth: 2003–2007

Observations began in 2003 by establishing a database that included demographics, nutrition, growth, common morbid events, and mortality. After sequential improvement steps, all infants received PN with glucose, amino acids, and lipid in stock solutions that began 1 h after birth. By 2 days of life all infants received PN that provided more than 50 kcal/kg/day.

Early PN was associated with better growth for the 2003–2007 cohort than the reference cohort. Instead of 3% in the reference cohort, over 50% of infants in the 2003–2007 cohort weighed more than the 10th percentile for intrauterine weight when they reached 36 weeks PMA. The improvement in growth at 36 weeks PMA occurred because less weight was lost in the PN phase of nutrition. Postnatal growth in the EN phase of nutrition was similar to the reference cohort. Because less weight was lost during the PN and transition phases, the growth curve of the 2003–2007 cohort in the EN phase of nutrition was shifted up. Greater early PN was not associated with more morbidity or mortality than the reference cohort. A detailed report for the 2003–2007 cohort was recently published [1].

It was concluded that less than 50 kcal/kg/day in the first 5 days of life had measurable adverse consequences on growth. Consequently, there was a concern that nutritional deficits in the first day of life could injure tissues with high metabolic requirements. Concern for PN provided at less than 50 kcal/kg/day in the first day of life led to a revision of the clinical nutrition practice in 2009. Ibrahim et al. concluded that providing more than 50 kcal/kg/day of PN at birth was safe [10]. However, concern that excessive quantities of PN may have adverse consequences explains the common practice of restricting early PN. The competing concerns were resolved by providing PN at birth that had previously been provided safely on the second day of life. By January 2009, infants received 50–70 kcal/kg/day in PN solutions beginning in the first hour after birth.

Observational Study of Increasing Early PN and Postnatal Growth: 2009–2010

The 2009 nutrition practice assured that infants received a minimum of 50 kcal/kg/day. Stock PN solutions contained glucose, 10 g/dL; amino acids (TrophAmine®10%, B. Braun Medical Inc., Irvine, CA), 2.5 g/dL; L-cysteine, 100 mg/dL; calcium, 300 mg/dL; heparin, 50 units/dL; and, they were provided at 110 mL/kg/day at 1 h after birth. A 20% lipid emulsion (Liposyn® III 20%, Hospira Inc., Lake Forest, IL) was provided separately to provide 2 g/kg/day for infants born before 26 weeks gestation and 3 g/kg/day for all other infants. Custom PN solutions containing glucose, amino acids, L-cysteine 40 mg/g amino acids, electrolytes, multiple vitamin solution (MVI®-Pediatric, Armour Pharmaceutical Co., Chicago, IL), and carnitine (7 mg/dL) were provided on the first afternoon after delivery. Stock solutions of normal saline were additionally provided to maintain catheter patency. Acetate replaced chloride for the correction of metabolic acidosis. Data was collected from 54 infants born in 2009–2010, and compared to the 84 infants born in 2003–2007. The demographic characteristics were similar for both cohorts (Table 13.1). The clinical care provided to both cohorts differed in the first 2 weeks of life chiefly due to the PN provided during the first 2 days of life (Fig. 13.1).

Ethics

The current review was completed in the context of quality improvement. Similar to the recent cohort report by Senterre and Rigo [7], a randomized control trial that provided inadequate early nutrition to one group was not ethically appropriate. Full formal IRB reviews approved the collection of postnatal growth after discharge at 1 year and the postnatal growth and developmental assessments at 2 years.

Table 13.1 Demographics, morbidity, and mortality for two cohorts

	2003–2007 Cohort		2009–2010 Cohort		
	n	%	*n*	%	*P*
Demographics					
Male	50	60	35	66	0.44
White ethnicity	65	77	39	74	0.61
Small for gestational age (z_{Fenton} <−1.27)	4	5	3	6	0.87
Singleton	61	73	34	64	0.30
Morbidity					
Chronic lung disease	38	45	19	36	0.28
Clinical sepsis	36	43	17	32	0.21
Blood stream infection	12	14	8	15	0.90
Severe intraventricular hemorrhage	4	5	3	6	0.82
NEC + SIP, > or = to Bell stage 2	1	1	4	8	0.08
Pressor agent	5	6	2	4	0.87
Indomethacin: prophylaxis for brain hemorrhage	48	57	34	64	0.42
Indomethacin: treatment for PDA	21	25	31	58	<0.001
PDA surgical ligation	8	10	4	8	0.69
Insulin for hyperglycemia	10	12	14	26	0.03
Conjugated bilirubin >34 μmol/L (>2 mg/dL)	17	20	19	36	0.04
Blood urea nitrogen >11 mmol/L (>30 mg/dL)	46	55	38	72	0.05
Postnatal steroid	30	36	20	38	0.81
Transfer to another NICU, no return	8	7	8	11	0.37
Cohort Size (Birth−(death + transfer))	84	100	54	100	
Necrotizing enterocolitis (NEC)					
Total NEC + SIP, > or = to Bell stage 2	5	5	9	12	0.11
NEC + SIP, transfered	4	4	5	7	0.20
Suspected NEC	1	1	4	5	0.16
Suspected SIP	4	4	5	7	0.20
NICU admissions <30 weeks	109	100	74	100	
Mortality					
Total survivors (cohort + transfers)	92	84	64	86	0.70
Death	17	16	10	14	0.70

P values in the table have not received a Bonferroni correction. After applying a Bonferroni correction for *P*, only increased indomethacin treatment for a symptomatic PDA was statistically different

NEC necrotizing enterocolitis, *SIP* spontaneous intestinal perforation, *PDA* patent ductus arteriosus, *NICU* neonatal intensive care unit

The entire project was reviewed and approved by the Research Institute of Deaconess Clinic in accordance to the policy and procedures of the Research Oversight and Privacy Committee of Deaconess Health System.

Morbidity and Mortality

The mortality and common morbidities were compared for the two cohorts. There were no differences in the mortality or in the need to transfer to another hospital. Although morbidities were similar, an increase in the incidence of patent ductus arteriosus (PDA) was both statistically and clinically significant. More infants in 2009–2010 received therapeutic indomethacin to induce PDA closure. However, there was no increase in the surgical treatment of PDA.

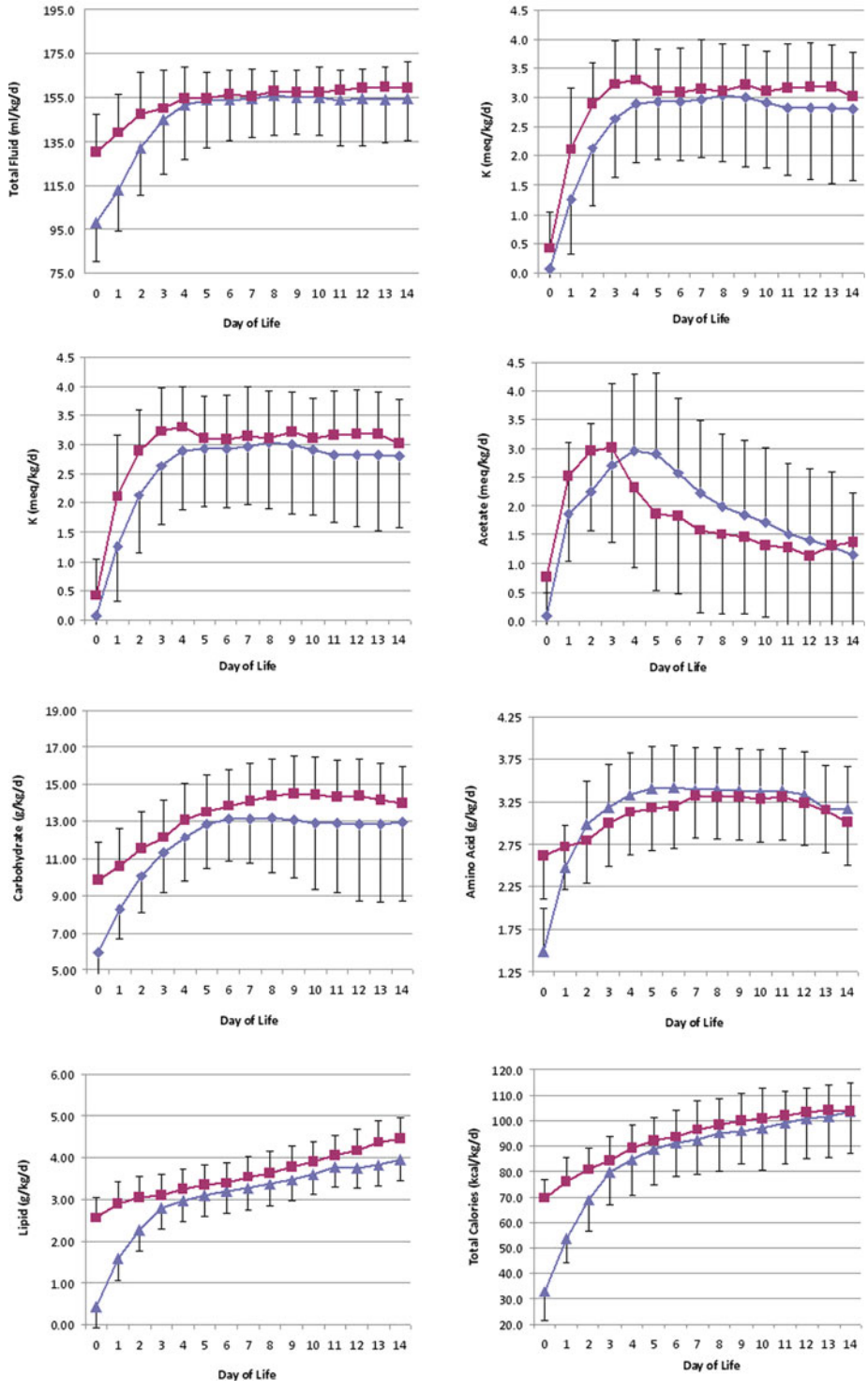

Fig. 13.1 Fluid, electrolyte, and macronutrient administration during the first 2 weeks of life. *Error bars* represent standard deviations. Nutrition on day "0" represents the day of birth and had a variable duration that was less than 24 h. Subsequent days lasted 24 h. No significant differences were observed after day 2 ($P > 0.05$). The 2003–2007 cohort appears in *blue* with *triangles*; the 2009–2010 cohort appears in *red* with *squares*

Reduction of chronic lung disease (CLD) and clinical sepsis (events without positive blood culture) were trends in the 2009–2010 cohort. Although not statistically significant, these trends may have clinical importance.

Values of blood urea nitrogen (BUN) greater than 11 mmol/L (30 mg/dL) increased in the 2009–2010 cohort. The BUN may increase due to catabolism of endogenous protein, excess amino acid administration relative to nitrogen utilization for protein synthesis, or insufficient administration of fluid for elimination of nitrogen by the kidney. The increase in amino acid administration at birth for the 2009–2010 cohort was accompanied by increased calorie and fluid administration. The maximum BUN values were not different for the two cohorts. The mean maximum BUN for the cohorts was as follows: 12.8 mmol/L (SD 5.3) for 2003–2007 and 11.4 mmol/L (SD 3.1) for 2009–2010 ($P > 0.5$).

There was a trend for conjugated bilirubin values greater than 34 μmol/L (2 mg/dL) to increase in the 2009–2010 cohort. Conjugated bilirubin elevations due to TPN typically occur more than 3 weeks after birth. Maximum conjugated bilirubin values were not different for the two cohorts. The mean maximum conjugated bilirubin was as follows: 27 μmol/L (SD 27) for 2003–2007 and 36 μmol/L (SD 36) for 2009–2010 ($P = 0.2$). However, only 55 of 84 (66%) infants in the 2003–2007 cohort had conjugated bilirubin measurements and all 54 (100%) of the 2009–2010 infants had measurements.

An increase in NEC was noticed in 2009. NEC occurred after introduction of bovine supplements to EN. NEC was not associated with exclusively human milk EN. In 2010, EN with bovine products was delayed until after EN exceeded 150 mL/kg/day and the age exceeded 32 weeks PMA.

The NEC category included episodes of suspected spontaneous intestinal perforation (SIP). An additional evaluation of NEC and SIP for all infants admitted to the neonatal intensive care unit (NICU) was included (Table 13.1).

Insulin was provided more frequently in 2009–2010 than in 2003–2007 due to an evolving change in clinical management of hyperglycemia. In earlier years it had been common practice to treat hyperglycemia by reducing glucose administration. The reduction of glucose reduced calories for the smallest infants that frequently had limited lipid calories. Lipid limitation prevented triglyceride level elevation (>1.7 mmol/L; >150 mg/dL). A priority to maintain calories at levels above 50 kcal/kg/day increased the rate of insulin use in 2009–2010.

Early PN, Nadir Weight, and Return to Birth Weight

The effect of increased PN provided in 2009–2010 was evaluated for short-term weight changes. The amount of weight lost after birth, the day of the nadir weight, and the day of the return to birth weight were not significantly different. These findings demonstrated that increased fluids in the first 2 days after birth did not lead to an accumulation of water. The diuresis and the associated water weight loss that is attributed to the transition from intrauterine to extrauterine life proceeded despite the increase in water administration (Table 13.2).

Tenth Percentile Growth at 36 Weeks PMA

Nutrition provided at less than 50 kcal/kg/day may have adverse consequences. Potential consequences include a catabolic state leading to poor postnatal somatic growth and injury to tissues in a state of high metabolic need. Enterocyte injury due to inadequate early PN might later cause malabsorption, reduce the efficacy of EN, and reduce growth during the EN phase. An improvement in growth at 36 weeks PMA would tend to support a concept of a minimum energy threshold for enterocytes. However, achievement of 10th percentile weight at 36 weeks PMA was observed less often in

Table 13.2 There was no effect of increased fluid and nutrition in 2009–2010 on the nadir weight, the day of nadir weight, or the day to return to birth weight. Mean (SD)

			Nadir weight	Nadir weight	Regain birth weight
GA	*N*	Cohort	% Weight lost[a]	Day	Day
24–25 weeks					
	13	2003–2007	7.2 (6.2)	3.2 (2.1)	6.0 (4.1)
	8	2009–2010	6.3 (4.5)	2.6 (1.5)	5.8 (5.1)
		P	0.74	0.48	0.90
26–27 weeks					
	26	2003–2007	5.2 (4.1)	2.5 (1.2)	6.0(3.4)
	12	2009–2010	4.5 (4.7)	1.9 (2.0)	4.8(4.8)
		P	0.31	0.25	0.40
28–29 weeks					
	45	2003–2007	6.7 (4.9)	3.0 (1.5)	5.9 (3.2)
	34	2009–2010	5.9 (5.9)	2.6 (1.9)	6.0 (4.9)
		P	0.50	0.27	0.88
Total					
	84	2003–2007	6.6 (5.0)	2.9 (1.5)	5.9 (3.6)
	54	2009–2010	5.6 (5.0)	2.4 (1.8)	5.7 (4.9)
		P	0.29	0.13	0.76

GA gestational age

[a]Values are presented as mean (SD) unless otherwise indicated

Table 13.3 Postnatal growth above the 10th percentile of Alexander et al. intrauterine growth at 36 weeks PMA for two cohorts of infants born less than 30 weeks gestation

	2003–2007		2009–2010		
Birth weight (g)	*n*	>10th centile (%)	*n*	>10th centile (%)	*P*
501–750	9	44	7	14	0.29
751–1,000	26	58	10	40	0.46
1,001–1,250	26	58	20	20	0.02
1,251–1,500	15	87	12	50	0.09
>1,500	4	100	1	100	1

Infants with birth weights less than the 10th percentile ($z < -1.27$) were excluded

2009–2010 compared with 2003–2007 (Table 13.3). The increased energy provided in the early PN phase did not improve growth in the EN phase.

While increased nutrition in the first 2 days of life may prove beneficial in other respects, it did not improve 10th percentile growth at 36 weeks PMA. Reduced use of bovine products for EN may have contributed to the reduction of 10th percentile growth in 2009–2010. In 2003–2007, 51 infants (61%) achieved the10th percentile of Alexander et al. intrauterine growth [11]. Only 16 infants (30%) in the 2009–2010 cohort achieved 10th percentile growth. The reduction in growth was statistically significant ($P < 0.001$). The 10th percentile growth of the 2009–2010 cohort remained better than the NICHD reference cohort (501–750 g, $P = 0.01$; 751–1,000 g, $P < 0.001$; 1,001–1,250 g, $P = 0.01$; 1,251–1,500 g, $P < 0.001$).

The infants in progressively larger weight categories had progressively better 10th percentile growth rates. In order to understand postnatal growth better, two additional methods to evaluate postnatal growth were evaluated: growth velocity (GV) and the change in z scores (Δz).

Methods to Measure Postnatal Growth of Premature Infants

Tenth Percentile Growth

The AAP Committee on Nutrition suggested that optimal postnatal growth of the premature infant should mimic intrauterine growth [12, 13]. However, fundamental physiologic changes occur with parturition. Weight loss occurs in the first days of life due to a decrease in body water. Infants in the 2009–2010 cohort received 135 mL/kg/day and 70 kcal/kg/day at birth and they typically lost 6% of their birth weight by the third day of life (Fig. 13.1 and Table 13.2). Using the Fenton standard of intrauterine growth [14], a 6% weight loss of a 1,000 g infant born at 27 weeks gestation results in a loss of 11 percentile points. The weight loss in the first days after birth is incongruous with normal intrauterine growth because healthy intrauterine growth sustains no loss.

Infants with birth weights close to the 10th percentile will predictably weigh less than the 10th percentile after they return to birth weight. If these infants grow at a rate that mimics intrauterine growth thereafter, they will demonstrate postnatal growth restriction by the 10th percentile method. The 10th percentile method of evaluating postnatal growth favors infants with larger sizes relative to their gestational ages. Because infants older than 29 weeks were excluded, infants in the 1,250–1,500 g category were relatively large for their gestational ages (Table 13.3).

Birth Weight and the Exponential Growth Velocity (GV) Model

Patel et al. reviewed methods to determine postnatal growth velocities [15, 16]. The best model used exponential growth based on two values: the weight on day 1 (birth) and a subsequent postnatal weight measured on the nth day.

$$\text{Growth Velocity} = \frac{[1000 \times \ln(W_n / W_1)]}{[D_n / D_1]}$$

Growth was determined by the GV method for the 2003–2007 and 2009–2010 cohorts (Table 13.4). The GV declined as the birth weight category increased; in contrast, 10th percentile growth improved as the birth weight category increased (Tables 13.3 and 13.4).

The 10th percentile and GV methods agreed that growth was different in 2009–2010 for the 1,001–1,250 g category.

Table 13.4 Growth velocities based on an exponential model of growth

Birth weight (g)	Cohort period	GA	Birth *z*	*n*	GV (g/kg/day)	SD	P^a	P^b
501–750	2003–2007	25.2	–0.43	13	15.0	2.0	0.38	0.13
	2009–2010	25.4	–0.99	11	13.5	2.9		
751–1,000	2003–2007	26.6	–0.25	26	14.3	2.4	0.33	0.34
	2009–2010	27.6	–0.48	10	13.4	2.4		
1,001–1,250	2003–2007	28.0	–0.06	26	14.1	2.0	<0.001	<0.001
	2009–2010	28.5	–0.05	20	11.7	1.7		
1,251–1,500	2003–2007	28.7	0.45	15	12.0	1.6	0.22	0.22
	2009–2010	29.0	0.44	12	11.2	1.9		

GA gestational age, *GV* growth velocity; *SD* standard deviation
[a] *U* test
[b] *t*-test

Table 13.5 The influence of gestational age on postnatal growth expressed by the exponential growth velocity model

Gestational age	Cohort period	Birth *z*	*n*	GV (g/kg/d)	SD	P^a	P^b
24–25	2003–2007	0.29	13	14.0	1.5	1	0.65
	2009–2010	–0.56	8	13.6	2.8		
26–27	2003–2007	–0.01	26	14.6	1.9	0.06	0.02
	2009–2010	–0.19	12	13.0	2.3		
28–29	2003–2007	–0.14	45	13.4	2.6	0.003	0.003
	2009–2010	–0.10	34	11.7	2.0		
All	2003–2007	–0.12	84	13.8	2.3	<0.001	<0.001
	2009–2010	–0.19	54	12.3	2.3		

GA gestational age, *GV* growth velocity, *SD* standard deviation
[a]*U* test
[b]*t*-test

Table 13.6 The influence of relative size at birth on postnatal growth expressed by the exponential growth velocity model

Birth *z*	Cohort period	GA	Birth *z*	*n*	GV (g/kg/day)	SD	P^a	P^b
<–0.5	2003–2007	27.8	–0.95	24	14.9	2.9	0.05	0.04
	2009–2010	25.5	–0.95	16	12.9	2.9		
–0.5 to 0.5	2003–2007	27.2	0.01	39	13.8	1.8	<0.001	<0.001
	2009–2010	28.1	–0.05	28	12.0	2.0		
>0.5	2003–2007	27.0	0.92	21	12.8	1.9	0.46	0.27
	2009–2010	28.3	0.75	10	12.0	2.0		

GA gestational age, *GV* growth velocity, *SD* standard deviation
[a]*U* test
[b]*t*-test

Gestational Age and the Exponential Growth Velocity (GV) Model

The cohorts were arranged by gestational age and evaluated for GV differences (Table 13.5). From this perspective, less GV was observed in 2009–2010 for older gestational age infants. This observation is the same as in Table 13.4 because older gestational age infants had larger birth weights.

Relative Size at Birth and the Exponential Growth Velocity (GV) Model

In addition to birth weight and gestational age, the relative size for gestational age may play a role in determining postnatal growth. Birth may relieve small for gestational age infants from restricting intrauterine conditions. Birth may deprive large for gestational age infants of their growth promoting intrauterine environment. When arranged by relative size at birth, infants in the 2003–2007 cohort with low birth *z* scores ($z < -0.5$) had better GV growth than those with high birth *z* scores ($z > 0.5$). This trend was not observed in the 2009–2010 cohort (Table 13.6).

Arrangement of the data based on birth weight, gestational age, and birth *z* score provides three perspectives of GV. There was a trend for the smallest infants and infants relatively small for their gestational age to have larger GV.

There was a trend for less 10th percentile and less GV growth in 2009–2010. The 10th percentile weight achievements increased with increasing birth weight categories while the GV declined with increasing birth weight categories. Percentile growth was evaluated statistically as an arbitrary

Table 13.7 Comparison of two cohorts by birth weight and Δ*z* growth from birth to 36 weeks PMA

					Δ*z* growth at 36 weeks PMA					
Birth weight (g)	Cohort period	GA	Birth *z*	*n*	W	*P*[a]	HC	*P*[a]	L	*P*[a]
501–750	2003–2007	25.2	−0.43	13	−1.39	0.90	−0.8	0.62	−1.5	0.11
	2009–2010	25.4	−0.99	11	−1.53		−1.0		−2.6	
751–1,000	2003–2007	26.6	−0.25	26	−0.88	0.52	−0.5	0.22	−1.0	0.52
	2009–2010	27.6	−0.48	10	−1.12		−0.8		−1.3	
1,001–1,250	2003–2007	28.0	−0.06	26	−0.74	0.001	−0.3	0.06	−1.0	0.19
	2009–2010	28.5	−0.05	20	−1.32		−0.7		−1.3	
1,251–1,500	2003–2007	28.7	0.45	15	−1.00	0.37	−0.7	0.34	−0.9	0.19
	2009–2010	29.0	0.44	12	−1.21		−0.9		−1.3	

PMA postmenstrual age, *GA* gestational age, *W* weight, *HC* head circumference, *L* length
[a]*U* test

nominal value, the 10th percentile. Growth velocities provided numerical values that were evaluated as continuous variables. Both methods identified that the 1,001–1,250 g category had significantly less growth in 2009–2010. The GV for all infants was 1.5 g/kg/day less in 2009–2010 than in 2003–2007 ($P < 0.001$) (Table 13.5).

The Δz Model of Postnatal Growth at 36 Weeks PMA

Postnatal growth has been expressed using *z* scores. The *z* score is also known as the standard deviation score (SDS). When *x* is the measured value in a population with a known mean (μ) and standard deviation (σ), then:

$$z = \frac{(x - \mu)}{\sigma}$$

Published studies of postnatal growth have used graphs of cohort *z* scores to demonstrate that *z* scores decline after birth [17–25]. A *z* score change (Δ*z*) from birth to 36 weeks PMA expresses growth in relation to a corresponding size for gestational age at birth.

$$\Delta z = z_{36\,\text{weeks}} - z_{\text{birth}}$$

Positive Δ*z* values identify postnatal growth that is faster than the rate of intrauterine growth. Negative Δ*z* values indicate slower rates of growth. The Δ*z* values are measured by standard deviation units rather than SI dimensions (g/day, g/kg/day, or cm/day). The Δ*z* method compares weight, head circumference, and length for their relative growth.

Birth Weight and the Δz Model of Postnatal Growth at 36 Weeks PMA

A *z* score reference provided by Fenton included intrauterine growth data originally published by Babson and Benda [14, 26]. The Fenton values for *z* were used to calculate Δ*z* growth for weight, head circumference, and length. There was a trend for reduced growth in the 2009–2010 cohort for 12 pairs of measurements (Table 13.7). The only significantly different value was the Δ*z* for weight in the birth weight 1,001–1,250 g category. This category was also significantly different when measured by the 10th percentile and GV methods.

Table 13.8 Two cohorts were compared by gestational age and Δ*z* growth from birth to 36 weeks PMA

				Δ*z* growth at 36 weeks PMA					
Gestational age (weeks)	Cohort period	Birth *z*	*n*	W	*P*[a]	HC	*P*[a]	L	*P*[a]
24–25	2003–2007	0.29	13	−1.56	0.80	−1.1	0.94	−2.0	0.11
	2009–2010	−0.56	8	−1.48		−1.0		−2.5	
26–27	2003–2007	−0.01	26	−0.70	0.11	−0.5	0.05	−0.9	0.02
	2009–2010	−0.19	12	−1.24		−1.0		−2.0	
28–29	2003–2007	−0.14	45	−0.90	0.004	−0.4	0.06	−0.9	0.19
	2009–2010	−0.10	34	−1.28		−0.7		−1.2	
All									
	2003–2007		84	−0.94	0.01	−0.5	0.05	−1.0	0.01
	2009–2010		54	−1.10		−0.7		−1.3	

PMA postmenstrual age, *W* weight, *HC* head circumference, *L* length
[a]*U* test

Table 13.9 Two cohorts were compared by relative size at birth and Δ*z* growth from birth to 36 weeks PMA

					Δ*z* growth at 36 weeks PMA					
Birth *z*	Cohort period	GA	Birth *z*	*n*	W	*P*[a]	HC	*P*[a]	L	*P*[a]
< −0.5	2003–2007	27.8	−0.95	24	−0.76	0.03	−0.27	0.09	−0.98	0.07
	2009–2010	25.5	−0.95	16	−1.46		−0.75		−1.91	
−0.5 to 0.5	2003–2007	27.2	0.01	39	−0.86	0.01	−0.53	0.07	−1.14	0.13
	2009–2010	28.1	−0.05	28	−1.29		−0.83		−1.43	
>0.5	2003–2007	27.0	0.92	21	−1.28	0.25	−0.81	0.97	−0.97	0.33
	2009–2010	28.3	0.75	10	−1.06		−0.95		−1.28	

PMA postmenstrual age, *W* weight, *HC* head circumference, *L* length
[a]*U* test

Gestational Age and the Δz Model of Postnatal Growth at 36 Weeks PMA

The two cohorts were arranged in three gestational age categories and their Δ*z* growth was evaluated (Table 13.8). Agreeing with the GV model, the 28–29 week gestation category demonstrated less Δ*z* weight growth in 2009–2010. In addition, the 26–27 week gestation category had significantly less growth for head circumference and length. Significantly less growth was demonstrated in 2009–2010 when all gestational ages were combined. The 2009–2010 cohort had less Δ*z* growth for weight, head circumference, and length by 0.2, 0.2, and 0.3 units, respectively.

Relative Size at Birth and the Δz Model of Postnatal Growth at 36 Weeks PMA

The two cohorts were arranged in three relative weight categories and their Δ*z* growth was evaluated (Table 13.9). The 2003–2009 cohort demonstrated a trend for Δ*z* weight gain to favor light for gestational age infants and the 2009–2010 cohort favored the heavy for gestational age infants. No clear trend pattern was observed for head circumference or length using this arrangement and none of the cohort comparisons were statistically different for head circumference and length.

Interpretation of Δz Growth at 36 Weeks PMA

The Δ*z* method used reference intrauterine growth data to measure postnatal growth. But, the intrauterine and postnatal periods have different physiologies. Accordingly, an adjustment is required. Using the Fenton growth reference, a 6% decline in weight after birth of a 1,000 g, a 27-week gestation infant corresponds to a decrease of 0.25 in the *z* score. For this reason, postnatal weight that mimics intrauterine growth will have Δ*z* values less than zero. Because the physiologic body water content continues to decline through 36 weeks PMA [5], the range of normal Δ*z* requires an additional negative adjustment. Allowing for redistribution of water and a modest allowance for normal variations in postnatal growth, a Δ*z* value of −0.5 represents normal intrauterine growth from birth through 36 weeks PMA. Accordingly, infants with Δ*z* values that exceed −0.5 have postnatal growth that exceeds normal intrauterine growth for weight.

When applying Δ*z* growth to the head circumference at 36 weeks PMA, an adjustment similar to the weight should be considered. Water loss in the head will produce corresponding losses of head volume and circumference measurements. Similar to weight, an adjustment of Δ*z* growth by −0.5 will occur in 1 week. If the head growth follows the intrauterine pattern thereafter, a value of −0.5 is appropriate for normal Δ*z* head growth through 36 weeks PMA.

Changing body water content does not affect bone length. The interconnecting tissues contribute little to the total length. An adjustment of normal Δ*z* growth for length is not necessary.

The Distribution of 2003–2007 Δz Growth at 36 weeks PMA

The mean values of cohort growth represent growth for the entire sample. Standard deviation and range values help describe the variability of growth in the sample (Table 13.10). The distribution of values in the sample provides an additional perspective of growth. The distribution of Δ*z* growth at 36 weeks PMA was expressed by dividing Δ*z* growth into five categories (Table 13.11). The first category, $\Delta z > 0$, represents growth clearly greater than the normal intrauterine rate. The second category, $0 > \Delta z > -0.5$, includes normal growth consistent with physiologic changes in body water after birth. The final category, $\Delta z < -2$, has been defined as growth failure in other studies and has been associated with poor neurodevelopmental outcome [27]. The intermediate growth categories were divided into equal ($\Delta z = 0.5$) increments.

The growth distribution presented in Table 13.11 provides an important perspective that is not apparent from mean values of Δ*z* growth. Some infants had normal postnatal growth; others grew poorly; and Δ*z* growth was broadly distributed.

Using the AAP recommendation to provide nutrition that supports growth at the intrauterine rate, it may be concluded that infants with $\Delta z > -0.5$ had normal growth and their nutritional requirements had been met. The same nutrition was associated with poor growth for the remainder. There was no explanation of their growth deficiencies.

The sample population distribution provided important information for choosing statistical tests. Small, asymmetric samples are more appropriately evaluated by the Mann–Whitney *U* test, rather than the *t*-test. The asymmetric distribution for weight in Table 13.11 demonstrates that the Mann–Whitney *U* test was more appropriate than the *t*-test in Table 13.5.

The distribution of Δ*z* for head circumference growth is distributed differently than Δ*z* growth for weight; it is more symmetric. The distribution indicates that brain growth differs from somatic growth. Poor neurodevelopmental outcome is associated with poor nutrition and poor growth [28–31]. For this reason, it is important to include head circumference measurements in the evaluation of postnatal growth. Three infants (4%) in the 2003–2007 cohort and none (0%) in the 2009–2010 cohort had a

Table 13.10 The 2003–2007 cohort growth expressed in kg and cm at three ages

			Birth[a]		36-week PMA				1 Year evaluation[b]			
GA	*n*	W	HC	L	W	HC	L	*n*	Age	W	HC	L
24.5 (0.5)	13	0.721 (0.11)	22.2 (0.7)	32 (2.3)	2.28 (0.28)	30.6 (0.8)	42.4 (2.5)	10	8.9 (0.7)	8.04 (0.7)	44 (1.1)	71.1 (1.6)
26.5 (0.5)	26	0.934 (0.15)	24.8 (1.0)	34.5 (2.5)	2.43 (0.4)	32.7 (1.2)	43.7 (2.5)	22	9.5 (0.9)	8.38 (1.5)	44.8 (2.1)	72.2 (3.8)
28.6 (0.5)	45	1.197 (0.25)	26.8 (1.6)	37.4 (2.7)	2.3 (0.4)	32.4 (1.3)	43.8 (2.5)	34	9.8 (1.6)	8.45 (1.0)	45.6 (2.2)	71.7 (2.9)
27.3 (1.7)	84	1.040 (0.27)	25.5 (2.1)	35.7 (3.1)	2.345 (0.37)	32.2 (1.4)	43.7 (2.4)	66	9.6 (1.3)	8.38 (1.12)	45.1 (2.1)	71.8 (3.1)

GA gestational age (weeks), *HC* head circumference (cm), *L* length (cm), PMA, postmenstrual age (weeks), *W* weight (kg)

[a]Values are presented as mean (SD) unless otherwise indicated

[b]The 1-year chronologic age evaluation reported in the table is corrected for premature birth: the corrected age (months)

Table 13.11 The 2003–2007 cohort growth expressed in terms of Δz from birth to 36 weeks PMA

		Distribution of Δz growth at 36 weeks postmenstrual age						
	GA	> 0	0.0 to > –0.5	–0.5 to > –1	–1 to > –1.5	–1.5 to > –2	< or = –2	Mean Δz
Weight								
	24–25	1	0	1	2	6	3	–1.56[ab]
	26–27	2	9	5	8	1	1	–0.70[a]
	28–29	2	10	18	7	6	2	–0.90[b]
	All	5	19	24	17	13	6	–0.94
Head circumference								
	24–25	0	2	2	6	2	1	–1.1[cd]
	26–27	7	5	7	5	1	1	–0.4[c]
	28–29	11	12	12	8	2	0	–0.4[d]
	All	18	19	21	19	5	2	–0.5
Length								
	24–25	0	0	1	3	2	7	–2.0[ef]
	26–27	5	5	7	1	3	5	–0.9[e]
	28–29	5	9	7	9	11	4	–0.9[f]
	All	10	14	15	13	16	16	–1.0

The table demonstrated the distribution symmetry of postnatal growth for individuals in the cohort
[a]$P=0.001$; [b]$P=0.002$; [c]$P=0.02$; [d]$P=0.003$; [e]$P=0.03$; [f]$P=0.02$

$\Delta z < -2$ for head circumference. Both early PN practices were successful at preventing poor head circumference growth.

There was a wide distribution of Δz for length. Sixteen infants (19%) in the 2003–2007 cohort and 12 (22%) in the 2009–2010 cohort had length $\Delta z < -2$. However, the following section shows that this was not a clinically significant problem. None had a $\Delta z < -2$ for length at 1 year.

The mean Δz growth for length and weight were equal. Equal weight and length Δz growth suggest proportional growth. However, after adjusting Δz growth of weight for water loss, the Δz growth for weight exceeded the Δz growth for length. Greater weight compared to length at 36 weeks PMA raises a potential concern for having increased body fat rather than symmetrically improving growth. An evaluation of weight for length at 1 year provided a different conclusion: they were not obese.

Δz Scores Measure Postnatal Growth at 1 Year

The Δz method evaluated growth for the 2003–2007 cohort at 1 year. Birth z scores of Fenton intrauterine growth and CDC data for term infant growth were compared [14, 32]. The z values at 1 year were computed after correcting the age at evaluation for premature birth. No other adjustments were required because the z scores were determined in the state of physiology that was appropriate to the reference standard.

$$\Delta z = z_{1\,\text{year}} - z_{\text{birth}}$$

Data for 66 infants (79%) of the 2003–2007 cohort were available for evaluation at 1 year. The distribution of Δz growth, mean Δz growth at 36 weeks PMA, and Δz growth at 1 year are presented (Table 13.12).

Positive changes in Δz demonstrated that there had been catch-up growth from 36 weeks PMA to 1 year. The weight Δz value of –0.9 at 36 weeks PMA improved to –0.7 at 1 year. Catch-up growth for weight was modest in this interval.

Table 13.12 The 2003–2007 cohort growth expressed in terms of Δz from birth to 36 weeks PMA and Δz from birth to 1-year chronologic age

		Distribution of Δz growth at 1 year Chronologic age						Mean Δz at 36-week PMA ($n=66$)	Mean Δz at 1-y CA ($n=66$)
	GA	>0	0.0 to >-0.5	-0.5 to >-1	-1 to >-1.5	-1.5 to >-2	< or = -2		
Weight									
	24–25	2	1	2	1	1	3	−1.5[ab]	−1.2
	26–27	5	3	7	1	2	4	−0.8[a]	−0.9
	28–29	11	9	5	4	3	2	−0.9[b]	−0.5
	All	18	13	14	6	6	9	−0.9	−0.7
Head circumference									
	24–25	3	1	2	3	1	0	−1.0[cd]	−0.3
	26–27	10	4	1	4	1	2	−0.5[c]	0
	28–29	19	5	7	1	0	2	−0.5[d]	0.3
	All	32	10	10	8	2	4	−0.5	0.1
Length									
	24–25	6	3	1	0	0	0	−1.9[ef]	0.3
	26–27	16	3	2	0	1	0	−0.9[e]	0.6
	28–29	18	6	5	5	0	0	−0.9[f]	0.2
	All	40	12	8	5	1	0	−1.1	0.4

The table demonstrates the distribution symmetry of postnatal growth for individuals in the cohort
PMA postmenstrual age; *CA* chronologic age
[a]$P=0.02$; [b]$P=0.02$; [c]$P=0.02$; [d]$P=0.03$; [e]$P=0.03$; [f]$P=0.02$

The growth deficits for head circumference at 36 weeks PMA were not present at 1 year; catch-up growth was complete. Thirty-one (47%) of the infants had Δz growth>0 for head circumference, consistent with a normal distribution of postnatal growth. The two infants with head circumference $\Delta z<-2$ at 36 weeks PMA had catch-up growth at 1 year: Δz growth at 1 year was 0.4 and −1.5. Four (6%) infants developed $\Delta z<-2$ head growth at 1 year that had not been present at 36 weeks PMA.

The Δz growth for length was normal at 1 year and exceeded the Δz for weight. These infants had weights that were relatively light for their length; therefore, they were not obese. A concern that obesity was a consequence of improved growth in the 2003–2007 cohort relative to the reference cohort was not supported by the measurements obtained at 1 year chronologic age. None of the 18% with $\Delta z<-2$ for length at 36 weeks PMA remained $\Delta z<-2$ for length at 1 year.

The Δz growth for infants born at 24–25 weeks gestation was less than older infants at 36 weeks PMA. There was a nonsignificant trend for 24–25 weeks gestation infants to have less Δz growth for weight and head circumference at 1 year.

Influence of Birth Weight, Birth z, and Gestational Age on Postnatal Growth

Table 13.9 demonstrated the ability of three methods to evaluate cohorts for statistically different growth. Each method provided similar conclusions. In a series of evaluations, a significant difference in 2009–2010 growth was identified for older, larger birth weight, smaller for gestational age infants. Consequently, the cohorts were evaluated by linear regression for possible associations of birth weight, gestational age, and relative size at birth. However, the *r* coefficients demonstrated only weak associations (Table 13.13). Gestational age and postnatal growth were evaluated by Spearman rank order regression analysis than also demonstrated only weak associations.

The weight, head circumference, and length relative size for gestational age at birth (z) was moderately associated with the subsequent sizes (z) at 36 weeks PMA. There was a moderate association

Table 13.13 Linear regression analysis for the associations of birth weight, birth *z*, and gestational age on postnatal growth indicated that there was no strong relationship

	Cohort period	Birth weight	Birth *z*	Gestational age
GV (g/kg/day)	2003–2007	0.42	0.40	0.12
	2009–2010	0.40	0.25	0.36
Δz Weight at 36	2003–2007	0.13	0.24	0.30
Weeks PMA	2009–2010	0.14	0.12	0.11

The *r* coefficients in the table, all <0.5, are regarded as weak
GV growth velocity, *PMA* postmenstrual age

Table 13.14 Linear regression analysis for the association of *z* scores at birth and 36 weeks PMA with subsequent *z* scores indicated a moderate association of *z* scores at birth with *z* scores at 36 weeks PMA

	Cohort period	Weight[a]	Head circumference	Length
Birth *z* to 36 week PMA *z*	2003–2007	0.65	0.55	0.56
	2009–2010	0.77	0.74	0.65
Birth *z* to1 year CA[b] *z*	2003–2007	0.37	0.49	0.31
	2009–2010	na	na	na
36 week PMA *z* to 1 year CA z	2003–2007	0.41	0.61	0.27
	2009–2010	na	na	na

Association strength increases as values for *r* approach 1; there is no association when the *r* coefficient is 0
PMA postmenstrual age, *CA* chronologic age
[a]All values in the table are expressed as values of *r*
[b]The 1-year chronologic age was corrected for premature birth: the corrected age

of the head circumference relative size for age (*z*) at birth, 36 weeks PMA and 1 year. Weight and length *z* scores at 1 year were weakly associated birth *z* scores (Table 13.14).

Assessment of Brain Development

The safety of early PN has not been established for the brain by demonstrating normal brain function during later development. Brain growth can be estimated by head circumference measurements. However, normal head circumference growth at 1 year does not establish the brain's quality. The Bayley Scales of Infant and Toddler Development® (BSID) have been used to measure the progress of early development [27, 29, 30, 33–35]. An evaluation program using the BSID Third Edition (BSID-III) was established in late 2007. Criteria for participation in the evaluation program included a birth weight less than 1 kg or a gestation age less than 28 weeks. The first cohort evaluated by the BSID-III was born in 2008. The sample size was small, and only 16 of 22 (73%) eligible infants participated. The nutrition provided to the 2008 cohort resembled that described for the 2003–2007 cohort. In 2008, stock PN solutions contained glucose, 10 g/dL; amino acids, 2.5 g/dL; L-cysteine, 100 mg/dL; calcium, 300 mg/dL; heparin, 50 unit/dL; and were provided at 80 mL/kg/day at 1 h after birth. Lipid was provided at 0.5–2.0 g/kg/day. PN on the day of birth provided 45–60 kcal/kg/day. Incremental daily increases were provided as previously described.

The 2008 BSID cohort consisted of infants with younger gestational ages and lower birth weights than the 2003–2007 and 2009–2010 cohorts. The 2008 BSID cohort had Δ*z* growth at 36 weeks that was similar to the 2003–2007 cohort (Tables 13.12 and 13.15). The Δ*z* catch-up growth at 2 years was greater than the Δ*z* growth of the 2003–2007 cohort at age 1 year (Tables 13.12 and 13.15).

The BSID-III scores for this sample were slightly lower than observed in the normal population. These scores were greater than the BSID-II scores previously published for premature infants (Table 13.15).

Table 13.15 The 2008 cohort growth is expressed in terms of Δz from birth to 36 weeks PMA and from birth to the assessment at 2 years

	GA	Birth z			Δz at 36 weeks PMA			Age[a]	Δz at Evaluation			Bayley cognitive	Bayley language	Bayley motor
	Weeks	Weight	HC	Length	Weight	HC	Length	Months	Weight	HC	Length			
Mean	27.6	−0.7	−0.7	−0.9	−1.0	−0.5	−1.4	22.2	−0.4	0.8	0.8	94	93	97
SD	1.5	0.7	0.7	0.7	0.7	0.9	1.2	2.2	0.9	1.0	1.1	11	21	10
Range, low	24	−1.7	−2.0	−1.9	−3.1	−2.6	−4.0	20.1	−2.4	−1.7	−2.7	70	59	79
Range, high	30	0.8	0.6	0.7	−0.4	0.1	−0.3	28.5	1.2	1.4	2.0	110	135	115
DQ < 70												0	2	0
70 < DQ < 85												3	3	2
85 < DQ < 115												13	8	13
DQ > 115												0	3	0

SD standard deviation, *DQ* developmental quotient

[a]Age was corrected for premature birth: the corrected age

Anderson et al. used the BSID-III to evaluate 200 premature infants and reported BSID-III scores that were similar to the 16 infants in the 2008 BSID-III cohort. However, Anderson also reported that a control group of 200 term infants had significantly higher scores than predicted by the BSID-III normative data; cautious interpretation of BSID-III scores was advised [35]. The BSID-III score similarity of the 2008 BSID cohort and the Anderson cohort scores supports the safety of early PN; but, cautious interpretation prevents a comparison with previous cohorts evaluated by the BSID-II.

Discussion

Koletzko et al. wrote in guidelines on pediatric PN for the European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN): "In the small preterm infant starvation for just one day may be detrimental and where it is clear that enteral feeds will not be tolerated soon PN must be instituted shortly after birth" [36]. In a thorough review of PN, Heird concluded that data from randomized trials are crucially needed for improvement [37]. Hans et al. in the United States and Lapillonne et al. in France conducted surveys of PN and discovered a widely diverse range of clinical practice [8, 9]. Delay of PN for several days was commonly reported. Senterre and Rigo published a prospective clinical trial of PN and EN that followed recent nutrition guidelines [7, 37, 38]. They observed no net increase in postnatal growth restriction in a cohort of 102 infants with birth weights less than 1,250 g. They provided an excellent review of recent studies of nutrition, growth, and development [7].

Senterre and Rigo studied infants born in 2006–2007 (2006–2007 cohort). Their cohort study followed a series of steps in previous years that had increased early nutrition. They avoided conducting a randomized clinical trial (RCT) because they felt that it would be unethical to provide inadequate nutrition to one of the randomized groups. The 2006–2007 infants received PN and EN that resembled the PN and EN provided for the 2003–2007 cohort. The size of the cohort and the cohort population were similar. Lacking randomized controlled trials, a comparison of the three cohorts, 2003–2007, 2006–2007, and 2009–2010, is important.

The three cohorts received predominantly PN in the first week of life. Their nadir weights all occurred on day 3, they lost 6–8% of birth weight, and they returned to birth weight on day 6–7. The standard deviations for these three values were large and they were similar for all three cohorts. The standard deviations demonstrated that although the cohort results were very similar, individuals within the cohorts exhibited wide variations in the first week. Increased PN in the first 2 days did not change these values for the 2009–2010 cohort.

The three cohorts received different EN during the transition phase. The 2006–2007 cohort initially received exclusively human milk. Human milk was introduced and increased in incremental steps. When 50 mL/kg/day of EN was achieved, a partial dose of bovine milk supplement (Human Milk Fortifier, Mead Johnson, Evansville, IN) was added. After 100 mL/kg/day of EN was achieved, the full bovine supplement was provided. In comparison, the 2003–2007 cohort received the same bovine supplement, but the partial dose was delayed until EN reached 150 mL/kg/day. After several days of a partial dose, the full bovine supplement was provided. Although bovine supplements were provided differently, the 2003–2007 and 2006–2007 had similar postnatal growth.

The 2006–2007 cohort was evaluated for postnatal growth restriction that was defined as 2 SD below the mean ($z=-2$) for the Usher and McLean standard of intrauterine growth [39]. Infants with birth weight $z<-2$ were excluded from the appropriate for gestational age (AGA) category. By comparison, the 10th percentile growth method in Table 13.3 used the Alexander standard for intrauterine growth and excluded infants with birth weights less than the 10th percentile. Alexander 10th percentile growth (male, 828 g; female 760 g) is similar to Usher $z=-2$ growth (813 g) at 28 weeks PMA. Although not identical, the two methods identify similar AGA growth thresholds at birth. At 36 weeks

gestation, the Alexander 10th percentile (male 2,407 g; female 2,300 g) is larger than Usher $z=-2$ growth (1,889 g).

The 2006–2007 cohort had 82 AGA infants and 94% remained above the Usher AGA standard ($z>-2$) at discharge. The 2003–2007 cohort had 80 AGA infants and 95% remained above the Usher AGA standard ($z>-2$) at 36 weeks PMA. The two cohorts appeared to have similar postnatal growth.

Both cohorts were evaluated by the GV method, but the 2006–2007 cohort GV was calculated differently from the Patel method: the weight on day 3 was substituted for the birth weight. The 2006–2007 AGA cohort was reported to have a GV of 15.5 g/kg/day. Because there were large standard deviations for nadir weight and the day of nadir weight, it is difficult to accurately compare the day-3 GV of the 2006–2007 cohort (15.5 g/kg/day) with the day-1 GV values determined for the 2003–2007 and 2009–2010 cohorts (11–15 g/kg/day).

An example is provided to demonstrate the difference in day-1 GV and day-3 GV values. A hypothetical infant weighed 1,000 g at 27 weeks gestation, declined 8% to weigh 920 g on day 3, then weighed 2,500 g on day 63 (36 weeks PMA). The GV determined by the birth weight is 14.5 g/kg/day; the GV from day 3 is 16.4 g/kg/day. Using the day 3 weight increased the GV by 1.9 g/kg/day. The mean GV of 84 infants in 2003–2007 was 13.8 g/kg/day (Table 13.5). If 1.9 g/kg/day had been added to compensate for the difference in GV methods, the two cohorts would have had the same GV (15.7 vs. 15.5 g/kg/day).

Both cohorts were evaluated for growth using Δz methods. The z reference was different for the two cohorts: 2006–2007 used Usher data and 2003–2007 used Fenton data. The 2006–2007 cohort was divided into six categories with Δz computed weekly until discharge. The 2003–2007 cohort Δz was measured at 36 weeks PMA. The 2006–2007 cohort Δz for weight ranged from −0.5 to 0.3 at the time of discharge from the NICU. The Δz for the 2003–2007 cohort at 36 weeks PMA ranged from −1.56 to −0.7. Because both cohorts had similar growth velocities, the difference in Δz values may be due to the difference in Usher and Fenton data.

An example is provided to demonstrate the difference in Usher and Fenton data. At 36 weeks PMA, an infant that weighed 2,589 g had an Usher $z=0$; the same infant had a Fenton $z=-0.46$. After adding 0.46 to the Δz weight of the 2003–2007 cohort, compensating for differences in the z standards, the 2006–2007 cohort continued to have greater Δz growth than the 2003–2007 cohort. The greater growth of the 2006–2007 cohort may be explained by greater EN the 2006–2007 cohort received in the transition and early EN phases.

The 2006–2007, 2003–2007, and 2009–2010 cohorts received early PN and avoided nutritional deficits in the first week after birth. The three cohorts had similar weight changes through the first week. They had incrementally decreased weight by discharge due to differences in EN in the transition and early EN phases. In 2006–2007, infants received enteral bovine supplements to human milk while in the transition phase. In 2003–2007, infants received enteral bovine supplements to human milk later, at the beginning of the EN phase. In 2009–2010 the EN supplements were further delayed until either the EN phase or until 32 weeks PMA, whichever came later. Compared to 2003–2007, earlier supplementation of EN in the transition phase for the 2006–2007 cohort was associated with a Δz weight increase in the range from 0 to 0.8. Compared to 2003–2007, additionally delayed supplementation of EN in the EN phase was associated with a Δz weight decrease of 0.2.

Although greater weight gains were associated with earlier supplementation, early supplementation of EN with bovine products may not confer a health advantage. In addition to increased weight, the 2006–2007 cohort had 9/109 infants (8%) with NEC. SIP was not identified separately for the 2006–2007 cohort. The 8% rate of NEC was greater than the 5/183 of infants (3%) with NEC the combined 2003–2007 and 2009–2010 cohorts ($P=0.046$).

Gordon et al. and Sharma et al. have identified the importance and difficulty of distinguishing SIP from NEC [40, 41]. SIP and NEC are identified in Table 13.1. According to a letter from T. Senterre, MD in September 2011, the NEC reported for the 2006–2007 cohort did not include SIP and some of

the 2006–2007 cohort infants received indomethacin prophylaxis. Due to a concern for its association with SIP [41], indomethacin prophylaxis for severe intracranial hemorrhage, we discontinued indomethacin prophylaxis in 2011. However, all of the 2003–2007 and 2009–2010 cohort infants received indomethacin prophylaxis.

Four infants in the 2009–2010 cohort developed NEC after introduction of bovine supplements to EN. Bovine supplementation was delayed in 2010 until 32 weeks PMA and no further NEC during EN was observed. Decreased use of bovine supplements during EN appeared to decrease postnatal weight gain. This decrease in growth was balanced by a decrease in NEC. Human milk-based supplementation (Prolact, Prolacta® Bioscience, Monrovia, CA) has not been associated with increased NEC [42].

Schanler reviewed evidence that demonstrated exclusive breast milk feeding is associated with reduced NEC. He also pointed out that lower weight gain associated with human milk feeding was also associated with improved brain development and reduced metabolic syndrome (obesity, hypertension, and diabetes) [43]. The brain's subsequent development may be a better indicator for the quality of early nutrition than the achievement of maximum weight gain.

A trend of reduced CLD was observed in 2009–2010. Increased fluid was provided in 2009–2010, which was previously reported to be associated with increased CLD [44–47]. The 2006–2007 cohort received more concentrated PN solutions and consequently less fluid in the first day. CLD rates were similar for the 2006–2007 and 2009–2010 cohorts (32% vs. 36%). Early fluid administration, early PN, and exclusive human milk for EN deserve reevaluation for their associations with CLD.

Early PN and subsequent EN practices continue to evolve. Large randomized controlled trials recommended by Hierd are expensive, difficult, and have rarely been published. Cohort studies have demonstrated that early PN prevents starvation that is associated with restricted postnatal growth and later developmental impairments. The 10th percentile, GV, and Δz methods provide quality improvement tools for NICUs to measure the growth consequences of changing their nutrition practices. Efforts to improve early growth must be balanced by changes in morbidity and long-term growth and development.

Summary

An evaluation of the safety and efficacy of early PN provided to premature infants was evaluated in the context of quality improvement. Infants born less than 30 weeks gestation were examined. The opportunity to evaluate qualitative differences in PN was limited by the scope of commercially available products. Quantitative changes in the PN solutions were evaluated from 2003 through 2010. The standard clinical PN practice was reviewed and increased annually. Small increments occurred through 2007. In 2009, the PN previously provided on day 2 was initiated at birth and provided 50–70 kcal/kg/day beginning 1 h after birth. The increase in PN did not change the weight lost after birth, the nadir weight day, or the time required to return to birth weight. An increase in the use of indomethacin for the treatment of a clinically significant PDA was observed, but no other common morbidities appeared to change significantly. The 10th percentile, exponential growth velocity (GV), and z score changes (Δz) were used to measure postnatal growth. The GV was 12–15 g/kg/day. The Δz scores at 36 weeks PMA were: −0.9, −0.5, and −1.1, for weight, head circumference and length, respectively. Increasing PN to 50–70 kcal/kg/day at birth did not indicate a clear advantage for postnatal growth at 36 weeks PMA.

The Δz scores for the 2003–2007 cohort at 1 year chronologic age were: −0.7, 0.1, and 0.4, for weight, head circumference and length, respectively. These infants were relatively light for their length at age 1 year. Improving growth at 36 weeks PMA by providing PN was associated with normal height at 1 year and was not associated with obesity.

The quantity of postnatal growth, GV and Δz, was not associated with birth weight, gestational age, or relative size at birth. The relative weight at birth (z) was moderately associated with the relative weight (z) at 36 weeks PMA, but not at 1 year. The relative head circumference (z) was moderately associated with the head circumference size (z) at 36 weeks and 1 year.

Infants born in 2008 received early PN at 45–60 kcal/kg/day from PN provided 1 h after birth. Infants with birth weights less than 1,000 g or ages less than 28 weeks gestation had BSID-III evaluations at age 2 years. The BSID-III scores were in the normal range. Normal BSID-III scores support the belief that early PN is safe.

This observational study demonstrated that increased macronutrients in PN provided at birth safely improved the postnatal growth of premature infants. The 10th percentile, GV, and Δz methods may be used for quality improvement studies when NICUs evaluate their early PN practices. When changing PN and EN practice patterns, improved growth should be balanced by changes in associated early morbidities and later growth and development achievements.

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Part III
Breast Feeding: Growth and Health

Chapter 14
Human Milk Oligosaccharides: Role in Infant Health

Evelyn Jantscher-Krenn and Lars Bode

Key Points

- Human milk oligosaccharides (HMO) are complex glycans that are highly abundant in human milk, but not in infant formula.
- HMO are considered prebiotics as they are preferentially metabolized by specific beneficial bacteria in the infant's intestine.
- HMO are considered antimicrobial as they serve as soluble decoy receptors that block the attachment of microbial pathogens to the host's mucosal surfaces in the gastrointestinal, respiratory, and urogenital tract.
- HMO are considered immune modulators as they may interfere with leukocyte extravasation and activation.
- HMO-derived sialic acid may be an essential nutrient for brain development and cognition.
- HMO may protect preterm infants from necrotizing enterocolitis.
- Most of the data on the beneficial effects of HMO stem from in vitro or ex vivo studies or are derived from animal models. Data from human intervention studies are currently not available.
- HMO effects are often highly structure-specific and the structurally different nonhuman oligosaccharides currently added to infant formula are likely not able to mimic the full spectrum of HMO benefits.

Keywords Human milk oligosaccharides • Structure • Function • Metabolism

Abbreviations

2′ FL	2′-Fucosyllactose
3′ SL	3′-Sialyllactose
3FL	3-Fucosyllactose
6′ SL	6′-Sialyllactose
BMO	Bovine milk oligosaccharides
DSLNT	Disialyllacto-*N*-tetraose
FOS	Fructooligosaccharides

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R.R. Watson et al. (eds.), *Nutrition in Infancy: Volume 1*, Nutrition and Health,
DOI 10.1007/978-1-62703-224-7_14,

Fruc	Fructose
Fuc	Fucose
Gal	Galactose
Glc	Glucose
GlcNAc	*N*-acetylglucosamine
GOS	Galactooligosaccharides
HMO	Human milk oligosaccharides
Lac	Lactose
LNFP1,2	Lacto-*N*-fucopentaose 1,2
LNnT	Lacto-*N*-neotetraose
LNT	Lacto-*N*-tetraose
NEC	Necrotizing enterocolitis
Neu5Ac	*N*-actetylneuraminic acid
Neu5Gc	*N*-glycolylneuraminic acid
PNC	Platelet-neutrophil complex
Sia	Sialic acid

Introduction

Human breast milk is widely considered the optimal nutrition for the newborn infant. Aside from providing the neonate with the nutritional needs for growth and development, breast milk also contains a plethora of bioactive factors that promote health and offer protection from infections. Human milk oligosaccharides (HMO), unconjugated, complex carbohydrates, are present in human milk at 10–20 g/L, a concentration only surpassed by lactose (Lac) and lipids, and often higher than that of total protein. Bovine milk, the basis of most infant formula, is a scarce source of oligosaccharides, which are also structurally different and less complex. High abundance and structural complexity of HMO are unique to human milk, raising questions about their biological roles and potential benefits for the human infant.

Research during the last decades has implicated functions for HMO in the healthy colonization of the neonatal gut, protection from infections, maturation of the immune system and neuronal development. This chapter reviews recent advances in HMO research and discusses HMO as putative prebiotics, anti-infective and anti-inflammatory agents, immune modulators, signaling molecules and nutrients for neurological development.

HMO Structures and Composition

The basic structural layout of HMO shows Lac at the reducing end, which can be elongated by repeating disaccharide units of galactose (Gal) and *N*-acetylglucosamine (GlcNAc). Up to 15 of these Gal/GlcNAc disaccharide building blocks can be linked via β1-3 or β1-6 glycosidic bonds, forming highly complex linear or branched HMO core structures (see Fig. 14.1). Chains ending in a lacto-*N*-biose unit (Galβ1-3GlcNAc) are classified as type 1; chains with a terminal N-acetyllactosamine (Galβ1-4GlcNAc) are categorized as type 2. Lac or the poly-lacto-*N*-biose/*N*-acetyllactosamine core can be modified by sialic acid (Sia) and/or fucose (Fuc). Sia (in humans exclusively as *N*-acetylneuraminic acid, Neu5Ac) occurs in α2-3 and/or α2-6 linkages and introduces a negatively charged carboxyl-group and acidic properties, which led to the term acidic HMO. In contrast, nonsialylated HMO are named neutral HMO. Acidic or neutral HMO can be decorated with Fuc in α1-2, α1-3, and/or α1-4 linkage.

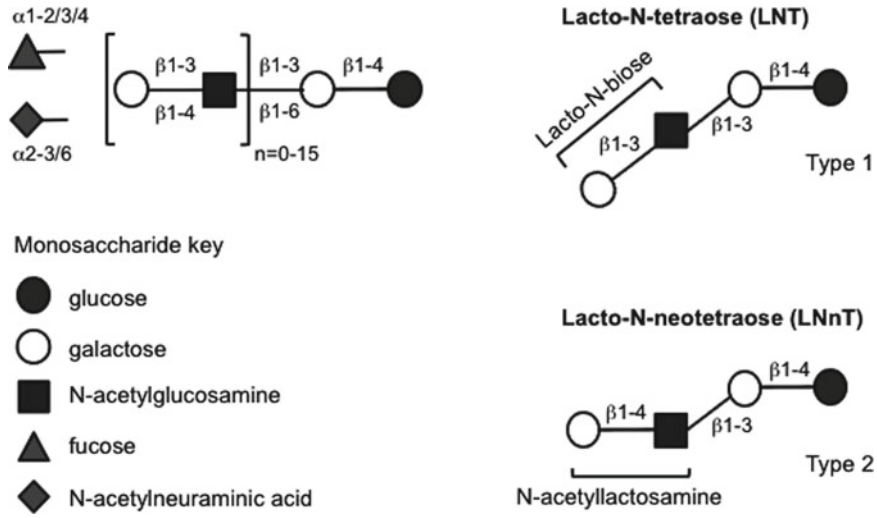

Fig. 14.1 Blueprint and core structures of HMO. Lac forms the reducing end and is elongated by up to 15 type 1 or type 2 disaccharide units. Core structures can be fucosylated in α1-2, -3 or -4 linkage and/or sialylated in α2-3 or -6 linkage

Table 14.1 Comparison of human and bovine milk oligosaccharides

	HMO	BMO
Abundance	>20 g/L in human colostrum	1–2 g/L in bovine colostrum
	5–15 g/L in mature milk	Trace amounts in mature bovine milk
Basic structure	Reducing end Lac; disaccharide repeats	Less stringent backbone structure
	Complex oligosaccharides	Mostly di- and trisaccharides
	>80% neutral	Approx. 10% neutral
Fucosylation	70% of HMO are fucosylated	Trace amounts of BMO are fucosylated
Sialylation	<20% of total HMO are sialylated	>90% of total BMO are sialylated
	Neu5Ac (~100%)	Neu5Ac (~90%), Neu5Gc (~10%)

Neutral HMO form the major fraction, with a high prevalence of fucosylated structures; less than 20% of HMO are sialylated. To date, the structures of more than a hundred different complex HMO have been elucidated (reviewed in Bode [1]).

Bovine milk oligosaccharides (BMO) are remarkably different in their structural layout. Disaccharides other than Lac can build the reducing end of a core BMO structure, or are found as such in bovine milk. Furthermore, the elongation of the BMO core structures is not limited to disaccharide repeats, resulting in various simple trisaccharides not found in human milk. Compared to HMO, BMO are shorter, less complex and carry more Sia. In addition to Neu5Ac, approximately 10% of the Sia on BMO is *N*-glycolylneuraminic acid (Neu5Gc), a specific nonhuman Sia derivative. In contrast to human milk, fucosylated oligosaccharides form only a marginal fraction in BMO (reviewed in Chichlowski et al. [2]). Major differences in the composition of human and bovine milk are listed in Table 14.1. Only a few oligosaccharides like 3′-sialyllactose (3′ SL) and 6′-sialyllactose (6′ SL) are common to both human and bovine milk.

Four milk groups. The HMO composition of a woman's milk depends largely on her genetic constitution. Based on the Lewis Secretor blood group system, four milk groups can be distinguished, depending on the activity of two gene loci encoding for two fucosyltransferases [3]. Individuals with an active *Se* locus, which encodes for the α1-2-fucoslyltransferase FUT2, are classified as Secretors. These

women express FUT2 in secretory tissues and generate α1-2-linked epitopes in their milk, which is characterized by 2′-fucosyllactose (2′ FL) and lacto-*N*-fucopentaose 1 (LNFP1). Nonsecretors are deficient in a functional FUT2 enzyme and therefore do not produce these specific HMO. The Lewis blood group status of an individual reflects the activity of the α1-3/4-fucosyltransferase FUT3, encoded by the *Le* gene. Lewis-negative women produce milk that lacks α1-4-fucosylated HMO. Based on the expression of FUT2 and FUT3, breast milk can be assigned to one of four groups: Lewis-positive Secretor, Lewis-negative Secretor, Lewis-positive Nonsecretor and Lewis-negative Nonsecretor [3].

Intrapersonal variations in HMO composition. The HMO composition of a woman's milk also varies during the course of lactation. In early stages of lactation, the total HMO concentration is generally higher and declines within the first 3 months [4, 5]. In colostrum, total HMO concentrations peak at over 20 g/L and drop to 5–12 g/L in transitional and mature milk. The relative abundance of sialylated HMO is highest in colostrum, and concentrations decrease during the transition to mature milk [6].

In cow milk, the BMO concentration peaks at parturition at approximately 20 times lower amounts compared to human colostrum, with 3′ SL being the most prominent BMO. Abundance and composition of BMO change rapidly, and mature bovine milk contains only trace amounts of oligosaccharides [6].

HMO Metabolism

To fully appreciate the possible health benefits for the infant, it is important to understand the fate of HMO in the breast-fed infant. In vivo data on the extent of HMO degradation, absorption, and fermentation are however limited. Studies on mother–infant pairs reported that the oligosaccharide profiles in the infant's feces and urine closely resemble the oligosaccharides in the mother's milk. These results suggested that HMO are mostly excreted unaltered with the feces, while a small percentage is absorbed intact into the circulation and excreted with the urine. Formula-fed infants present entirely different fecal glycan profiles [7]. Furthermore, ex vivo and in vitro studies demonstrated that HMO are resistant to the low pH in the stomach and to pancreas and brush border enzymes, further strengthening the general idea that HMO are nondigestible to the host [8, 9].

Nevertheless, the view of HMO as "inert" to intestinal breakdown is currently being challenged. It is now becoming evident that partial HMO degradation and bioconversion take place in the infant's intestine. In recent studies, sialylated HMO or other specific HMO structures as well as blood type-specific bioconversion products of HMO accumulated in the feces of breast-fed infants, resulting in profiles remarkably different to the HMO profiles in their mother's milk [10]. Early post-partum, fecal profiles match those in the respective milk, indicating minimal HMO utilization in the gut lumen. At 2 months of age, HMO metabolism products appear in the feces, suggesting a higher level of degradation and personalized re-modeling of HMO. Once solid food is introduced in addition to breast milk, oligosaccharides derived from these new carbohydrate sources can be found in the infant's feces [11]. Together, these findings indicate an active gastrointestinal metabolism of HMO depending on the age of the breast-fed infant, and the individual adaption and maturation of the gastrointestinal system [11]. Overall, HMO utilization might occur to a higher degree as previously anticipated. The resulting changes in HMO composition and the occurrence of degradation products might be of biological significance. Also, it remains unclear to which extent the infant's own intestinal enzymes or the microbiota contribute to HMO degradation and remodeling in the intestine.

While efforts to directly measure HMO in infant blood have not been successful, HMO are regularly found in urine of breast-fed, but not formula-fed infants [12], providing indirect evidence for intestinal

absorption. Metabolic labeling studies [13] estimate a 1% intestinal absorbance rate, but the exact kinetics remain poorly understood. The hypothesis that HMO are absorbed is further supported by in vitro studies demonstrating that intestinal epithelial cells mediate active and passive HMO transport [14]. How these translocations contribute to intestinal absorption in vivo has yet to be investigated.

HMO as Prebiotics

Historically, HMO have been mainly thought of as prebiotics that stimulate the colonization of beneficial microorganisms in the intestine of the breast-fed neonate. Already in 1900, *Bifidobacteria* were found enriched in the stool of breast-fed compared to formula-fed infants [15], an observation that initiated the search for the "bifidogenic factor" and eventually led to the discovery of the first HMO in 1954 [16]. Today, the differences in the intestinal microbial composition seem less apparent and not entirely due to a predominance of *Bifidobacteria* or *Lactobacilli*. Nevertheless, the intestinal community of breast-fed infants seems to be less complex and more stable than that of formula-fed infants (reviewed in Morelli [17]). Species in the genus *Bifidobacteria* are frequently isolated from breast-fed infants and have been shown to grow on HMO in vitro [18]. Several bifidobacterial strains employ a dedicated metabolic pathway, the Galacto-N-biose/Lacto-N-biose (GNB/LNB) pathway, for degrading type 1 core structures after the extracellular enzymatic breakdown to the disaccharides lacto-N-biose 1 and Lac. Furthermore, various bifidobacterial strains can also degrade the type 2 chain Lacto-*N*-neotetraose (LNnT), or possess extracellular fucosidases and sialidases, releasing unsubstituted HMO backbones for further degradation (reviewed in Fushinobu [19]).

B. longum infantis (short: *B. infantis*) seems to be the single most adapted species to comprehensively utilize HMO and is able to use HMO as sole carbon source [20]. The genome of *B. infantis* contains a unique cluster of ABC transporters and intracellular glycosylhydrolases (HMO-1 cluster) allowing intracellular HMO uptake, degradation and fermentation via catabolic pathways [21]. In addition, *B. infantis* employs enzymes to selectively digest type 1 or type 2 chains after intracellular uptake [22] and is able to utilize certain sialylated HMO.

HMO utilization does not seem to be limited to the genus *Bifidobacteria*. *Bacteroides* strains, for example, are also capable of metabolizing HMO [23]. Other genera like *Lactobacilli* cannot degrade HMO themselves but are able to utilize intermediates and metabolites released by *Bifidobacteria* [24]. Due to different degrees of adaptation to HMO usage, structures unique to HMO might select for a specific composition of the bacterial community [23]. However, there is no evidence from human studies that different HMO compositions shape the assembly of microbiota in breast-fed infants. In fact, a recent study found no significant differences in the infant's intestinal microbiota composition between the Secretor- and Lewis-dependent milk groups, contradicting an association of genera to specific HMO fucosylation patterns [25].

HMO as Antimicrobials

Aside from reducing the risk for infections by promoting a healthy gut-colonization, HMO might also serve as a direct line of defense against bacterial, viral and protozoan pathogens (see Fig. 14.2). It was noticed early on that breast-fed infants have lower incidences of infectious diseases of the intestinal, urinary, and respiratory tract [26]. Many pathogens such as *Escherichia coli*, *Campylobacter jejuni*, *Shigella* strains, *Vibrio cholera* and *Salmonella* employ ligand–receptor interactions to attach to the host's mucosal surfaces and initiate infection [1, 27]. Pathogens can either express lectins, proteins

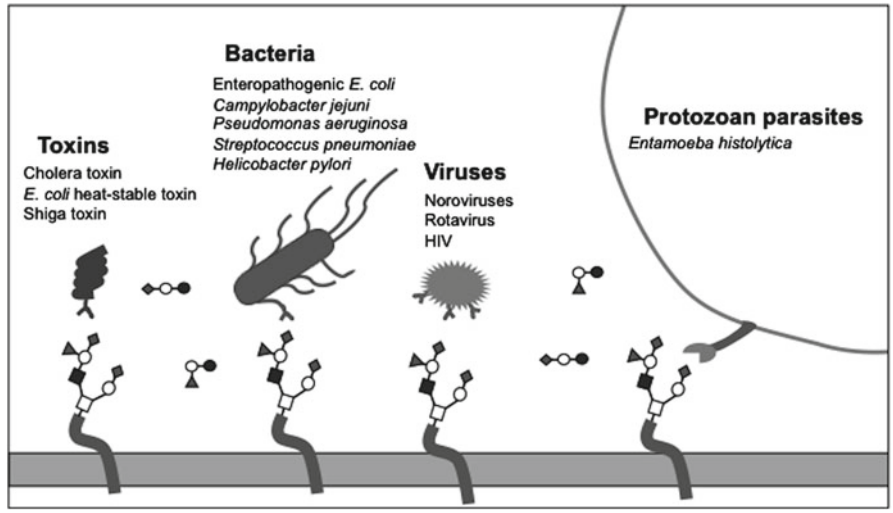

Fig. 14.2 Antiadhesive effects of HMO. HMO structurally resemble host glycans and function as soluble decoy receptors that block the attachment of toxins, bacteria, viruses and protozoan parasites to mucosal surfaces. Listed are examples of microbial pathogens with reported in vitro and ex vivo antiadhesive effects

that bind to host epithelial glycan receptors, or they can mimic host glycan structures to dock to the cognate lectins expressed on the side of the host. Some HMO structurally resemble the glycan epitopes on the host surface and could therefore function as soluble decoy receptors, resulting in reduced adhesion and enhanced pathogen clearance [27]. For example, α1-2-fucosylated HMO like 2′ FL have been shown to interfere with the binding of several enteric pathogens in vitro, including *C. jejuni* [27, 28]. Ex vivo studies showed that 2′ FL inhibited *Campylobacter* colonization of human intestinal mucosa [28]. As outlined above, α1-2-fucosylated oligosaccharides are only present in the milk of Secretor women, and a study in Mexico showed that the expression of α1-2-fucosylated HMO in the mother's milk is correlated to a lower incidence of infant *Campylobacter* and *Calicivirus* diarrhea [29]. Other specific HMO have been shown to effectively prevent and attenuate pneumococcal pneumonia in rabbits and rat pups in vivo [30].

In vitro, antiadhesive effects of HMO have also been described against viruses such as *Calicivirus* strains [31], or HIV-gp120, the glycoprotein critically involved in HIV entry upon binding to DC-SIGN [32]. Similarly, protozoan parasites such as *Entamoeba (E.) histolytica* also employ lectins to bind to human cells and might be inhibited by certain HMO epitopes. Our lab recently showed that physiological concentrations of specific HMO can block *E. histolytica* adhesion to and cytotoxicity against human intestinal cells in vitro [33].

In conclusion, breast-feeding is known to reduce the risk of infections caused by bacteria, viruses, or protozoan parasites. Evidently, HMO have antiadhesive effects on these infectious agents in vitro, and HMO functions seem to be highly structure-specific. If different HMO protect from different pathogens, it follows that a diverse mixture of structurally distinct HMO in breast milk offers the infant a greater level of defense than a single HMO could do. Accordingly, individual differences in HMO composition in milk due to genetic and other factors might explain the different degree of protection in breast-fed infants. However, to date, clinical intervention studies to link specific HMO to protection from certain infectious diseases are not available.

HMO as Signaling Molecules

To keep pathogens in check, HMO may not only interact with the microbial side, but might also act on the host cells. Exposure of enterocytes to 3′ SL, one of the predominant sialylated HMO, changed cell surface glycan profiles in vitro [34]. These HMO-induced glycome modifications led to a dramatic reduction in binding of enteropathogenic *E. coli* (EPEC) to CaCo-2 cells. HMO-mediated alteration of surface glycans on host cells might be an alternative defense strategy against pathogen binding. It is not known whether 3′ SL also regulates other glycan-related genes, or whether different HMO have similar or differential effects.

If HMO can act as signaling molecules, one can speculate that their roles might go beyond direct defense mechanisms against pathogens. In vitro studies reporting that HMO affect proliferation, differentiation and apoptosis in intestinal cell lines supported this notion and raised speculations on whether HMO are involved in the regulation of intestinal growth and maturation in the breast-fed infant [35]. How HMO signal and influence gene expression or possible other downstream effects remains unknown. Also, whether these in vitro observations have implications for the breast-fed infant has to be investigated.

HMO as Immune Modulators

Cell–cell interactions of the innate and adapted immune system are largely mediated by lectins, and HMO are potential interaction partners for several human lectins, such as selectins, siglecs or galectins [31]. Estimated concentrations of HMO in the circulation range from 100 to 200 μg/mL, which make systemic effects seem plausible.

The physiological binding determinants of selectins are sialyl-Le^x and sialyl-Le^y, epitopes present also in sialylated and fucosylated HMO. P- and L-selectins are critically involved in leukocyte deceleration and adhesion to endothelial cells, leading to extravasation at sites of inflammation [36]. Additionally, P-selectins regulate formation and activation of platelet-neutrophil complexes (PNC), highly active neutrophils primed for adhesion, phagocytosis and production of reactive oxygen species [37]. In vitro and ex vivo models showed that physiological concentrations of sialylated HMO reduce neutrophil rolling and adhesion to activated endothelial cells [38]. It was further demonstrated that sialylated HMO impede the formation of PNC [39], suggesting that HMO function as anti-inflammatory agents.

There is substantial evidence that breastfeeding obviates allergies in infants and the development of autoimmune diseases later in life. Furthermore, it is acknowledged that HMO contribute to the maturation of the naive immune system [40]. Beneficial effects of HMO on the immune response have mainly been accounted to the growth and metabolism of microbial commensals in the gut leading to oral tolerance and protection against pathogens. Nevertheless, an increasing number of studies suggests that HMO can affect immune cells in a direct, microbiota-independent way [41–44].

In neonates, the immune system is immature and biased toward a Th2 profile to avoid adverse inflammatory conditions. Sialylated HMO stimulated cytokine production and activated cord blood-derived T cells from neonates ex vivo [44], indicating that HMO could have direct immune modulatory effects, promoting a shift in T cells response toward a more balanced Th1/Th2-cytokine production and low-level immunity. These findings suggest a role for HMO in guiding the postnatal maturation of the immune system and in preventing allergies.

HMO as Protective Agents Against Necrotizing Enterocolitis

Breast-fed infants have a lower risk to develop necrotizing enterocolitis (NEC) than formula-fed infants. Hallmarks of this life-threatening disease that affects almost 10% of very-low-birth-weight preterm infants are excessive inflammation, bacterial colonization, and impaired barrier function, which can lead to intestinal necrosis and bacterial sepsis. Our lab recently showed that pooled HMO prevent NEC in a neonatal rat model. Out of the pool of HMO, a single HMO, disialyllacto-*N*-tetraose (DSLNT), could be identified as the protective agent, and its function was highly structure-specific. Galactooligosaccharides (GOS), currently added to infant formula had no effect [45]. How DSLNT prevents NEC and whether these results translate to human infants has yet to be determined.

HMO as Nutrients for Brain Development

Breastfeeding has long been associated with higher intelligence in children [46], although it is challenging to provide direct evidence for a nutritional factor. Recently, sialylated HMO have obtained great interest as a potential source of nutrients to improve neurological development. Postmortem analysis of Sia concentrations in brain gangliosides and glycoproteins revealed higher amounts in breast-fed than in formula-fed infants [47], suggesting differences in synaptogenesis and neuronal development. Sia concentrations in brain gangliosides and glycoproteins have been associated with learning ability. Administration of free or conjugated Sia enhanced cognitive and behavioral performance in rats and piglets [48, 49]. In suckling rat pups, the occurrence of maximal Sia concentration in milk in early lactation is concurrent with the up-regulation of enzymes involved in Sia catabolism in the colon. At weaning, when Sia levels in rat milk were the lowest, a change in colonic enzyme expression seems to expedite de novo synthesis [50]. The differential expression of intestinal enzymes associated with Sia utilization and anabolism suggests adaption of the intestinal system to the transient high dietary source of Sia early in lactation. These observations imply that the high 3′ SL concentration in mother's milk meets the enormous demand of the growing brain for Sia. Whether supplementation of formulas with Sia is effective in stimulating brain development in infants has yet to be investigated.

Alternatives for HMO in Formula

Bovine milk-based infant formula contains marginal levels of complex oligosaccharides. Addition of HMO to infant formula is currently not feasible due to the limited availability and extremely high costs. At present, infant formula manufacturers are supplementing their products with nonhuman oligosaccharides in an attempt to mimic the effects of HMO. Commonly added oligosaccharides are GOS and fructooligosaccharides (FOS). GOS consist of one to seven Gal units linked to a reducing end Lac. FOS are short-chain oligomers build of β1-2-linked fructose (Fruc) residues bound to a reducing end glucose (Glc). Apart from the common building block Gal in GOS, these nondigestible dietary oligosaccharides do not share structural similarities with HMO. Nevertheless, GOS and FOS have reportedly shown prebiotic [51] and immunomodulatory [52] effects similar to HMO. Whereas some HMO effects can potentially be mimicked by GOS/FOS, there are most certainly limitations to their potential use as functionally equivalent alternatives to HMO. For example, a single specific HMO, DSLNT, could prevent NEC in neonatal rats whereas GOS had no effect [45]. In addition, although considered save for the use in infants, studies on long-term effects of feeding nonhuman oligosaccharides during the neonatal period are not available.

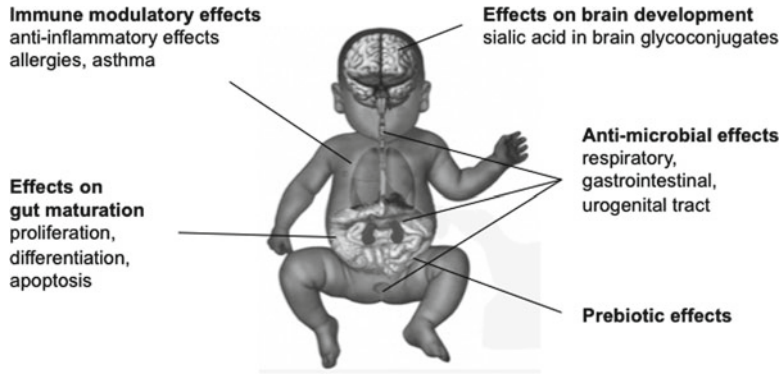

Fig. 14.3 Schematic overview of the potential health benefits of HMO in breast-fed infants. HMO are indigestible and reach the colon intact where they serve as prebiotics and promote healthy gut colonization. HMO block adhesion of microbial pathogens to mucosal surfaces, preventing infections of the respiratory, gastrointestinal and urogenital tract. HMO could serve as signaling molecules and guide growth and maturation of the intestine and affect mucosal immunity. Systemic HMO effects might include attenuation of selectin-mediated inflammatory events. HMO-derived sialic acid may be incorporated in the rapidly growing brain and support neuronal development. HMO might reduce the risk of necrotizing enterocolitis, but the underlying mechanisms remain unknown

Concluding Remarks

HMO seem to have a multitude of benefits for the breast-fed infant that go beyond the prebiotic aspects (see Fig. 14.3). The potential benefits of HMO in infections and allergies, gut maturation or brain development remain to be confirmed in vivo. However, accumulating evidence from in vitro data warrants further research directed toward possible applications of these bioactive components.

It is becoming evident that the specific structure of individual HMO determines their function. This structure–function relationship might have implications on the supplementation of infant formula with non-HMO. Structurally different oligosaccharides are likely not able to imitate all HMO effects, and potential side effects have to be considered and further investigated.

The individual mix of oligosaccharides in breast milk seems to be optimized for the changing needs of the developing infant. The fact that certain HMO in breast milk are age-dependently expressed, and that infants process HMO very differently depending on their age and maturity suggests that the qualitative and quantitative oligosaccharide composition in milk is fine-tuned to the demands of the infant. Whether these observations have implications, e.g. for the nutrition of preterm infants with nonage-matched donor milk, has yet to be investigated. In the end, the beneficial effects of HMO add yet another reason to encourage mothers to breastfeed their infants.

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Chapter 15
The Impact of Infant Feeding on Later Metabolic Health

Wendy Oddy and Margaret F. McHugh

Key Points

- Postnatal nutritional influences impact on the risk of later child and adult overweight and obesity.
- A longer duration of breastfeeding in early infancy protects against overweight and metabolic syndrome in childhood and into adulthood.
- Early formula feeding increases early weight gain in infancy that leads to increased body mass index in childhood and metabolic risk in later life interventions to promote breastfeeding may have long-term benefits.

Keywords Breastfeeding • Formula feeding • Early nutrition • Child health and growth • Child overweight and obesity • Metabolic syndrome • Weight gain in infancy

Introduction

The objective of this chapter is to summarize the recent research related to the effect of infant feeding practices on the development of metabolic risk factors, overweight and obesity in early and later childhood. The Barker hypothesis provides a link between antenatal nutrition, postnatal growth, and subsequent adult disease [1, 2]. In fact, events in early life may program the function of a number of organ systems [2]. The fetal origins hypothesis states that fetal undernutrition in middle to late gestation leads to disproportionate fetal growth programming later coronary heart disease [3]. One public health strategy to challenge this hypothesis is the promotion of breastfeeding of all infants because breastfeeding may attenuate subsequent programming effects. Breastfeeding has been shown to protect against child obesity and cardiovascular risk outcomes [4], and is "dose related"; the longer an infant is breastfed, the lower the risk of obesity [5].

Our aim of this chapter is to determine whether earlier regular formula feeding influences growth, particularly in overweight children and associated metabolic risk. Our hypothesis is that early and regular formula feeding promotes early growth, which could adversely program cardiovascular health and several researchers have reported such observations. The public health importance of this question

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R.R. Watson et al. (eds.), *Nutrition in Infancy: Volume 1*, Nutrition and Health,
DOI 10.1007/978-1-62703-224-7_15,

arises from the possibility that knowledge of any specific postnatal nutritional influence on later child health may provide an opportunity for intervention during infancy.

Metabolic Syndrome

Metabolic syndrome (MetS) refers to a cluster of factors that significantly increase the risk of developing cardiovascular disease (CVD) and diabetes mellitus type-2 (DMT2) [6]. The main risk factors involved are overweight, central adiposity, atherogenic dyslipidemia, hypertension, and markers of impaired glucose metabolism [6, 7] with the more recent addition of pro-inflammatory and pro-thrombotic states [8]. This cluster of risk factors has been labeled "metabolic syndrome," although the definition of the syndrome is still being debated.

An epidemic of obesity and diabetes has emerged worldwide in the past two decades [9], mirrored by an increase in the number of people being diagnosed with MetS. In 1998 the World Health Organization (WHO) made the first attempt at defining MetS and since then a number of organizations including the European Group for the study of Insulin Resistance (EGIR), the National Cholesterol Education Program Adult Treatment Panel III (NCEP:ATPIII), the American Heart Association/National Heart, Lung, and Blood Institute (AHA/NHLBI) and the International Diabetes Federation (IDF) have followed suit. The definitions are based on the core risk factors (overweight, central adiposity, atherogenic dyslipidemia, hypertension, and markers of impaired glucose metabolism) but do not agree completely, with each organization incorporating different combinations and cut-offs for these factors. The NCEP:ATPIII and IDF definitions are the most widely used [10]. Although there is no consensus regarding the definition, there is agreement that the term "metabolic syndrome" refers to the presence of multiple metabolic risk factors that increase the risk of developing CVD by twofold and diabetes mellitus type-2, fivefold over the next decade, compared to those without the syndrome [11].

The Relevance of Obesity in Metabolic Syndrome

The National Cholesterol Education Program Adult Treatment Panel III (NCEP:ATPIII) refers to obesity as an *underlying* risk factor for CVD and diabetes mellitus type-2, meaning that obesity itself is a risk factor, and its presence raises the likelihood of the development of other major risk factors that include dyslipidemia, hypertension, and impaired glucose metabolism [12]. Obesity is also linked to newly emerging risk factors including insulin resistance, and pro-inflammatory and pro-thrombotic states [13]. When clustered together these risk factors in a patient are referred to as the "metabolic syndrome." Bosello suggests that obesity, the most frequent cause of metabolic problems, may in fact be an essential factor of metabolic syndrome [14]. This theory is supported by the high prevalence of metabolic syndrome in obese adolescents [15, 16] and adults [13].

Obesity is essentially excess body fat with varying definitions of its measurement including body mass index (BMI), percentage body fat, waist circumference, and other anthropometric measurements that include visceral and subcutaneous fat deposits, with the former having a more important role in metabolic dysfunction [14]. Adipose tissue functions as an endocrine organ releasing factors that regulate energy balance, glucose, and lipids [17]. With excess adipose tissue (i.e., obesity) comes the secretion of excessive levels of these factors such as nonesterified fatty acids, TNF-α and IL-6.

Nonesterified fatty acids (*NEFAs*) are released from adipocytes and when in excess (as in obesity) can cause insulin resistance in muscle tissue resulting in elevated glucose levels, or hyperglycemia.

NEFAs have an effect on the liver, causing fatty liver disease and insulin resistance, resulting in excess glucose production paired with decreased glucose utilization, contributing further to hyperglycemia [13]. The high fat content of the affected liver promotes the overproduction of VLDL, rich in triglycerides and apoprotein-B, and decreasing HDL levels, resulting in atherogenic dyslipidemia [14] greatly increasing the risk of atherosclerosis.

Tumor necrosis factor (*TNF-α*) *and interleukin-6* (*IL-6*) are secreted by adipose tissue at an increased rate in obesity and are thought to interfere with the action of insulin, suppressing lipolysis resulting in insulin resistance, hyperglycemia and dyslipidemia [17]. Plasminogen activation inhibitor (PAI-1) is also released from adipose tissue and contributes to an increased pro-thrombotic state [13]. The promotion of insulin resistance and hyperglycemia, contributes to the pathways by which obesity predisposes for the development of diabetes mellitus type-2 [14]. The combination of hyperglycemia, raised insulin levels, and hyperlipidemia contributes to increased endothelial dysfunction which increases CVD risk [14]. Normal endothelial cell function is an important protective factor against atherosclerosis and essential in maintaining cardiovascular health, allowing normal vasodilatation of the vessel, providing healthy interaction with passing blood cells, and protecting the underlying smooth muscle from damage [18]. Endothelial dysfunction, on the other hand, can lead to increased blood pressure, decreased lipid oxidation, and a buildup of plaque in the vessel wall leading to atherosclerosis [19], and is an early predictor of adverse cardiovascular events [20].

Genetic Influence on Childhood Obesity

Genetic influence evidenced by parental obesity is the strongest determinant of childhood obesity [21–23], and studies that have not controlled for the genetic influence on childhood obesity are likely to overestimate the influence of environmental factors including early diet. Early infant feeding is one of the most powerful environmental factors determining early growth and development and may influence gene expression [24]. Exciting research has emerged in nutrient–gene interaction knowledge [25] that has shown nutrients to influence gene expression and translation. This is an area of cutting-edge research [26], and a possible role and plausible mechanism of breastfeeding in the prevention of obesity must be considered along with genetic and environmental influences [27].

The prevalence of metabolic syndrome is significantly related to weight status in adolescence [15], as well as in adults. In this chapter we discuss the evidence regarding the influence of breastfeeding on overweight and obesity, hence indirectly influencing the development of metabolic syndrome later in life. A definitive link between breastfeeding, obesity, and metabolic syndrome may highlight a pathway to arresting this continually growing health epidemic.

Breastfeeding and Metabolic Syndrome

There has been interest in feeding methods and the growth of infants and child and adult obesity for many years. However in early studies the difficulty of isolating confounding factors led to inconclusive results. For example in a paper in 1980 Kramer recognized the difficulty of studying obesity and breastfeeding and in particular the difficulty of isolating the effects of social class and associated factors [28]. To overcome these difficulties Kramer undertook a further study and found that being overweight at 12 months was related to feeding method—breastfed babies were lighter [29] (we now know that breastfed infants are likely to be about 0.5 Z scores less at 12 months than formula fed infants, about 4–500 g).

The risk factors leading to MetS have traditionally been treated by modifications to lifestyle or by medication once they have become a health problem in the patient. In 1991, Lucas suggested the concept of "programming" in humans, where early nutrition in infancy may influence later health outcomes including overweight [30]. Developmental programming postulates long-term detrimental effects on adult health due to nutritional imprinting during critical developmental periods. Since then, nutrition in infancy has been investigated as a method of intervention to reduce health problems later in life. More specifically, studies of breastfeeding in infancy have shown protective effects against the components of metabolic syndrome that continue into adulthood and reduce the likelihood of developing metabolic disease in later life.

Substantial evidence over 40 years indicates that early nutrition and growth affects long-term cardiovascular health [31]. The theory is that a high nutrient diet in infancy adversely programs the principal components of the metabolic syndrome by promoting growth acceleration (upward centile crossing) [31]; therefore slower growth benefits later CVD and its risk factors. Singhal [32] showed that early growth acceleration programmed the abnormal vascular biology associated with early atherosclerosis, whereas slower growth was beneficial. Baird showed that infants who were at the highest end of the distribution of weight or BMI or who grow rapidly during infancy are at increased risk of subsequent obesity [33].

Epidemiological Evidence

In 1981, Kramer was the first to show a significantly protective effect of breastfeeding on childhood obesity [28]. Since then much time and effort has gone into understanding the relationship between breastfeeding, early growth, and later obesity. Despite many studies, there is relatively little understanding or evidence about how breastfeeding relates to later obesity. Plausible theories exist on the mechanisms that may be involved, and a number of observational studies and meta-analyses show small protective effects of breastfeeding on obesity as well as others that show no effect and shed light on the possibility of unknown confounders and publication bias [34].

Three comprehensive meta-analyses were conducted over the past decade. Meta-analysis of nine studies with over 69,000 participants [35] showed that breastfeeding has a consistent protective effect against childhood obesity (OR: 0.78; 95% CI: 0.71, 0.85), with four studies showing a dose–response effect for the duration of breastfeeding. A meta-analysis of 17 studies in 2005 [5] found a dose–response relationship, where an increased duration of breastfeeding is related to a decreased risk of overweight later in life. More specifically this meta-analysis reported a 4% decrease in risk with each additional month of breastfeeding. When restricted to exclusive breastfeeding (two studies), the risk of overweight is decreased by 6% per month of breastfeeding [5] suggesting that exclusivity of breastfeeding may be central to the mechanism whereby it protects against obesity [36].

Another meta-analysis including 28 studies concluded that breastfeeding reduces the risk of obesity compared to formula feeding (OR: 0.87; 95% CI: 0.85–0.89) [37]. Separate analysis of six studies that had adjusted for the three major potential confounding factors (parental obesity, maternal smoking, and social class) resulted in a significant decrease in the protective effect of breastfeeding (from an OR of 0.86–0.93) highlighting the heavy influence of confounding factors. In a second meta-analysis reported by the same authors [34], those who were breastfed had a lower BMI than those who were formula fed. However, when 11 studies, adjusted for the same confounding factors, were analyzed separately, there was no longer a significant difference in BMI between those breastfed and those formula fed. These authors concluded that any observed protective effect of breastfeeding on BMI was likely due to lack of adjustment for confounding factors.

Publication bias may be a factor as the 2005 meta-analysis [34] shows smaller studies indicate bigger protective effects of breastfeeding than larger studies [5, 35]. Funnel plot analysis concluded that there was no publication bias in these meta-analyses, but an explanation for the difference in results

between one meta-analysis [5] and another [34] was that there was a difference in the reference groups used [38]. Nonexclusive formula feeding infants (i.e., infants who were mainly formula fed but were supplemented with breastfeeding) were included in one study, while the other study [5] had included infants only exclusively formula fed. These findings provide further evidence that breastfeeding has a causal relationship with obesity and that by supplementing the "formula fed" reference group with breastfeeding, this group showed less of a difference from the breastfed group [38].

A German study of 9,357 children showed that breastfeeding had a protective effect against obesity and overweight which remained significant after adjusting for social class and lifestyle [39]. A dose–response relationship was shown with the duration of breastfeeding, indicating a possible casual effect associated with a shorter duration.

A recent study, consisting of 822 young adults (18–28 years) from the Netherlands [40], demonstrated that exclusive breastfeeding had a significant protective dose–response effect on measures of body fat mass and visceral fat mass (BMI, waist circumference, and waist–hip ratio).

Beyerlein and von Kries [41] suggest that discrepancy in the findings of studies looking at breastfeeding and obesity may be due to the different effects of breastfeeding on normal-weight vs. overweight populations. Their data show a protective effect of breastfeeding in those within the highest BMI percentiles (>90th) [42].

Conflicting Evidence

There is much conflicting evidence related to breastfeeding and obesity. This may be partially due to large variations in the definition of "breastfeeding" which includes "ever/never breastfed"; "predominantly breastfed"; "predominant and/or exclusive breastfeeding"; "any breastfeeding"; "some breast milk"; "more breast milk than formula"; as well as the lack of consistency in measurement of duration of breastfeeding, with some studies using a continuous timeframe, others using categories, or arbitrary cut-offs, i.e., "more or less than 6 months"; "less than 1 month."

A World Health Organization review in 2007 concluded that there are plausible mechanisms for the relationship between breastfeeding and obesity and that the literature indicates a small protective effect of breastfeeding in spite of possible publication bias and confounding [43]. However, studies looking at siblings, where confounding is assumed to be minimized due to similar upbringing and socioeconomic status, report mixed findings. Two studies found that breastfeeding has a protective effect against obesity [44, 45] and one study concluded that the difference was likely to be due to unmeasured confounding [46]. Another recent study attempted to remove confounding factors and assess the effect of breastfeeding on obesity by comparing two cohorts with different confounding structures (i.e., high income vs. low–middle income countries) [47]. The authors stated that if there was a causal effect of breastfeeding, then it should be apparent in both cohorts irrespective of the differing confounding structures. An association was found in the British cohort (high income) [48], but not in the Brazilian cohort (low–middle income) [49], indicating confounding. This study looked at breastfeeding up to 3 months only at which point breastfed and formula fed infants do not generally diverge in weight [50] and therefore no firm conclusions can be drawn.

Even with consistent definitions, observational studies are not able to establish a causal relationship between breastfeeding and obesity [36]. Randomized controlled trials are the "gold standard" for determining causality, but it would be unethical to carry out such a trial comparing breastfeeding and formula feeding given the proven health [51, 52] and developmental benefits of breastfeeding [53]. A randomized control trial in relation to breastfeeding promotion was carried out in Belarus [51]. The PROBIT study could not randomize infants to breastfeeding but instead randomized hospitals to either breastfeeding promotion or not. Although increasing the average duration of breastfeeding, the trial showed no significant differences in BMI between trial groups at 6.5 or 11.5 years of age [54].

Socioeconomic, psychological, behavioral, ethnic, and cultural influences additionally affect the emergence of childhood obesity such as food preferences, food availability, physical activity, and sedentary behavior [55]. Because obesity is multifactorial, disentangling the breastfeeding effect is difficult and requires control of confounding variables for which information may not always be available or complete. The extensive literature highlights the conflicting existing evidence on this topic. Therefore we investigate the mechanisms and biological plausibility of the hypothesis.

Mechanisms that May Influence Later Obesity

A number of mechanisms may influence later obesity. Generally breastfed infants are leaner than formula-fed infants [56–58] and behavioral and hormonal mechanisms may explain this difference [59–63].

Behavioral Mechanisms

The first mechanism is behavioral as bottle feeding may promote more parental control and less self-regulation than breastfeeding. Focus groups [64] of low-income mothers participating in a nutrition program revealed that most believed a heavy infant was a healthy infant and supplemented the diets of their infants to alleviate fears that their child was not getting enough to eat. Thus while formula-fed infants may be governed by judgment of the feeding parent, breastfed infants have more discretion over their milk consumption than formula-fed infants. It is argued that regulation of intake differs between breast and bottle-fed babies and that breastfeeding enables the infant to develop the capacity to self-regulate as opposed to responding to the judgment exercised by the parent or career in the case of formula feeding [56]. Maternal feeding styles that are less controlling and more responsive to infant cues of hunger and satiety may allow infants greater self-regulation of energy intake [65]. Furthermore, mode of infant feeding may influence acceptance of solid foods at a later age [66], with breastfed children less likely to be fussy eaters. Food preferences subsequent to breastfeeding may be affected by mode of feeding as breastfed infants may more readily accept novel foods [60, 66, 67].

Mechanisms influencing behavior are related to the physical act of breastfeeding. The first theory is that a breastfed infant self-regulates his/her energy intake based on energy requirements [68] and ceases feeding in response to internal cues which may be lost with the reduced self-control during bottle feeding [69]. One study showed that infants who were fed from the bottle early in infancy were more likely to finish a bottle in late infancy compared to those breastfed in early infancy. It was also shown that the type of milk (formula or expressed breast milk) had no influence on whether the bottle was finished, demonstrating that it may be the physical act of suckling rather than the composition of the milk that was important [69]. Hence, formula-fed infants are more likely to have larger meals, further apart, consuming up to 20–30% higher volume than breastfed infants [70].

The smell, taste, and composition of breast milk vary from morning to night and from day to day, between breastfeeds and even during a breastfeed, as opposed to the invariable content of formula, depending on maternal diet, maternal age, and whether the milk is fore or hind milk. Maternal milk exposes infants to a variety of flavors that influence their food choices and dietary habits later in life [7]. The varying fat content during a breastfeed may signal to the infant that their meal is coming to an end [69] or more recently Keratas et al. suggested that different levels of hormones in hind milk, toward the end of a feed, may signal satiety in the infant, resulting in cessation of feeding [71].

The theory of reverse causation in relation to growth suggests that infants who have lower growth trajectories, and therefore lower energy requirements, are satisfied with breastfeeding for longer.

Children who have already been "programmed" to be larger require higher energy intake and demand more food, resulting in a mother supplementing with formula or solid food earlier [72].

Bioactive Compounds in Milk

Breast milk has a unique and varied composition when compared to the constant composition of formula. Breast milk has higher fat content and lower protein content, as well as bioactive factors absent in formula [73]. In regard to risk of later obesity, the most important differences between breast milk and formula appear to be related to protein content and the presence of hormones and growth factors [73]. Plausible biological mechanisms underlying the protective effect of breastfeeding against obesity are based on the unique composition of human milk and the metabolic and physiological responses to human milk [74, 75]. Breastfed infants may absorb less energy per volume than formula-fed infants as well as receive modifying growth factors that may inhibit adipocyte differentiation [74, 76].

Hormones

A number of hormones in breast milk play an important part in energy metabolism, appetite regulation, and food intake [73]. Differences in feeding habits, i.e., breast milk or formula, result in different plasma levels of these hormones, and it may be these differences that cause the variation in early growth, later dietary habits, and obesity [73].

Appetite is controlled by a series of complex process which originate in the hypothalamus. Hormones, such as leptin and ghrelin found in breast milk, play a key role in signaling between the hypothalamus, the gastrointestinal tract, and adipose tissue [73]. These signaling pathways are developed early in postnatal life, with low birth weight and rapid catch-up growth being linked to up-regulation of these pathways, resulting in an increased appetite [77].

Leptin is a peptide hormone found in breast milk that signals satiety and decreases the sensation of hunger in a feeding infant. Breastfed infants have higher plasma leptin levels than formula-fed infants [78]. Leptin controls early growth and development and may also control energy homeostasis, food intake, and body composition during this period reducing the rate and amount of early growth [73]. During crucial periods, leptin acts on neural pathways that may control food regulation and decrease adiposity later in life [79]. As a regulator of food intake and energy metabolism leptin has been shown to be higher in breastfed than bottle-fed infants [80]. However Lonnerdal and Havel [81] found that serum leptin levels were not higher in breastfed infants than in those fed formula and concluded that the contribution from breast milk may be unlikely to explain observed differences in body composition resulting from feeding mode. Leptin was shown not to be present in infant formula, even though previously it was thought to be [82].

Ghrelin is another hormone found in breast milk instrumental in both short-term and long-term feeding habits as well as long-term energy metabolism. Higher ghrelin levels are related to an increased food intake and decreased energy output, which results in promotion of adiposity [83]. Breastfed infants have lower levels of ghrelin than formula-fed infants, suggesting an inhibitory effect of breast milk and an inverse relationship between ghrelin levels and weight gain in infancy [78]. High ghrelin levels may influence fasting time between meals of formula-fed infants, as the increased appetite of formula-fed babies results in an increased feeding volume per feed [78].

The hormone adiponectin is present in breast milk but its role in growth and development is not fully understood. High plasma levels of adiponectin are inversely related to adiposity and positively related to insulin sensitivity [84]. Lower adiponectin levels are associated with obesity and diabetes mellitus type-2 later in life and higher levels have been shown in breastfed infants [84].

Growth Acceleration Hypothesis (Early Weight Gain)

The adverse long-term effects of early growth acceleration emerge as fundamental in later overweight and obesity [85]. Childhood growth acceleration (erroneously called catch-up growth) is associated with later insulin resistance, obesity [86], and CVD [87], dyslipidemia, raised insulin concentration, and increased insulin growth factor 1 [88]. Growth acceleration is highest in early infancy suggesting that this period may be critical. Furthermore, early programming of the hypothalamic-pituitary-adrenal (HPA) axis could directly affect later CVD and non-insulin-dependent diabetes (NIDDM).

The *growth acceleration hypothesis* suggests that rapid early weight gain, rather than the specific mechanisms that cause it, may program for later obesity as well as the other aspects of metabolic syndrome including high cholesterol, high blood pressure, and insulin resistance [36]. This hypothesis is strengthened by the results of studies of early infant growth showing that upward centile crossing, for weight and length in infancy, leads to an increase in obesity risk later in life [33]. Rapid growth in the first few months of life leads to elevated risk of obesity in breastfed as well as formula-fed infants [36]; however as breastfeeding has been shown to promote slower growth, obesity is less likely in breastfed infants [89, 90]. These data support the link between a longer duration of breastfeeding and a decreased risk of later obesity.

A crucial period during postnatal growth relating to obesity risk has been hypothesized; however the timing of this period remains uncertain, with some suggesting the crucial period to be in the first few weeks of life [36] while others suggest that up to 2 years may have an effect [91]. Regardless of this discrepancy, breastfeeding is a key factor in influencing infant health during this period.

In 2010 Singhal et al. [92] looked at two randomized control trial cohorts to assess how infant diet relates to infant growth rate and later obesity. Infants were randomly allocated to either control formula or nutrient-enriched formula [93]. The results provided evidence toward a causal link between the rate of weight gain in infancy and later obesity, showing that infants who gain weight at a faster rate early on, have an increased risk of obesity later [92]. Therefore, the mechanism by which breastfeeding contributes to a lower risk of obesity later in life may be via the promotion of a slower growth pattern in infancy.

Accelerated postnatal weight gain may be intrinsically damaging because fetal growth restriction leads to reduced cell numbers, and subsequent catch-up growth is achieved by overgrowth of a limited cell mass [86]. The increased risks for diseases in adulthood such as type-2 diabetes and hypertension, associated with small size at birth, are exacerbated in those children who become obese [4, 86, 94] and the importance of nutrition in early childhood growth is emphasized by the marked difference in growth rates between breast and bottle-fed babies [95, 96].

Early Protein Hypothesis

The *early protein hypothesis* proposes that the higher protein content of formula (up to 70% higher [63]) is responsible for an increased growth rate and adiposity during the influential period of infancy [39]. The elevated protein intake of formula stimulates the release of insulin and insulin growth factors, both of which may enhance growth in 1–2-year-olds [97, 98]. Raised insulin levels have been observed in formula-fed infants as early as six days after birth [99], and may cause increased fat deposition and early development of adipocytes [100]. Raised insulin levels may also program higher long-term insulin concentrations which could contribute to later obesity [36]. The reduction of human growth hormone secretion in infants with high protein levels may play a role in obesity by reducing the breakdown of fat by lipolysis [39]. Breastfeeding, on the other hand, has a protective effect on obesity by inducing lower plasma insulin levels, thereby decreasing fat storage and preventing early adipocyte development [101].

A recent study that compared the BMI of infants fed high protein formula versus low protein formula is supportive of the early protein hypothesis [102]. This study found a higher BMI at 2 years in the high protein group, with the low protein group having BMI values closer to that of breastfed infants [102]. A further explanation may be that plasma insulin levels are higher in formula-fed infants than those who are breastfed [60, 81, 103] which may be due to the higher protein content of formula that in turn influences levels of circulating amino acid [103, 104]. While this difference could well explain higher levels of fat deposition in formula-fed infants, it would be expected to have a far greater effect on adipocyte size rather than adipocyte number at this stage of life [105] and thus the effect may be transient.

Breastfeeding may protect against overfeeding, calorie excess, and hence future obesity [100]. Formula-fed infants have higher total energy [106], protein [59], and micronutrient intakes [107] than do breastfed infants and this may stimulate increased secretion of insulin [60], higher output of hepatic glucose [61], and insulin growth factor (IGF binding protein-1) [62]. The phenomenon of early nutrition having long-term effects on growth, metabolism, and health [4] has been termed "nutritional programming" and has been defined as a long-term change in the structure and function of an organism resulting from a stimulus acting at a critical period of development in early life [30, 59, 108]. Infants receiving formula consume 66–70% more protein compared with breastfed infants [63, 109], a fact that may explain why breastfed infants are leaner than formula-fed infants at 1 year [56]. However it cannot be excluded that differences in energy intake or other confounding factors play a role in the development of infant adiposity [56, 63, 110]. Indeed, a longitudinal study of children did not indicate that total energy intake at 12 weeks was a major determinant of body fatness at 2–3.5 years [111].

Growth velocity may be a relevant influence in the causal pathway of obesity as suggested for fetal programming of metabolic disease [112, 113] and associations between protein intake and growth velocity and weight gain have been reported [61, 109]. Infants 1 week of age who were fed formula with a higher protein: energy ratio showed a tendency for higher body weight gains than those fed formula with a lower ratio [109] and infants fed formula with a higher protein:energy ratio compared with the breastfed group had a higher BMI [114]. The biological mechanism that may potentiate an association between early life dietary protein intake and obesity may be linked to glucose metabolism [59]. Formula-fed infants with high protein intakes may have a higher insulin secretion and high hepatic glucose output [61, 99] because IGF-1 is regulated by dietary protein intake [62] and both insulin and IGF-1 are required for pre-adipocyte differentiation and adipogenesis induction. Alternatively, reduced amino acid concentrations induce IGF-1 expression participating in down-regulation of growth [115]. These changes in formula-fed compared to breastfed infants may have effects on circulating amino acid concentrations such as protein-related alterations of energy expenditure, influences on hormones and growth factors, and adipose tissue metabolism in response to perturbations of amino acid homeostasis brought about by gene expression regulation [59].

Breastfeeding and Endothelial Function

Although a limited number of studies have looked into the direct relationship between breastfeeding and endothelial function, a Finnish study in 2009 showed an enhanced endothelial function in 24- to 39-year-old men who were breastfed compared to formula fed, regardless of current risk factors [18]. Other studies have also shown positive correlations between breastfeeding and improved endothelial function [19, 116, 117]. It is not yet fully understood how breastfeeding may directly influence endothelial function, but it has been suggested that the presence of long-chain polyunsaturated fatty acids (LCPUFAs) in breast milk may enhance the development of blood vessels, as LCPUFAs are important structural and functional components of vessel walls [18]. The absence or reduction of available LCPUFAs during critical periods of development, as may be the case in formula feeding,

may cause suboptimal endothelial formation and function [19]. Therefore there is evidence that a longer duration of breastfeeding may both directly (via LCPFUAs) and indirectly (via hyperglycemia, raised insulin levels, and hyperlipidemia) affect endothelial function and subsequently decrease the risk of cardiovascular events.

Breastfeeding and Cholesterol Levels

A meta-analysis in 2002 investigated the relationship between breastfeeding and cholesterol levels during infancy, adolescence, and adulthood [118] and showed that breastfed infants had higher total cholesterol and LDL cholesterol levels, which is consistent with the higher cholesterol content of breast milk compared to formula. Conversely, adults who were breastfed were found to have lower cholesterol levels, suggesting a mechanism where raised cholesterol levels in infancy programs a more efficient cholesterol metabolism later in life [119]. There is inconsistency in the literature regarding whether breastfeeding directly influences lipid profile later in life, or whether these findings are due to publication bias and confounding [120] and more research is needed in this area.

Adiposity Rebound

The BMI curve rises during the first year of life so that 1-year-old children appear chubby, but the curve decreases following the first year to about 6 years of age when fatness increases again [105]. This increase is termed the adiposity rebound. The duration of fatness decreases after 1 year of age and varies between children so that the adiposity rebound can occur between 4 and 8 years with the earlier rebound, the higher the adiposity at the end of growth. In fact among children who become obese the adiposity rebound occurs as early as 3 years of age when compared to about 6 years for children of normal BMI [105].

Adipocyte cell size increases during the first year of life and then decreases, increasing again from approximately 6 years of age. Transient obesity in early childhood could involve the increase in cell size but persistent obesity commencing with an early adiposity rebound could be associated with early cell multiplication. One aspect which requires clarification is the impact of breastfeeding on the timing of the adiposity rebound [121]. The duration of fatness decrease after 1 year of age is a better predictor of adult fatness than fatness in early childhood [105]. For this reason an understanding of the role of infant feeding mode on the adiposity rebound in future research is of utmost importance.

Case Study: West Australian Pregnancy Cohort (Raine) Study

The West Australian Pregnancy Cohort (Raine) Study is a prospective birth cohort study followed up from 16 to 20 weeks gestation to 14 years of age that provided infant feeding data [122]. These data were confirmed by the child health research nurse and standard anthropometric assessments of height and weight, using strict protocols, were conducted by a small group of extensively trained staff at 1, 3, 6, 8, 10, and 14 years [122] .

Length was measured to the nearest 0.1 cm using the Harpenden Neonatometer at birth and 1-year follow-up, and thereafter using a Holtain stadiometer. Weight was assessed to the nearest 100 g, using calibrated hospital scales at birth and a Wedderburn digital chair scales thereafter.

Our previous findings suggest that infants fed breast milk for a shorter duration had a higher height and weight and calculated BMI at 1 year, and experienced more overweight and obesity

when compared with infants fed other sources of milk at less than 4 months of age and following adjustment for maternal factors and parity throughout childhood (OR 1.87; 95% CI 1.21, 2.89; $p=0.005$) [123, 124].

Adiposity rebound, defined as the last minimum (nadir) BMI before the continuous increase with age [125], was calculated in a subset of individuals ($n=171$) for whom a complete set of BMI data were available. This small sample was due to limited anthropometric measurements taken at the 2-year follow-up [105]. Adiposity rebound was based on the child's age in months. BMI and age at nadir were calculated for both the raw BMI and predicted BMI (based on the longitudinal LMM which adjusts for age, gender, weight status, and gestational age). Adiposity rebound occurred for the normal weight group at 5.3 years (SD = 2.2), for the overweight group at 3.8 years (SD = 2.2), and for the obese group at 2.6 years (SD = 1.4). There were no statistically significant differences between the overweight and obese groups in the timing or BMI at adiposity rebound. The timing of adiposity rebound (age at nadir) was earlier ($p=0.005$), and the BMI at nadir was higher ($p=0.003$) for the group who stopped breastfeeding ≤4 months. Only BMI at nadir was higher ($p=0.002$) for the group who introduced milk ≤4 months.

We found that early infant feeding influenced the timing and BMI at adiposity rebound and that this influence remained until adolescence. The age when breastfeeding stopped and the age when milk other than breast milk was introduced played a significant role in the trajectory of BMI from birth to 14 years, especially in the 4-month cut-point group differences for BMI peak at age 1 year, with this difference consistent over time (Fig. 15.1).

The timing of the adiposity rebound may be identified as a marker for later obesity [126] with our data depicting significantly different pathways for the weight status groups. As shown in Fig. 15.1, those who were breastfed for >4 months had lower mean BMI. Using our data to statistically model population behavior, breastfeeding was shown to play an important role in the timing of the adiposity rebound, and both breastfeeding and the age when other milk was introduced were important contributors to BMI at adiposity rebound. Our results support early feeding literature [36] that suggests formula-feeding compared to breastfeeding results in accelerated weight gain in the infant, with probably upward BMI centile crossing [127] as depicted in the adiposity rebound nadir results.

Several factors strengthen confidence in the validity of our findings. Duration of full breastfeeding as an independent factor demonstrated a weak association with child BMI at ages 3, 6, 8, and 14 years. Adjustment was made for a number of associated factors including parity, maternal education, smoking behavior, and maternal BMI (before pregnancy). However, rapid growth during the first year of life was associated with increased BMI at the age of 6 and 8 years in both boys and girls [128] providing the link between infant feeding and later obesity.

Conclusion

Metabolic syndrome is associated with a twofold increased risk of developing CVD and a fivefold risk of developing diabetes mellitus type-2 [11]. The mechanisms by which metabolic risk factors contribute to these diseases are complex and not completely understood. Obesity may be the main mediator in metabolic syndrome and further disease, and nutrition during early infancy has an effect on the development of later obesity. We highlight the potential for early intervention in the development of obesity, metabolic syndrome, and further health problems such as CVD and DMT2, by early nutritional interventions including breastfeeding.

As with other programming effects, the effect of early diet and growth on later cardiovascular health may amplify with age; therefore the early postnatal period is particularly important for targeting interventions. Our findings suggest that the promotion of breastfeeding decreases the risk of overnutrition and overgrowth particularly in the early weeks of life. A possible adverse effect of formula

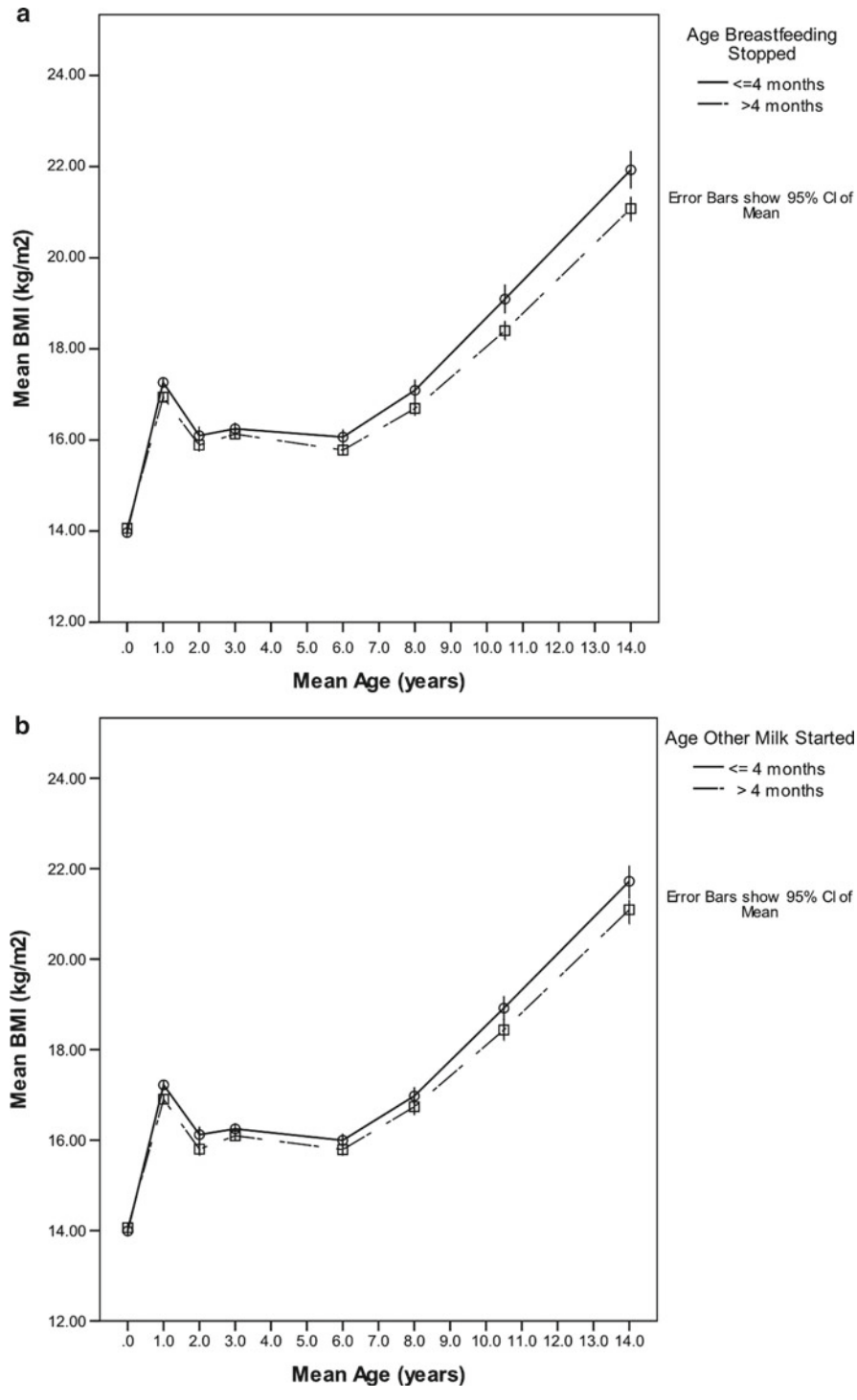

Fig. 15.1 Mean BMI over mean age based on age breastfeeding stopped (**a**) ($n = 1{,}330$) and age other milk started (**b**) groups ≤ 4months and >4 months ($n = 1{,}320$) [122]

milk on postnatal weight gain and infant health remains of contemporary public health relevance. Because postnatal factors may be amenable to intervention, the contribution of postnatal programming to cardiovascular health is of particular importance to science and public health. Further research is of high priority in the interests of population health—the magnitude of the effect size suggests that early nutrition and growth will make a major contribution to long-term cardiovascular risk.

To summarize our current knowledge:

- Overweight infants are more likely to become overweight children, adolescents, and adults
- Breastfeeding to 6 months of age reduces the rate of overweight and obesity
- Given the other known benefits of breastfeeding, increasing the prevalence of exclusive breastfeeding to 6 months would be a very worthwhile public health measure
- A possible adverse effect of formula milk on postnatal weight gain and infant health remains of contemporary public health significance

Acknowledgment WH Oddy is supported by a National Health and Medical Research Council of Australia Population Health Fellowship. Work for this chapter conducted by Ms McHugh was funded from a National Heart Foundation/ Beyond Blue Strategic Research Initiative.

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Chapter 16
Methods to Improve the Use of Breastfeeding

Asefeh Faraz

Key Points

- Healthcare providers play an integral role in providing breastfeeding education and support to mothers and their families.
- Educational classes are the most effective intervention shown to improve the initiation and/or duration of breastfeeding.
- Peer support programs and group breastfeeding classes are effective modes of increasing breastfeeding initiation and continuation.
- A woman's partner, family, friends, and peers are valuable allies in promoting breastfeeding.

Keywords Breastfeeding initiation • Breastfeeding continuation • Health promotion • Partner/family support • Peer support • Education

Introduction

The nutritional benefits of breast milk as well as the psychosocial benefits of bonding between mother and infant have been well established in the literature, and widely disseminated to the public. The American Academy of Pediatrics (AAP) recommends exclusive breastfeeding for the initial 6 months postpartum, with continued breastfeeding through at least the first year of life, or as long as desired by both mother and infant [1]. The Department of Health & Human Services *Healthy People 2020* goals aimed to increase breastfeeding rates to 81.9% immediately postpartum, 60.6% at 6 months, and 34.1% at 1 year [2]. However, the United States (U.S.) has continued to fall short of these goals, with the latest statistics from the National Immunization Survey (NIS) revealing breastfeeding continuation at merely 43% at 6 months and 22% at 1 year [3]. Exclusive breastfeeding rates are even lower, at only 33% at 3 months and 13% at 6 months [3]. Furthermore, only one state in the U.S. has met all five *Healthy People 2020* objectives (Table 16.1). In order to improve breastfeeding rates internationally, the World Health Organization (WHO) in conjunction with the United Nations Children's Fund (UNICEF) developed the Baby-Friendly Hospital Initiative (BFHI) in 1991 (Table 16.2), and the U.S. Preventive Services Task Force (USPSTF) made evidence-based primary care-based intervention recommendations in 1999 to support breastfeeding. Despite increasing awareness of the importance

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R.R. Watson et al. (eds.), *Nutrition in Infancy: Volume 1*, Nutrition and Health,
DOI 10.1007/978-1-62703-224-7_16,

Table 16.1 Healthy People 2020 objectives

1. 81.9% of mothers initiating breastfeeding
2. 60.6% of mothers breastfeeding their infants at 6 months of age
3. 34.1% of mothers breastfeeding their infants at 12 months of age
4. 46.2% of mothers exclusively breastfeeding their infant through 3 months of age
5. 25.5% of mothers exclusively breastfeeding their infant through 6 months of age

Note: From "Breastfeeding: Data Report Card," by CDC, 2011

Table 16.2 Ten steps to successful breastfeeding

1. Maintain a written breastfeeding policy that is routinely communicated to all health care staff
2. Train all health care staff in skills necessary to implement this policy
3. Inform all pregnant women about the benefits and management of breastfeeding
4. Help mothers initiate breastfeeding within an hour of birth
5. Show mothers how to breastfeed and how to sustain lactation, even if they are separated from their infants
6. Give infants no food or drink other than breastmilk, unless medically indicated
7. Practice "rooming-in"—allow mothers and infants to remain together 24 h a day
8. Encourage unrestricted breastfeeding
9. Give no pacifiers or artificial nipples to breastfeeding infants
10. Foster the establishment of breastfeeding support groups and refer mothers to them on discharge from the hospital or clinic

Note: From "The Baby-Friendly Hospital Initiative," by WHO and UNICEF, 2004.

of breastfeeding, as well as the various efforts to improve breastfeeding rates, there remains a need for strategies and programs to increase exclusive and predominant breastfeeding initiation and continuation in the U.S. and abroad.

Advantages of Breastfeeding

Benefits for the Infant

The myriad of physiologic and psychosocial benefits that result from breastfeeding are compelling reasons to engage in this health-promoting behavior. There are vital nutrients in breast milk, including iron [4]. Furthermore, the immunoglobulin IgG present in colostrum has protective effects immunologically for the vulnerable and developing infant immune system [4]. These include decreased incidence of respiratory tract infections, otitis media, diarrhea, and necrotizing enterocolitis [5, 6]. These illnesses can be serious and even life threatening in infants; by decreasing their risk, the infant mortality rate is also drastically reduced. There is also some evidence of a relationship between breastfeeding and decreased childhood obesity, as well as decreased prevalence of type 1 and type 2 diabetes mellitus [7–9]. Enhanced mother-infant bonding and emotional adjustment later in childhood are psychosocial benefits associated with breastfeeding [7].

Benefits for the Mother

Breastfeeding is perhaps best known for its effect on postpartum weight loss in women, but its effects go far beyond this noticeable advantage. Temporary contraception as a result of delayed ovulation as well as rapid return of uterine tone in the postpartum period are other immediate benefits [10, 11]. Long-term effects of breastfeeding extend into the postmenopausal period, protecting women against osteoporotic hip fractures [12]. Breastfeeding has also been linked to decreased rates of premenopausal breast cancer, as well as ovarian and endometrial cancers [13–17].

Historical Background

Until the twentieth century, breastfeeding was common practice. However, with the changes that have come about in the last century, most notably with the advent of the formula industry and the changing female role outside of the home, breastfeeding is no longer the obvious option it once was for all women.

Barriers to Breastfeeding

The Working Mother

More women are working outside the home in addition to their principal roles as caregivers [4]. Currently, in the United States, more than half of women with children under 1 year of age work outside the home. Returning to work presents a particular challenge to continuing breastfeeding, as convenience becomes a major factor. For example, bottle feeding is easier for the working mother than pumping and storing milk throughout the day, or finding the time to breastfeed during a busy workday. Furthermore, employers are often less than supportive in their policies for providing adequate time and facilities for proper breastfeeding or pumping. Although there are laws mandating time and space for breastfeeding and/or pumping at work [18], only ten states have statutes in place, and many don't mandate that employers provide breaks or places to pump [19]. These factors lead to fewer working moms breastfeeding than stay-at-home moms. In fact, only 10% of working moms breastfeed, compared to three times as many stay-at-home moms [4].

The Formula Industry

The advent and production of formula has drastically influenced breastfeeding practices. Aggressive marketing tactics encourage mothers to use formula as breast milk substitute or supplementation. In response to this, WHO devised the International Code of Marketing of Breast-Milk Substitutes in 1981 to protect mothers and healthcare providers (HCPs) from industrial pressure by formula companies [20]. Key conditions include formula manufacturer prohibition from providing free formula samples to mothers or healthcare facilities, as well as incentives to HCPs (Table 16.3). These provisions are intended to decrease the negative effects of providing formula on breastfeeding, as well as decrease influence on HCPs.

Table 16.3 Ten provisions of the International Code of Marketing of Breast-Milk Substitutes

1.	No advertising of breast-milk substitutes to the public
2.	No free samples of breast-milk substitutes/related products to mothers
3.	No promotion of breast-milk substitutes/related products to health facilities
4.	No company "mothercraft" nurses to advise mothers
5.	No gifts or personal samples to health care workers
6.	No words or pictures idealizing artificial feeding, including pictures of infants on the labels of the product
7.	Information to health workers must be scientific and factual
8.	All information on artificial feeding, including the labels, should explain the benefits of breastfeeding and the costs and hazards associated with artificial feeding
9.	Unsuitable products, such as sweetened condensed milk, should not be promoted for babies
10.	All breast-milk substitute products should be of a high quality and take into account the climactic and storage conditions of the country where they are used

Note: From WHO, 1981

Practice & Procedures

Strategies to Promote Breastfeeding

Breastfeeding Self-Efficacy Scale

The Breastfeeding Self-Efficacy Scale (BSES), developed in 2003 by Torres, Torres, Rodriguez and Dennis, measures breastfeeding confidence [21]. The BSES is a 33-item self-report, Likert-type scale, which has been shown to accurately measure maternal confidence and be a significant predictor of breastfeeding. The BSES has also been translated into Spanish, and been shown as an effective instrument to identify Hispanic women at high risk for prematurely discontinuing breastfeeding. This self-assessment can be provided to women in the prenatal period and used by HCPs as a tool in guiding discussions about breastfeeding.

Hospitals (BFHI)

While the decision to breastfeed is contemplated before the birth of a child, the hospital experience is a critical juncture in the initiation of breastfeeding. The Baby Friendly Hospital Initiative, developed jointly by the WHO and UNICEF in 1991, and updated and expanded in 2009, aims to address this vital period. In order to receive Baby Friendly Hospital designation, a hospital or birth center must demonstrate the *Ten Steps to Successful Breastfeeding* have been implemented. Mean breastfeeding rates in Baby-Friendly hospitals have been demonstrated to be markedly higher than the national average, 83.9–69.5%, respectively [22]. Furthermore, the mean rate of exclusive breastfeeding during the hospital stay in these hospitals was 78.4% compared to the national mean of 46.3% [22]. There are 110 Baby-Friendly birth facilities in the United States as of May 2011 (http:\\www.babyfriendlyusa.org/eng/03.html).

Healthcare Providers

HCPs play an integral role in providing breastfeeding education and support to mothers and their families. During prenatal visits, a thorough intake by clinicians should emphasize past medical history, family history, social history, and medications. Past medical history should assess for conditions that may affect breastfeeding, such as TB or /HIV. Family history questions should elicit how much exposure the patient has had to first-degree female relatives, particularly their mother, who have breastfed. With regard to social history, it is important to assess the patient's living situation and support network, including partners, family members, and friends. Her work situation should be discussed, with particular attention to employer policies on maternity leave and breastfeeding accommodations. Any medications the mother is taking and their impact on breastfeeding should be reviewed. Women may be unaware of the transmission of medications through breast milk, and the alternative method of feeding or pumping prior to taking medications [23].

The physical exam related to breastfeeding is essential, though it may be brief. A careful breast exam is necessary, assessing for masses or nipple conditions, including but not limited to skin abnormalities or signs of infection. Women may have concerns about the adequacy of their breasts or nipples for breastfeeding. These concerns may include size and shape of breasts or nipples, inverted nipples, prior infections, surgical procedures, nipple jewelry, or breast implants. HCPs can provide education regarding these various breast conditions to alleviate mothers' concerns and encourage breastfeeding. Additionally, anticipatory guidance regarding common breast and nipple conditions

related to breastfeeding, including breast engorgement, mastitis, and nipple soreness should be provided. The prenatal visits are opportunities for HCPs to assess mothers' attitudes toward initiating breastfeeding as well as perceived challenges to continued breastfeeding. Sensitive listening and supportive education by HCPs can address mothers' fears and worries regarding breastfeeding, thereby promoting breastfeeding.

The postpartum period is another critical time to assess for obstacles and challenges, which may lead many women to cease breastfeeding. Risk factors for early termination of breastfeeding include delayed breastfeeding initiation, pacifier use, and formula supplementation [24]. HCPs have an opportunity to assess these risk factors and intervene at the initial well-child visit 3–5 days postpartum, and for the first 6 months postpartum. During these visits, HCPs can ensure proper technique, troubleshoot, and monitor the mother's and infant's progress. Mothers should be educated on typical feeding, sleep, and stool patterns of breastfeeding infants. Adequate weight gain should be assessed at each visit, and education provided that formula supplementation is most likely unnecessary. Inadequate infant weight gain is usually unassociated with breastfeeding. Anxiety in the mother and gastroesophageal reflux in the infant are some causes of inadequate weight gain, which should carefully be assessed and addressed.

Group Breastfeeding Classes

A systematic review and meta-analysis of the effectiveness of primary care-based interventions on improving initiation and/or duration of breastfeeding found that educational classes were the most effective intervention [25]. To further support the breastfeeding mother and reinforce individual teaching, a referral should be made to a group breastfeeding class. The group setting facilitates information exchange among participants and allows for greater time spent on education and anticipatory guidance than the primary care setting. These classes may be led by a clinician, but are often led by nurses or lactation consultants. Basic content, such as the benefits of breastfeeding and anatomy and physiology, is combined with hands-on skills training to practice proper techniques and become familiar with equipment use for a comprehensive learning experience. Various modes for learning include videos, dolls, and observing a newborn breastfeeding [26]. Smaller workgroups can then be used to discuss common breastfeeding myths, fears and concerns the mothers may have. These smaller groups also provide an opportunity to brainstorm and discuss solutions to breastfeeding problems, which can then be shared with the larger group to benefit all participants. At the end of the interactive class, all participants devise personalized breastfeeding plans to incorporate their personal lifestyle, priorities and needs with their newfound knowledge. Partners and family members are also encouraged to attend these group classes with the breastfeeding mothers, and participate in creating personalized breastfeeding plans. By doing so, they are explicitly stating how they will support the breastfeeding mother, making support more tangible and realistic to achieve.

Lactation Consultants/Breastfeeding Advocates

When a mother feels unsupported by her family and employer, she may choose to elicit the help of a personal breastfeeding advocate, available through La Leche League International (LLLI). The volunteer "leaders" prepared by LLLI coach breastfeeding women in easing communication with employers, partners, and even HCPs. La Leche League Leaders are volunteer mothers who are members of LLLI, with at least 9 months of breastfeeding experience, and have completed an accreditation-training program. This program includes education and training on breastfeeding management, child development, parenting, communication skills, and supporting and counseling mothers [27]. Prior to having a difficult conversation, mothers have the opportunity to practice a dialogue and are prepared with a

rehearsed mental script; this communication practice may increase their confidence during their interactions and help get their needs met [28]. Having a true breastfeeding ally can help women feel more supported and confident in approaching intimidating settings and stressful situations when attempting to elicit breastfeeding support from unresponsive employers, family members, or partners.

Workplace/Employers

Just as more workplaces are becoming more childcare friendly, it is vital that they also become breastfeeding friendly, as breastfeeding continuation rates have been shown to rapidly decline in mothers returning to work [23]. Causes include lack of schedule flexibility and workplace accommodations to breastfeeding or expressing and storing milk, lack of employer and coworker support, and perceived or real decreased milk supply [29–31]. Vital components of a successful workplace program are time, space, support, and gatekeepers [32, 33]. A private Nursing Mother Room (NMR) with adequate lighting, ventilation, seating, an outlet, a sink, and refrigerator should be centrally located in the workplace [32, 33]. Strategies for providing adequate time for breastfeeding or milk expression include flexible work schedules, scheduled breaks for feeding or pumping, and job sharing. Ideally a supportive breastfeeding work environment is created by employers for continued breastfeeding after mothers return to work. Workplace support of breastfeeding mothers benefit families as well as the employer. These benefits include decreased absenteeism and increased productivity and loyalty, decreased turnover, enhanced employer public image, and decreased healthcare costs [32–34].

Peer/Social Support

Perceived social support has been identified as a predictor in successful breastfeeding [35]. Women's social networks are highly influential in decision making, and can either hinder or facilitate the decision to breastfeed [36]. A systematic review evaluating programs to promote breastfeeding found that peer support programs were independently effective in increasing breastfeeding initiation and duration [37]. Peer counseling programs may be hospital, clinical or community based, and counselors may either be paid or volunteers. Peer counselors should ideally be of similar racial and socioeconomic backgrounds as the mothers they are supporting. Peer mothers support and counsel breastfeeding women in order to provide encouragement and assistance in preventing and addressing breastfeeding problems [38]. Peer counselors may provide support during the prenatal or postpartum period, via telephone, in the clinical or home setting. Peer mothers are especially helpful during the initial postpartum period, although prolonged counseling is also beneficial. Peer counselors receive training, and are monitored by a healthcare professional specializing in lactation management, such as a healthcare professional or IBCLC. Integration of peer support programs into the overall healthcare system contributes to the ongoing success of the program and provides access for breastfeeding mothers.

Partner/Family Support

A woman's partner and family can be important allies or obstacles to breastfeeding. Women whose mothers, close relatives, or friends breastfed are more likely to breastfeed themselves [39]. A woman's partner also plays an integral role on whether or not she will breastfeed, particularly their attitudes toward and support of breastfeeding [39]. In fact, partners can be so influential in the mother's decision to breastfeed that focusing on the partner's beliefs is just as important in predicting

breastfeeding behavior by the mother [40]. A randomized controlled trial found that 74% of mothers whose partners attended a breastfeeding education and promotion class initiated breastfeeding as compared to only 41% of mothers whose partners attended a control group class on infant care only [41]. This highlights the importance of involving fathers in the breastfeeding discussion, and aiming interventions at fathers to support women in their decision to breastfeed.

Discussion

With so many compelling reasons to breastfeed exclusively, it is difficult to imagine why breastfeeding is not standard practice. However, there still exist barriers to breastfeeding such as the workplace and the formula industry. In order to improve breastfeeding rates, healthcare providers play a key role in connecting women to available resources and support. It should also be emphasized that a woman's partner, family, friends and peers are valuable allies in promoting breastfeeding. Research has shown the efficacy of peer support programs and group breastfeeding classes in increasing breastfeeding initiation and continuation. The most critical period for breastfeeding support seems to be immediately postpartum, in the hospital and during initial visits with community providers. Another vital period is when women are returning to work, and having the support of their colleagues and employers in continuing to breastfeed. HCPs and breastfeeding coaches should continue to follow up with breastfeeding mothers during the first 6 months to year postpartum to ensure exclusive breastfeeding continuation and provide support as obstacles are encountered. Through this comprehensive approach, breastfeeding initiation and duration rates can continue to improve and the health of mothers and infants enhanced.

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Chapter 17
Early Breastfeeding Cessation in Infants: Causes and Solutions

Antonio Oliver-Roig

Key Points

- Women at greater risk of early breastfeeding cessation tend to be younger, with a low-income and unsupported, with less experience and lower self-efficacy. These mothers wish to breastfeed for shorter durations and have negative attitudes towards breastfeeding. Most women discontinue breastfeeding prematurely because of perceived difficulties rather than maternal choice. The impact of breastfeeding problems may be related to women's emotional discomfort rather than severity. Decisions taken by mothers about stopping breastfeeding are negatively influenced by poor legal, work, and social environments, by professional activities that may hinder the initiation and continuing of breastfeeding and by the cultural assumptions that make formula feeding the norm.
- Breastfeeding support should adapt to the moment and needs of each woman and should be provided by people with the appropriate specialized training. It is necessary to provide access to resources for population groups at risk and to develop interventions aimed at supporting these specific groups. Breastfeeding is linked to the adequation of professional activities surrounding childbirth. The Baby-friendly Hospital Initiative and culturally sensitive participatory support programs should be routinely implemented and promoted by health care administrators and providers, instead of developing interventions that focus exclusively on the individual decisions of mothers.

Keywords Breastfeeding • Early cessation • Factors • Breastfeeding support • Breastfeeding programs • Health policy • Equity

Introduction

Breastfeeding is the most natural and healthiest way to feed a child during early life given the advantages it offers mothers, infants, and young children [1, 2], in both the short and long term. It also provides social and financial benefits for individuals and groups alike, due to the money saved on formula milk, less absenteeism from work among breastfeeding families, and reduced health care costs, as a result of the lower risk of child illness [1, 3].

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R.R. Watson et al. (eds.), *Nutrition in Infancy: Volume 1*, Nutrition and Health,
DOI 10.1007/978-1-62703-224-7_17,

Table 17.1 Infant feeding practices [14, 15]

Exclusive breastfeeding	The infant receives only breast milk without any other liquid or solid (even water). Oral rehydration solutions, drops, and syrups are allowed
Predominant breastfeeding	The infant receives breast milk as the main source of food, it may drink water, water-based drinks, or fruit juices but no other liquid or solid food (including infant formula)
Full breastfeeding	It includes exclusive and predominant breastfeeding
Partial breastfeeding	The infant receives breast milk, liquids including non-human milk and formula, and solid or semisolid foods
Any breastfeeding	It includes any of the breastfeeding practices
Not breastfeeding	The infant does not receive any breast milk

Early Breastfeeding Cessation and Health Outcomes

There is a dose–response relationship between human milk and human health and, not only initiation, but also exclusivity and duration of breastfeeding affect health outcomes. The World Health Organization recommends exclusive breastfeeding during the first 6 months of life and continued breastfeeding with adequate complementary foods until at least 2 years of age [4].

Both in developing countries [5] and in the developed world [2], short term exclusive breastfeeding or early breastfeeding cessation involve a significant increase in the risk of infectious diseases and a host of chronic diseases and conditions.

In low-income countries [6, 7], or in cases of humanitarian emergency [8], the consequences of introducing formula supplements, and particularly early breastfeeding cessation, are much worse than in high-income countries. Suboptimum breastfeeding in such regions results in 1.4 million deaths per year (12% of under-5 deaths) and 10% of disease burden in children under 5 [5].

In studies carried out in high-income countries, a lower duration of full or exclusive breastfeeding has been related to a greater risk of gastrointestinal infection, hospitalization as a result of infections during the first year of life, atopic dermatitis or Sudden Infant Death Syndrome [2, 9, 10]. Meanwhile, those children breastfed for a shorter duration have been observed to be at higher risk of infections, hospitalization, Sudden Infant Death Syndrome, childhood lymphoid malignancy, type 1 diabetes, asthma, necrotizing enterocolitis in preterm infants, obesity in adolescence or as an adult, adult high blood pressure and later life type 2 diabetes [2, 10, 11].

Infant Feeding Practices

The lack of a common definition of breastfeeding practices is one of the problems that hinder a fair comparison of true incidence, breastfeeding duration rates, and research results from different studies [12, 13]. For the purposes of this chapter, we use definitions for breastfeeding practices (Table 17.1) consistent with those defined by the WHO [14].

During the last century, breastfeeding rates fell dramatically worldwide and particularly in developed countries. Although these rates have been increasing in many regions [16–18] since the 1990s, few women breastfeed exclusively and most stop breastfeeding within the first few months postpartum, even in societies where breastfeeding is still the norm:

- In Africa, Asia, Latin America and the Caribbean, breastfeeding is practiced by a vast majority of mothers, although the most frequent pattern is predominant or partial breastfeeding [5, 19]. Only 47–57% of children under 2 months and 25–31% of those between 2 and 5 months are exclusively breastfed. Children in these regions stop breastfeeding when aged 6–11 months at rates of 6, 10 and 32% respectively [5].

Table 17.2 Factors associated with early breastfeeding cessation.

Individual factors	Group level factors	Society level factors
Biophysical factors	Hospital and health services	Cultural beliefs affecting breastfeeding negatively
Delayed onset of lactation	Lack of specific training and skills of health professionals	Bottle-feeding culture
Mother's perception of insufficient milk supply	Hospital practices that make breastfeeding difficult	Acculturation in women from societies where breastfeeding is the norm
Use of formula supplements	Few support resources	Disapproval of public breastfeeding
Incorrect suckling technique	Community, work, and family environment	Lifestyles hindering breastfeeding
Infant health problems	Lack of support from significant others	
Mother's attributes	Difficulties after returning to work	
Short intended duration	Public policy environment	
Decisión made later on	Low priority of breastfeeding	
Negative attitudes towards breastfeeding	Lack of policies protecting, promoting, and supporting breastfeeding	
Negative or without breastfeeding previous experience	Weak legislation based on the International Code of Marketing of Breast-milk substitutes	
Lower self-efficacy perception		
Breastfeeding problems and lower degree of satisfaction with breastfeeding		
Younger age		
Not being married		
Low-income and low-educational level		

- In Europe, Australia, Canada and Unites States, no reliable overall results are available on exclusive breastfeeding rates due to the lack of homogeneity in the studies. Initiation and duration rates show great variability in these regions, with lower breastfeeding rates after 6 months of life than the rest. In Europe and Australia, the breastfeeding initiation rate ranges from 74 to 99.5%, compared with 27–83% in Canada and the United States [12]. At 6 months of age, breastfeeding oscillates between 19 and 52% in Europe, 50–52% in Australia, 31–41% in Canada, and 19–32.5% in the United States [12].

Aim of This Chapter

Multiple factors have been associated with early breastfeeding cessation. However, when just one of the risk factor exists in a given situation this does not necessarily imply breastfeeding cessation; unless other positive factors are also present [20]. As early breastfeeding cessation is usually the result of a combination of various factors, it is best to analyze these causes using the broadest possible approach.

This chapter reviews the research literature available regarding a mother's decision to cease breastfeeding in the early stages, as a complex phenomenon. It also proposes some solutions to this public health problem. In order to clarify this topic, the factors and interventions associated with early breastfeeding cessation have been summarized and discussed under the following three levels of factors (see Table 17.2) [21]:

- Individual level factors: including factors related to the mother-child dyad, directly linked to the mother's decision regarding initiation and duration of breastfeeding.
- Group level factors: describing environmental aspects that have a direct impact on women and their children, including at the hospital and health facilities. Group level and society level factors may interact either positively or negatively with maternal decisions.
- Society level factors: including aspects related to the background in which mothers' feeding practices occur. These influence acceptability and expectations regarding breastfeeding.

Causes of Early Breastfeeding Cessation

Individual Level Factors

Biophysical Factors

The proximate determinants of breastfeeding are the biophysical factors related to crucial aspects of breastfeeding such as the initiation of milk production and its subsequent volume or composition.

- A delay in the initiation of breastfeeding is related to excess infant weight loss in the short-term, and has been linked with shorter breastfeeding duration [22, 23]. Variables such as primiparity, obesity, placental retention, caesarean section delivery, a long labor, stress during parturition, and formula feeding prior to lactogenesis have all been connected with a delayed onset of lactation [19, 23].
- The mother's belief that her milk supply may be insufficient to satisfy her baby's appetite or to ensure appropriate weight gain is a biological factor with a strong psychological component. This is associated with a greater early cessation of exclusive and any breastfeeding [22, 24, 25]. It is the most cited reason for mixed breastfeeding or not breastfeeding, throughout the breastfeeding period [13, 20, 26, 27].
- Insufficient milk supply is rarely caused by primary factors, such as breast abnormalities or hormonal problems, such as the Sheehan syndrome, congenital absence of prolactin, or breast reduction surgery [26, 28]. A mother's obesity or smoking status, linked to a greater risk of early breastfeeding cessation, could be related to the initiation of milk production and its subsequent volume or composition [26, 29].
- It is believed that a mother's perception of insufficient milk supply masks other underlying factors. Almost all mothers, if the child is positioned correctly and receiving feeds on demand, can produce enough breast milk for one child or even more, including those who believe they do not produce sufficient milk [30], even in societies where women's diets are poor [31].
- However, the perception of inadequate milk supply is frequently related to the mother's breastfeeding practices, particularly as regards time patterns of frequency, duration and intervals between feedings, which will all influence the volume and quality of the milk as well as the satisfaction of the baby's appetite. Insufficient milk usually results from mothers limiting frequency or duration of feeds due to nipple pain or return to work, or giving formula supplements [32].
- Breastfeeding is a demand/supply system and breast milk production, after breastfeeding has been established correctly, will vary according to the infant's needs [33]. The regular introduction of formula supplements to substitute breast milk is frequent in mothers who perceive breastfeeding problems or difficulties [34–36]. It also leads to a decline in breast milk production as the infant's demand decreases. Once regular formula supplements are introduced, breastfeeding frequency and suckling duration [36] are reduced and early breastfeeding cessation is

more likely [26, 32, 36]. This effect is greater the smaller the child is when supplements are introduced [36].

- An incorrect suckling technique interferes with milk transfer [37] and is related with breastfeeding problems in the early postpartum period, such as nipple pain [19], a greater risk of exclusive breastfeeding cessation at 6 months and a lower any breastfeeding duration [38–40].
- Significant infant health problems such as premature birth, hospitalization in a neonatal intensive care unit, a large baby or excess infant weight loss, cleft lip and cleft palate can all cause major obstacles to breastfeeding, as well as physical separation and emotional distress, and, consequently, a greater risk of early cessation [26, 28, 32, 41].
- Further studies are required to determine the relationship between early breastfeeding cessation and other variables that may affect the initiation of milk production or subsequent volume, such as the type of birth or labor analgesia, which present contradictory results in different studies [13, 26]. On the other hand, and contrary to popular belief, the use of a pacifier from birth by healthy term breastfeeding infants does not seem to affect breastfeeding duration [42].

The Mother's Intention and Attitudes

Women at higher risk of early breastfeeding cessation wish to breastfeed for less time, make the decision later on and have negative attitudes towards breastfeeding [13].

The intention to breastfeed refers to the method and time a woman plans to breastfeed her child and is one of the main predictors of early breastfeeding cessation. Prenatal intentions to never initiate, ambivalence whether to breastfeed or intentions to stop breastfeeding early are related with higher risk for earlier breastfeeding termination [13, 43]. Intended duration during pregnancy remained a risk factor even if an increase in the intended duration exists after birth and after controlling for the influence of initial breastfeeding experiences [43].

The intention to breastfeed is highly related with maternal attitudes towards breastfeeding and perceptions of others' attitudes towards this practice [43]. Women with a positive attitude towards breastfeeding, who value it as convenient, easy and healthy, tend to breastfeed for longer than those who consider it to be inconvenient, difficult, unpleasant or restricting on their lifestyle [13, 20, 35, 44].

In general, women who believe they are good at breastfeeding have a more positive attitude towards this practice; they are more decisive and see any difficulties as "normal." Meanwhile, women who stop breastfeeding earlier are more likely to have doubts when any problems arise; they are anxious and inflexible about their breastfeeding and focus on the negative sides of breastfeeding [13].

Previous Experience and Maternal Confidence

Primiparous women are at a greater risk of delayed onset of lactation, problems with effective breastfeeding and excess neonatal weight loss in the child [23]. This may be due to the fact that these women have less skills to deal with the task of breastfeeding and any difficulties that may arise, as well as lower levels of perceived self-efficacy [20, 45]. Furthermore, having previously breastfed another child increases the probabilities of a longer duration of breastfeeding [46]. There is also a positive relationship between the duration and mother's evaluation of previous breastfeeding experience and current breastfeeding duration [47].

Maternal breastfeeding self-efficacy is a mother's perceived ability to breastfeed her infant and has been showed to predict breastfeeding duration and exclusivity rates [24]. Lower breastfeeding self-efficacy scores have been associated with the mother's belief that she has an insufficient milk supply [13, 24].

Breastfeeding Experiences

Many women consider breastfeeding to be totally natural and instinctive, and they do not expect to have any problems after the birth. However, it is inevitable that problems will arise during the breastfeeding period. It is almost universal, even among motivated women receiving good breastfeeding advice [23, 40]. During the first days and weeks, problems with breastfeeding are an important cause of early breastfeeding cessation or the introduction of milk formula supplements [32, 35, 48, 49]. Most women discontinue breastfeeding prematurely because of perceived difficulties rather than maternal choice [13].

Breastfeeding problems are more likely to arise during the first 2–6 weeks post-partum [20, 25], and most could be easily resolved with the right help. The most frequently reported breastfeeding problems during the first few weeks post-partum are related to breastfeeding technique, such as sore, cracked or bleeding nipples, poor attachment and not enough milk and, subsequently, problems related to the infant are reported, such as breast refusal, unsettled baby, and also to the mother's perception of not having enough milk [20, 25].

Individually, most breastfeeding problems are not reliable predictors of early breastfeeding cessation [25], as many women suffering frequent breastfeeding problems, such as sore nipples, continue to breastfeed. Also, some of these problems may be considered as "normal" breastfeeding conditions in certain situations [20, 25].

The impact of breastfeeding problems may be related to unrealistic expectations rather than to their severity [20]. A mother's lower degree of satisfaction with breastfeeding, or her negative appraisal of the process, is more closely linked to early cessation than the actual existence of any problems [20, 25, 43]. This association decreases after the first few weeks post-partum, possibly due to the fact that women who continue breastfeeding develop greater self-efficacy [43].

Socio-Demographic Characteristics of Mothers

Studies on the socio-demographic characteristics of mothers analyze data that determine the relationship between breastfeeding rates and aspects that are relatively far-removed from the breastfeeding process itself, which probably do not directly affect the decision made by these women. The influence of these variables may vary over time in particular communities and have varying effects on different populations or on different types of breastfeeding practices [47, 50]. However, these data are essential for drawing up health policies and should be considered as a population's "risk markers," as they make it possible to predict health outcomes, control the evolution of breastfeeding indicators and also pinpoint health inequalities within a particular population [21, 51].

Women who are older, married, well-educated and with a higher income (inverse relationship in developing countries) are all associated with greater breastfeeding initiation, exclusivity and duration in most studies [24, 26].

Group Level Factors

Hospital and Health Services

The characteristics of the place where the birth takes place and the type of care the mother receives during the postpartum stay are related with breastfeeding initiation and duration. The health system is one of the factors that most negatively affect falling breastfeeding rates [52]. Amongst the aspects

contributing to this situation are health care professionals' lack of clinical training and skills to manage breastfeeding problems [19, 53], the shortage of resources aimed at supporting breastfeeding mothers, or practices that make breastfeeding difficult and reduce women's supply of breast milk [52, 54].

When the birth occurs in a home-like institutional setting, the number of infants breastfed at 6 and 8 weeks is greater than for those births that take place in a conventional center [55]. On the other hand, the risk of early cessation of exclusive or any breastfeeding is higher the more obstacles a hospital presents for breastfeeding initiation and continuation [56–58]. Such obstacles include a delay in skin-to-skin contact of mothers and their healthy newborn infants, the unnecessary separation of mothers and their babies during the stay or routine provision of infant formula supplements [13, 37, 59].

Other factors related with early breastfeeding cessation that depend on health services are inappropriate recommendations for discontinuing breastfeeding or initiating formula supplementation, an early hospital discharge in some populations, the lack of routine follow-up care, conflicting advice, the lack of encouragement from health care professionals and the distribution of free formula samples [1, 13, 19, 26, 60].

Community and Family Environment

The attitudes and practices of breastfeeding mothers are influenced by those in their close circle, particularly their partners, as well as grandmothers and other people from the mother's social network [20, 24, 26, 35].

In the postpartum, the activities carried out by mothers can leave them feeling exhausted and anxious, particularly during the first few weeks [34]. The factors that affect the amount of energy, time and ability of the mother to solve problems, such as a lack of support from significant others, poor knowledge or no breastfeeding experience, negative attitudes towards breastfeeding, a high relationship distress and lack of help with household chores from those who live with the mother, are all related with early weaning [13, 26, 35]. The social support that a mother receives can vary with the age of the child and may affect breastfeeding duration, according to what is considered to be socially acceptable [60].

Work Environment

Working outside of the home has frequently been cited as a reason for early weaning from breastfeeding, although the decision to begin breastfeeding is not associated with the intention to return to paid employment after the birth [13]. In both high- and low-income countries, returning to work during the first year postpartum is related with a shorter duration of full and any breastfeeding [13, 35].

The difficulties that women may face at work include a negative attitude towards breastfeeding mothers in the workplace and the difficulty to continue breastfeeding when separated from their child, which some consider to be impossible to overcome [26, 61]. Therefore, a longer maternity leave is associated positively with breastfeeding duration, while more intense working days have a negative impact [26, 62, 63].

Public Policy

Placing breastfeeding low down on a country's list of priorities as regards health concerns in public health policies has a negative impact on breastfeeding [50].

The policies and recommendations for promoting breastfeeding should be based on the WHO Global Strategy on Infant and Young Child Feeding [4], including promotional components such as information, education, and communication for the public and health care workers, the Baby-friendly Hospital Initiative (BFHI), and community-based activities [64]. However, in many countries and regions, the promotion of breastfeeding is a rhetorical subject, centered on women's individual responsibility, but with no interventions to provide adequate breastfeeding support for new mothers or policies that help women to continue breastfeeding [61, 65].

In order to protect breastfeeding, it is necessary to comply with the International Code of Marketing of Breast Milk Substitutes [66], and to support mothers in the workplace [64]. The International Code is systematically infringed, and manufacturers of breast milk substitutes are using national health care systems to promote their products and to distribute free samples to mothers, in low-income and developed countries [67, 68]. Countries with weak legislation based on the International Code and a lack of policies to facilitate breastfeeding at work have lower breastfeeding rates [64].

Society Level Factors

Breastfeeding is not only an instinctive behavior; it is something women learn to do and is influenced by social and cultural factors. Despite its physiological base, the meaning of breastfeeding and the way in which it forms part of cultural contexts vary globally [66].

Differences in exclusivity and duration of breastfeeding will depend to a great extent on the mother's knowledge about the breast milk production process and also cultural beliefs [50]. There are cultural assumptions, in particular in communities, that affect how an infant is fed and the values, attitudes, beliefs, and expectations associated with this behavior. These cultural assumptions can override healthy activities and include, among others, aspects such as the type of interaction between mothers and their babies, the way mothers integrate breastfeeding into the family routine, how breastfeeding is carried out, the notions of being a "good mother," and the way breastfeeding is related with tendencies and fashions [66, 69].

In the developing world, where breastfeeding is an almost universal practice, the introduction of ritual liquids, such as glucose water or water, from the very first weeks, is based on a variety of beliefs and rituals [19]. For instance, some may seek the beneficial effect of certain herbs to make the child "strong." Glucose water may also be administered to delay the first feed to enable the mother to gain greater rest after the birth or where the colostrum is considered to be harmful to the child. There may also be a belief that, besides milk, babies need other liquids just like adults. Furthermore, infant formula or prepared cereals can often be given prematurely in the belief that breast milk does not cover the infant's needs adequately.

In many Western societies, cultural values have made formula feeding the norm [61]. The so-called bottle-feeding culture, predominant in contexts where breastfeeding is less common, can undermine attempts to breastfeed as breastfeeding mothers may feel "different," the lack of expertise and support from informal networks, its impact on self-confidence, and the assumption of rules of bottle feeding to feed babies from the breast [69]. Furthermore, aspects such as the difficulty in integrating breastfeeding practices into daily life and a disapproval of public breastfeeding or of breastfeeding of young children due to the sexualization of breast could all influence a woman's decision to stop breastfeeding at an early stage [69–71].

Proof of the impact these cultural aspects have on breastfeeding is the fall in breastfeeding rates among the population who have emigrated from countries where breastfeeding is common, during the acculturation processes [72, 73]. Furthermore, the effect of the destination culture is greater the longer the period of residence in the new country [74].

Table 17.3 Some solutions to early breastfeeding cessation

Individual level	Group level	Society level
Interactive, practical, antenatal, and postnatal educational interventions	Include significant others in education and support programs	Culturally sensitive participatory interventions
Collaborative approach between antenatal and postnatal interventions	Foster the establishment of breastfeeding support groups	
Availability of professionals with specific knowledge and skills	Promote work environments which support breastfeeding	
Post-discharge services including breastfeeding support from professional or lay people	Promote comprehensive and coordinated strategies, considering risk population groups and cultural diversity	
	Carry out multifaceted interventions based on Baby-friendly Hospital Initiative	
	Media campaigns	
	Breastfeeding education for schools	
	Policies supporting breastfeeding in public and in the workplace	
	Adhesion of governments to the International Code of Marketing of Breast Milk substitutes	

Some Solutions to Early Breastfeeding Cessation

Due to the complexity of the problem of early breastfeeding cessation, any interventions to improve rates should take into account all levels, individual, group, and society (see Table 17.3), as interventions aimed at just one level could be cancelled out by the negative factors linked to the other levels [21]. For example, developing interventions that focus exclusively on the individual decisions of mothers may be rather useless in a society where bottle-feeding is the cultural norm, with hospitals that carry out professional practices that hinder the initiation and continuation of breastfeeding and a context with inadequate policies to support mothers and infants. Combined interventions to support, protect, and promote breastfeeding are more likely to be effective than single interventions to reduce early breastfeeding cessation rates [24].

Individual Level

Interventions During Pregnancy

Educational interventions have been recommended to improve mothers' intentions and attitudes [24]. Antenatal education, both individual and group, has proved to be useful to increase initiation rates and exclusive or any breastfeeding duration [75, 76].

Antenatal interventions are an appropriate context to screen pregnant women about their intentions and to deal with any self-doubts and breastfeeding concerns [13]. Interventions based on lecturing or demonstrations are not effective. In order to be so, group education needs to be interactive [76].

However, educational interventions may be insufficient to prepare new mothers for the breastfeeding experience, particularly if a great deal of information is provided about the benefits of breastfeeding, but little about the practical side [76, 77]. Before they start breastfeeding, mothers need information about how to do it best, such as practical details about positioning, supply and demand, onset of lactation, or the disadvantages of formula supplements [50]. Information about how to overcome

breastfeeding difficulties and how to deal with unsettled babies is also particularly important to reduce early breastfeeding cessation.

Continuous behaviors, such as breastfeeding over time, are dynamic processes. Initiation of breastfeeding can be influenced by positive expectations about the likelihood and value of future outcomes, and continuation by perceived satisfaction with the outcomes obtained [43]. Therefore, a collaborative approach must be developed between antenatal interventions to promote breastfeeding and postnatal support interventions. Interventions, including support and education, developed jointly during the ante and postnatal periods are more effective in increasing the exclusive and any breastfeeding rates to a higher degree, with a greater impact in developing countries [76, 78].

Interventions After Birth

The success of any breastfeeding support intervention depends on the availability of professionals with specific knowledge and skills, and continued attention [53, 61, 76]. All relevant health professionals should acquire the necessary knowledge and skills to protect, promote, and support breastfeeding [64]. Early discharge from maternity wards should be accompanied by post-discharge services including breastfeeding support [50].

Home visits soon after birth, telephone support, and access to a community breastfeeding center are all effective interventions to prolong breastfeeding after the birth [26, 76], although women prefer a face-to-face approach [76]. In different countries and contexts, it has been established that contact with professionals, or with trained lay people, offering support which is supplementary to standard care with the purpose of facilitating continued breastfeeding, is effective to prolong exclusive and any breastfeeding; this increase is greater when joint interventions including lay people and professionals are carried out [79].

Breastfeeding support must be adapted to the moment and needs of each woman [60]. There are two key moments in early breastfeeding cessation [80]: (1) the first few weeks postpartum, when a great many women stop breastfeeding [81] and when most problems and difficulties arise, linked to women's skills and ability to adjust to the new situation [34, 82], and (2) later cessation, when breastfeeding has become an easier and more natural practice [82], due to the integration of breastfeeding into women's daily lives and the return to paid work.

The support interventions during the first few weeks should be particularly aimed at solving the initial problems and difficulties with breastfeeding and improving women's emotional comfort [43, 70]. A practical hands-off teaching approach with professional support and encouragement prolongs lactation, but technical education without supportive elements is not effective [76]. When breastfeeding has been correctly initiated, support interventions should concentrate on providing resources and information that helps mothers prolong breastfeeding, such as providing guidelines for pumping and storing breast milk, and information about available resources when the moment comes for the breastfeeding mother to be separated from her child and return to paid work.

The support perceived by a mother includes activities such as care, concern, respect, understanding, advice, encouragement, and practical help [24]. The way in which professionals provide breastfeeding support determines whether it is considered to be supportive and helpful or judgmental and pressurizing [60]. This is particularly important as the idealized image of breastfeeding, far-removed from a sometimes difficult reality, may cause problems or early breastfeeding cessation to be associated with feelings of guilt, failure, or low self-esteem [70, 71, 83, 84]. It would be beyond the aims and space limitations of this chapter to describe support characteristics for breastfeeding technique, such as skills to listen and learn and to build confidence and give support, or to solve such problems as real or perceived inadequate milk supply. Nevertheless, this information is available in other texts [84].

Table 17.4 Ten steps to successful breastfeeding [88]

Every facility providing maternity services and care for newborn infants should
1. Have a written breastfeeding policy that is routinely communicated to all health care staff
2. Train all health care staff in skills necessary to implement this policy
3. Inform all pregnant women about the benefits and management of breastfeeding
4. Help mothers initiate breastfeeding within a half-hour of birth
5. Show mothers how to breastfeed, and how to maintain lactation even if they should be separated from their infants
6. Give newborn infants no food or drink other than breastmilk unless medically indicated
7. Practise rooming in—allow mothers and infants to remain together 24 h a day
8. Encourage breastfeeding on demand
9. Give no artificial teats or pacifiers (also called dummies or soothers) to breastfeeding infants
10. Foster the establishment of breastfeeding support groups and refer mothers to them on discharge from the hospital or clinic

Group Level

Community and Family Environment

Proper social support makes it easier to overcome the initial difficulties encountered when breastfeeding as well as the feelings of guilt and self-doubt [60]. Family and social networks are considered by most women to be an important source of postnatal support for breastfeeding mothers, even more so than health professionals, due to the continuous nature of contact [60]. To include significant others in education and support programs could have a positive effect on breastfeeding duration [26, 76, 85].

Breastfeeding support groups play an important role in maintaining breastfeeding practices and such groups are promoted by BFHI interventions. Some women who lack support in their social network seek other forms of support occasionally from formal support groups, which can sometimes be their only source of support [86]. These groups are organized by pro-breastfeeding associations [87] and are made up of volunteers with breastfeeding experience and similar characteristics to the women who attend these groups in search of advice. Furthermore, voluntary supporters place greater emphasis on emotional support and a mother's self-esteem, as well as on the knowledge she already has and on the need to understand her, compared with the support offered by health professionals.

Work Environment

There is little evidence about the effect of protective breastfeeding interventions in the workplace to increase breastfeeding duration [2, 64]. A work environment that supports breastfeeding, including facilities for expressing breast milk, or even breastfeeding at work and providing opportunities for mothers to take extended maternity leave, are all positive determinants to increase breastfeeding rates [50, 64].

Adaptation of Health Care Providers' Activities

The BFHI is a program based on common sense and existing evidence [52], aimed at improving breastfeeding practices in health care services [88]. It is one of the most effective and also cost-effective interventions for overall improvement in breastfeeding rates [89, 90]. A hospital is considered to be baby-friendly when at least 75% of mothers are exclusively breastfeeding their babies from

birth to discharge and when the hospital demonstrates compliance with the criteria for evaluating the implementation of the ten steps shown in Table 17.4 [88].

This intervention can be applied in developed and developing countries with the most important effects on populations with a low socio-economic background [91]. Sufficient proof is available regarding this intervention's effectiveness in improving exclusive and any breastfeeding rates in the short and long term [57, 91–94] and in reducing general morbid-mortality [92].

However, several kinds of obstacle have been detected regarding the implementation and maintenance of the changes necessary to establish BFHI good practices in hospitals, including the predominant focus on treatment as opposed to prevention, poor breastfeeding knowledge and attention of health care professionals, a lack of consensus among professionals, and the difficulty to modify long-standing routine working practices [58, 95, 96].

The main challenge faced by hospitals, particularly in industrialized countries where BFHI implementation is lower [97], is how to introduce and maintain the necessary changes. Combining different improvement strategies is probably the most useful approach. These strategies should involve all organizational levels, be developed in specific contexts and include activities such as the participation of all interest groups (mothers, managers, and professionals), training, external BFHI assessments, feedback of information, and new resources to support breastfeeding [58, 98, 99].

Public Policy

Both in high- and low-income countries, mid- and long-term national strategies are necessary to generate appropriate policy and cultural environments to promote breastfeeding. Recommendations exist to improve breastfeeding rates within the context of public health policies, mainstream clinical practice, and local interventions [13, 50, 64, 75]:

- Strategies and policies to promote breastfeeding should be comprehensive, coordinated, developed at a national, regional, and local level and have sufficient economic resources. Furthermore, they should include interventions such as national media campaigns, breastfeeding education for primary and secondary schools, policies to support breastfeeding in public and in the workplace, as well as adhesion of governments to the International Code of Marketing of Breast Milk Substitutes.
- Countries should carry out routine multifaceted interventions based on the BFHI, specifically promoting the BFHI accreditation of hospitals, improving support practices for mothers in the hospital environment and in the community, and eliminating professional routines that hinder breastfeeding.
- The protection, promotion, and support of breastfeeding should be adapted to the specific needs of the local environment. It is necessary to consider aspects related to cultural diversity, facilitate access to resources, and develop support interventions geared specifically at risk population groups who breastfeed less than their peers, such as the youngest women and those with less resources and social support.

Society Level

Recommendations to encourage breastfeeding, both in low-income countries and in western societies, imply making important changes to women's lifestyles [100], which could in fact hinder the programs' success [64].

For example, in Western countries, models range from advising women to offer the breast at regular intervals to another model based on the demand of the baby. Many women may prefer the first alternative,

despite its negative effects on the duration of breastfeeding, as they consider that it fits in better with their lifestyle. In other countries, the widely accepted belief that it is necessary to introduce food and liquids other than breast milk at an early stage may clash with the recommendation of exclusive breastfeeding for the first 6 months. Culturally sensitive participatory interventions, to find creative local ways to overcome cultural obstacles, are necessary to be able to effectively develop evidence-based interventions at a local level [64, 76].

Discussion

There is a dose–response relationship between human milk and human health. Exclusivity and duration of breastfeeding affect health outcomes. However, few women exclusively breastfeed and most stop breastfeeding within the first few months postpartum. A mother's decision on early breastfeeding cessation is a complex issue, influenced by a combination of factors that act at different levels: individual, group, and society.

Women at greater risk of early breastfeeding cessation tend to be younger, with a low-income and unsupported, with less experience and lower self-efficacy. These mothers wish to breastfeed for shorter durations and have negative attitudes towards breastfeeding. Most women discontinue breastfeeding prematurely because of perceived difficulties rather than maternal choice. The impact of breastfeeding problems may be related to women's emotional discomfort rather than severity. Decisions taken by mothers about stopping breastfeeding are negatively influenced by poor legal, work, and social environments, by professional activities that may hinder the initiation and continuing of breastfeeding and by the cultural assumptions that make formula feeding the norm.

Breastfeeding support should adapt to the moment and needs of each woman and should be provided by people with the appropriate specialized training. It is necessary to provide access to resources for population groups at risk and to develop interventions aimed at supporting these specific groups. Breastfeeding is linked to the adequation of professional activities surrounding childbirth. The BFHI and culturally sensitive participatory support programs should be routinely implemented and promoted by health care administrators and providers, instead of developing interventions that focus exclusively on the individual decisions of mothers.

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Chapter 18
Salt, Diet, and Metabolic Factors Affecting Breastfeeding

Sergio Verd

Key Points

1. High salt preference women are at greater risk for premature discontinuation of exclusive breastfeeding.
2. There is evidence that when food-energy intake falls to exceptionally low levels, milk output falls dramatically.
3. Type 1 diabetes in mothers is not an independent risk factor for shorter duration of breastfeeding.
4. Babies with subsequent high uricaemia are twice as likely to have ceased exclusive breastfeeding early than those with subsequent low uricaemia.
5. Antenatal high levels of androgens or corticosteroids are linked with subsequent poor breastfeeding outcomes.
6. Research from temperate regions (latitude 39°–43° North) confirms longer duration of exclusive breastfeeding among babies born in summer.

Keywords Pregnancy • Infant • Newborn • Breastfeeding • Uric acid • Vitamin D • Metabolic syndrome X

Introduction

The first week postpartum is a critical period for the establishment of breastfeeding. During this time, both the mother and the infant are learning how to breastfeed [1]. Sociocultural factors are strongly associated with the initiation of breastfeeding. Lactation problems are common even among mothers who are highly motivated to breastfeed. Lactation difficulties during the first week postpartum are of public health concern because women who plan to breastfeed for at least 6 months but experience physical discomforts of breastfeeding and uncertainty about the satisfaction of their infant, have a shorter breastfeeding duration than do their counterparts and lower breastfeeding success with subsequent children. Providing maternal support and structured antenatal and postpartum breastfeeding education is the most effective means of achieving breastfeeding success. In addition, immediate skin-to-skin contact between mother and infant and early initiation of breastfeeding are shown to improve breastfeeding outcomes [2]. To promote better breastfeeding outcomes, it is important to

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R.R. Watson et al. (eds.), *Nutrition in Infancy: Volume 1*, Nutrition and Health,
DOI 10.1007/978-1-62703-224-7_18,

evaluate potentially modifiable factors controlling this process. Both sociocultural and physiological factors are strongly associated with the initiation of breastfeeding [3]. Extensive research on various social, psychological, emotional, and environmental factors that may have an impact on whether an infant is successfully breastfed or bottle-fed has been undertaken. Conversely, there has been little research on the incidence of physiological factors on human lactation problems; the aim of this chapter is to provide information on this topic.

Salt

The concentrations of major minerals (calcium, phosphorus, magnesium, sodium, and potassium) in human milk are not affected by the diet [4]. Instead, it is fully understood that 0.14% sodium in grazed forage is necessary to support >30 kg of milk production per cow. Said in a clearer way, for dairy cows to produce 20 kg of milk per day, 30 g of sodium chloride is needed and 15 g is inadequate [5, 6]. Breastfeeding is popularly surrounded by a wide range of folklore with cultural and familial roots. Folklore can originate by detection of actual associations between seemingly unrelated events and perpetuated through oral tradition. These ideas have stood the test of time and some of this folklore may have truth. In many African and European cultures, alternative remedies such as salt are used to improve breastfeeding performance [7].

There was no scientific evidence to support the intake of salt to avoid early breastfeeding cessation, the impact of maternal diet on the onset of lactation remains inconclusive, but there is plenty of evidence that lactating animals, both wild [7] and domestic [5, 6], actively seek salt sources.

The objective of our trial [8] was to compare the effects of mother's high salt preference (HSP) with mother's salt dislike (SDL) on discontinuation of exclusive breastfeeding (EBF) during the first week of life. We have decided to evaluate conscious salt use by asking participant mothers about their salty taste preference (three levels liking score) during a semi-structured interview with the mother on food preferences and restrictions. Women have been categorized as long-standing high salt preference, no salt preference (NSP), or salt dislike; in all, 327 mother–baby dyads fulfilled the criteria of the study. There were 74 (22.6%) salt preference mothers, 109 (33.3%) no salt preference mothers, and 144 (44%) salt dislike mothers.

Three dyads have been excluded from the analyses because mothers have changed their salt preference along pregnancy and lactation. The infants' mean birth weight was 3,245 g (SD: 409). Mean gestational age was 39.6 weeks (SD: 1.2). The cesarean section rate was 31%.

Of the 327 mothers who ever breastfed, 58 (17.2%) discontinued EBF by 8 days after delivery. The discontinuation of EBF by 1 week was referred to as the premature discontinuation of breastfeeding (PDBF).

During this period, 27% of HSP, 17.4% of NSP, and 13.1% of SDL mothers discontinued EBF. In our univariate analysis, more mothers in SDL category than mothers in HSP category continued EBF beyond 7 days postpartum (odds ratio [OR]: 2.43 [95% confidence interval (CI): 1.20–4.92]) and the effect was not small: HSP compared to SDL was associated with a 106% increase in PDBF. PDBF did not differ between mothers in SDL category and NSP category (odds ratio [OR]: 1.38 [95% confidence interval (CI):0.69–2.77]) or mothers in HSP category and NSP category (OR: 1.75 [95% CI: 0.86–3.57]). Statistically significant associations between SP and PDBF were found in any of our multivariable models ($p=0.043$).

In this study, we identified a deleterious association of mother's high salt preference with early lactational outcomes. What is new here is our finding that HSP women were at greater risk for premature discontinuation of exclusive breastfeeding. The reasons may be biological, psychological, or cultural. This is also the first study to suggest that milk production or constituents is affected by the diet of well-nourished women in industrialized countries.

The metabolic syndrome, social stress, and polycystic ovary syndrome (an outcome of underdiagnosed congenital adrenal hyperplasia), are also known to curtail breastfeeding [9–11] and can also be related to high salt intake [12]. Finally, it is possible that the women who report low salt preference have a greater awareness of healthy diet and lifestyle, and by the same token may be more motivated to breastfeed their babies.

Diet

The importance of nutrition on milk production has been extensively studied in dairy cows, and feeding standards based on the level of milk production have long been considered to be an important determinant of the profitability of the dairy industry. The influence of maternal diet on the level of milk production in women is much less clear.

This section deals with consideration of maternal protein and fluid intakes. Studies on the influence of other nutrients have dealt primarily with milk composition rather than volume [13].

Severe undernutrition is widely regarded as detrimental to human milk production, but there are very few supporting data. There have been several attempts to document the effects of famine on milk volume, but quantitative data are generally lacking. Historical accounts of mothers breastfeeding during wartime sieges in Europe provide mostly anecdotal evidence of insufficient milk production among some women [14].

A comprehensive food supplementation study was conducted in The Gambia between 1976 and 1982 [15, 16]. The nutritional status of the Gambian women prior to food supplementation was not extremely poor. The supplement provided a net increase of 723 kcal daily and ~57 g of protein. Nevertheless, the authors found no effect of food supplementation on milk volume at any stage of lactation. Milk volume declined during the wet season despite supplementation. The range of variation in milk volume was the same before and after supplementation, suggesting that energy supplementation did not even increase the milk volume of women with low milk volumes.

Short-term fasting has been the subject of a few investigations. Again in The Gambia, Prentice et al. [17, 18] reported that milk volume was unaffected in women during Ramadan when no food or fluid is consumed from 5 a.m. to 7:30 p.m. (although intake after 7:30 p.m. may be considerable). Similarly, it was found that the rate of milk secretion was no different from the baseline among five lactating women who ate no food for 20 h [19].

Strode and colleagues [20] examined the effects of energy restriction among presumably well-nourished mothers. The experimental group reduced their energy intake by an average of 32% (range, 19–53%) below baseline intakes for 1 week; the control group maintained their usual intake. Among the eight mothers who restricted their intake to no less than 1,500 kcal/day, there was no reduction in milk intake by their infants. However, milk intake by infants of the six mothers who decreased their energy intake below 1,500 kcal/day was reduced by an average of 15% (109 g/day) during the week after restriction had ceased.

Therefore, there is only evidence that when food-energy intake falls to exceptionally low levels the mother's capacity to adapt is exceeded and milk output falls dramatically.

An explanation for these findings may be that the relative energy costs of lactation are much lower for humans than for most other species, and it is not known whether there is an energy threshold for humans. It is already known [21] that energy costs at peak milk output, as a function of maternal body weight, are 4- to 15-fold lower for humans than for either laboratory or domesticated animals. For example, the energy requirements of lactation in humans can be met by increasing energy intake by ~25%, whereas in rats, energy intake must increase by 300% or more. Thus, a similar reduction in energy intake as a percentage of total intake is likely to result in a smaller decrease in milk volume of humans and other primates than of litter-bearing animals.

Metabolic Factors

The metabolic syndrome (MS) is a clustering of metabolic abnormalities: insulin resistance, dyslipidemia, hypertension, and obesity. In addition, hyperandrogenemia has been identified as an important risk factor for MS and dyslipidemias in premenopausal women and adolescents [22–24]. The rise in serum androgens is accompanied by excess insulin secretion, suggesting that insulin directly stimulates ovarian androgen production [25]. Even more, a causal role for uric acid in the metabolic syndrome has been suggested [26]. And finally, low serum concentrations of vitamin D are significantly associated with obesity status, abdominal obesity, high blood pressure, fasting hyperglycemia, and the metabolic syndrome [27].

On the other hand, the metabolic syndrome is known to curtail breastfeeding. Women who are prone to developing MS may have difficulty initiating lactogenesis; several studies have suggested that maternal obesity or diabetes may be associated with decreased breastfeeding initiation and duration [28–32]. Duration of lactation is associated with lower prevalence of MS in a dose–response manner in midlife, parous women.

This section deals with many components of the metabolic syndrome that are associated with early cessation of breastfeeding.

Diabetes and Breastfeeding

Some 40 years ago, a history of increased incidence of mastitis in women with type 1 diabetes (T1D) led professionals to question the ability of women with T1D to produce enough milk to support breastfeeding [33].

Initiation of breastfeeding for mothers with diabetes often implies a challenge. This is due to increased occurrence of complicated pregnancy and labor [34], and neonatal morbidity [35, 36]. Furthermore early mother–child separation can further hinder breastfeeding [37].

On the other hand, lactation may be more difficult for women with diabetes and their infants have a more immature sucking pattern [31]. There is a delay of lactogenesis in women with T1D based on concentration of lactose in the colostrum of T1D women compared with control women; this delay is more likely to occur with poor metabolic control [38]. Women with gestational diabetes (GDM) have been observed to have no marked delays compared with control women at 40–50 h postpartum [39]. However, GDM women have more difficulty expressing colostrum from their breasts during the first 2 days of lactation. GDM mothers have been found to be less likely to breastfeed long term than healthy mothers, especially those who are insulin dependent or obese [40].

More recently, in an attempt to overcome these various obstacles to successful breastfeeding, a focused effort has been made that includes different steps. Antenatal classes and individual counseling about benefits and difficulties in initiating breastfeeding offered to the women are valuable because the prevalence of breastfeeding at 4 months among cases was comparable to that in the background population despite increased morbidity of the infants [41].

It was unknown whether it was maternal diabetes itself or other maternal and neonatal factors, such as medical management of their newborns, what may interfere with maternal milk production or the likelihood of breastfeeding. Findings from multivariate studies have indicated that T1D in mothers is not an independent risk factor for shorter duration of breastfeeding. However, factors associated with maternal diabetes, such as problems with establishing breastfeeding, early postpartum due to the higher degree of maternal and neonatal complications, affects the likelihood of long-term breastfeeding.

Finally, a few studies have examined the impact of neonatal feeding practices by women with metabolic abnormalities on subsequent offspring obesity or diabetes [42, 43]. In a study from Germany, infants were provided with human milk from their mothers with diabetes or donor human milk from women with normal glucose tolerance [42]. Children who consumed a higher amount of human milk

from mothers with diabetes during the first week of life were more likely to have a higher % relative body weight at 2 years of age [43]. It is unknown which components in human milk contributed to this difference. Therefore, it is a matter for future research to answer the question: is unsuccessful breastfeeding among diabetic mothers related to specific components in their milk?

Mother's Overweight and Obesity

In 1992, Rutishauser & Carlin reported a negative relationship between maternal obesity and breastfeeding duration [44]. Since then, a number of studies have found lower rates of breastfeeding in women who are overweight and obese compared to women of normal weight [29, 30, 45]. Some researchers have attributed this to physiological causes. High pre-pregnancy body mass index (BMI) is associated with delayed onset of lactogenesis II ("milk coming in") [46]. Delayed onset of lactogenesis II among overweight and obese women is explained by lower prolactin concentrations in response to suckling at 48-h postpartum compared to normal-weight women [47]. Delayed lactogenesis II among overweight women in addition to excessive gestational weight gain have been associated with the early cessation of breastfeeding [46, 48]. However, as obese women are more likely to belong to subgroups of women with lower rates of breastfeeding than normal-weight women, such as lower socioeconomic status and higher depression [47, 49], it is necessary to adjust for these potential confounding factors. Controlling for parity, socioeconomic status, maternal education, and other factors that often covary with maternal obesity and breastfeeding did not change these results. These results suggest that excessive fatness in the reproductive period may inhibit lactational performance in women [30].

On multivariate analysis from Australian longitudinal studies, for women who initiated breastfeeding, overweight women had an odds ratio (OR) of 1.52 [95% confidence interval (CI) 1.02, 2.28] and obese women had an OR of 2.54 (95% CI 1.70, 3.79) of stopping breastfeeding by 1 week compared with normal-weight women (adjusted for maternal age, education, smoking, level of socioeconomic disadvantage, cesarean birth, admission to special care nursery). For women who breastfed for at least 1 week, overweight women had an adjusted OR of 1.26 (1.04, 1.53) and obese women had an adjusted OR of 1.38 (1.10, 1.73) of ceasing to breastfeed before 6 months, compared with normal-weight women. In conclusion, among overweight/obese women who initiate breastfeeding, higher rates of cessation of breastfeeding in both the immediate postpartum period and in the first 6 months contribute to the shorter duration [50].

Uric Acid Metabolism and Early Breastfeeding Outcomes

Among breastfed and dehydrated infants, evidence shows that greater weight loss is associated with a reddish stain in the diaper along with infants' higher serum uric acid concentrations [51]. It is generally accepted that dehydration in infancy favors precipitation of uric acid crystals. These facts have led us to wonder if it works the other way round. Are breastfed newborn infants with uricaemia in the normal upper range specially prone to fail to thrive and therefore to become dehydrated, with evidence of reddish stain in the diaper caused by uric acid crystals?

To try to complete the picture, we present preliminary data on uricaemia from successfully and from not successfully exclusively breastfed infants [52]. Unfortunately uric acid was removed from routine laboratory panels in the early 1980s [53]. Therefore we have got data from not more than 153 children for whom early breastfeeding outcomes had been ascertained and serum uric acid tests had been performed at any time and were currently available. Mothers were told that we were interested in learning about breastfeeding in general, and oral consent to participate in the study was obtained.

Table 18.1 Association between uricaemia and discontinuation of exclusive breastfeeding in the first month of life

	Exclusive breastfeeding <30 days	Exclusive breastfeeding ≥30 days
Uricaemia <3 mg/dL	6 (17.2%)	29 (82.8%)
Uricaemia ≥3 mg/dL	43 (36.7%)	75 (63.3%)

We have set a cut-off for low uricaemia at <3 mg/dL and for high uricaemia at ≥3 mg/dL to compare children in the lowest quartile of uric acid with those in the second, third, and top quartiles. Thirty-five patients have qualified for low uricaemia and 118 patients for high uricaemia. The findings of the biochemical tests are shown in Table 18.1. By postnatal day 30, babies with subsequent high uricaemia were twice as likely to have ceased exclusive breastfeeding than those with subsequent low uricaemia (OR: 2.77 [95% CI 1.06–7.20]).

The metabolic syndrome is known to curtail breastfeeding and a causal role for uric acid in the metabolic syndrome has been suggested [26]. Our finding is intriguing but it is in agreement with this body of knowledge.

Major Endocrine Changes Occurring During Pregnancy and Breastfeeding

Major endocrine changes occurring during pregnancy are crucial for mammary glandular development [54]. Recently it has been reported that breastfeeding is negatively associated with maternal androgen levels in pregnancy [55]. Furthermore, in-utero exposure to glucocorticoids has recently been shown to reduce the volume of milk production on days 1–10 postpartum [56]. There is also an association between smoking during pregnancy and ensuring breastfeeding [57, 58]. A combination of these mechanisms is a fourth possibility.

A number of papers report an association between high levels of androgens during gestation and subsequent poor breastfeeding outcomes: (1) in women who were treated with androgens, atrophy of the breast was observed [59], it seems that one physiological role of testosterone is to limit the estrogenic stimulation of the breast [60]; (2) it has been reported that breastfeeding rates are lower among pregnant women with polycystic ovary syndrome, an outcome of underdiagnosed congenital adrenal hyperplasia [11]; (3) Dehydroepiandrosterone levels in the third trimester are negatively associated with breastfeeding duration [55].

On the other hand, during the first 3 days of breastfeeding, plasma and milk cortisol levels decline significantly [61]. Lactating women expressing transitional (postpartum days 4–14) and mature milk (postpartum days 15–180) have significantly lower serum cortisol concentrations than lactating women expressing colostrum (postpartum days 1–3) [62]. Antenatal corticosteroids, given to enhance fetal maturation, have an adverse effect on the success of subsequent lactation [56]. High doses of pharmacologic corticosteroids may interfere postpartum declining cortisol, a biochemical marker of the difference between colostrum and transitional milk.

Classical observations in lactating women indicate that smoking decreases prolactin concentrations [63] and shortens the duration of breastfeeding [64, 65], which results in the infants of smoking mothers to grow at a slower rate than the infants of nonsmoking mothers. Cortisol concentrations are greater in newborns whose mothers smoked when compared to corresponding controls [66]. Although a causal relationship between maternal smoking and high cortisol concentrations in cord blood has not been established, elevated stress hormones in newborns whose mothers smoked during pregnancy is a common finding. Glucocorticoids and tobacco exposure in utero are inextricably linked and it is hard to evaluate the relative contribution of each on breastfeeding. Further, a robust association between maternal androgens and smoking during pregnancy has been described elsewhere [55].

Vitamin D, Seasonal Variation of Birth Month, and Breastfeeding

There is an inverse relation between 25-hydroxyvitamin D (25(OH)D) concentration and BMI [67]: 25(OH)D is an independent predictor for BMI. It is known that the higher the BMI of the mother, the less likely to initiate breastfeeding successfully [30]: BMI > 29, 3.65-fold less likely and BMI > 26, 1.5 fold less likely. We know now that hypovitaminosis D is associated with insulin resistance [67] and several papers have shown that insulin resistance or diabetes preclude breastfeeding.

It is also known that at temperate latitudes serum 25(OH)D exhibits an annual cyclic variation, with a peak after summer sun exposure and a nadir around 175 days later, after winter sun deprivation [68]. Worldwide, commonly recommended daily intake of vitamin D is not sufficient if sunlight exposure is limited.

We undertook a study to examine if there is an annual cycle of early breastfeeding cessation following the seasonal fluctuation of 25(OH)D concentration [69]. Information extracted from medical records was used to examine the relationship between failure to breastfeed beyond 7 days of life and birth in September or in March. All singleton, full term, and without significant perinatal morbidity children attending the same pediatric clinic in Majorca (Latitude = 39°N; Longitude = 3°E), Spain, born in September 1999–2004 or in March 2000–2005 were recruited in total, 118 mother–infant pairs were recruited and were eligible for the study. Of 118 eligible subjects, there were 59 born in March (BM) and 59 born in September (BS). Failure to breastfeed more than 1 week had been recorded in 10 (16.9%) babies BM and in 1 (1.6%) baby BS. The analysis showed that BM was associated with an increase in proportion of failure in onset of breastfeeding [odds ratio [OR] 11.83; 95% confidence intervals [CI] 1.46–259.49; $p = 0.012$] compared with BS.

There are three previous papers addressing this subject, with different results: (1) the Bedouin Infant Feeding Study reported that women who delivered in the spring–summer had an increased rate of milk insufficiency compared with those who delivered during the rest of the year [70], cultural differences about sunlight avoidance could explain these results, several surveys recognize that Spaniards are reckless with respect to sun exposure meanwhile Bedouins have a strong tradition of sun protection. (2) A study on seasonal variation of diabetes and breastfeeding from the South-East region of Sweden [71] has shown that children born during the summer were exclusively breastfed for a mean period of 2.2 months, corresponding figures for children born during winter were 2.8 months ($p < 0.04$), spring 2.5 months (n.s.), and autumn 2.7 months ($p < 0.05$); an explanation for this finding is that Sweden is not located in a temperate latitude, therefore an annual cyclic variation of serum 25(OH)D is not expected. (3) Conversely, a research from Xinjiang, a Chinese temperate region (latitude 43° North), confirms longer duration of exclusive breastfeeding among babies born in summer [72].

Research from temperate regions (Majorca and China) show seasonal differences in the rates of early termination of breastfeeding, following the cycle of 25(OH)D levels. We already knew that in most populations females have been found to be lighter skinned than males; this may be required to permit synthesis of the relatively higher amounts of 25(OH)D necessary during pregnancy and lactation [73].

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Chapter 19
Early Childhood Exposure to Environmental Tobacco Smoke and its Effects on Allergy and Asthma

Juliana Pugmire and Ronald Ross Watson

Key Points

- Environmental tobacco smoke (ETS) exposure is particularly harmful during critical windows of early development.
- Maternal smoking during pregnancy has some of the strongest effects on health outcomes in early infancy.
- Effects of early life ETS exposure on total serum IgE levels and allergic sensitization are conflicted.
- Health consequences of ETS exposure in utero and early infancy may extend out into adulthood.
- Infants and children of all ages should be shielded from ETS exposure.

Keywords Environmental tobacco smoke exposure • Infant • Child • Health outcomes • Allergy • Atopy • Asthma • Respiratory symptoms • Lung function • Total serum IgE • Immune response

Introduction

Tobacco use is one of the world's leading public health concerns. Globally and domestically, active and passive smoking are associated with an array of deleterious health outcomes. Environmental tobacco smoke (ETS), also referred to as passive smoke and second-hand smoke, exists in all countries and cultures and there is no level of exposure to ETS that is risk free [1]. Over 50% of children worldwide are exposed to ETS in their homes while 60% of US children between ages 3 and 11 years are exposed [1, 2].

The U.S. surgeon general report of 2006 reported the consequences of ETS [1]. Children are more vulnerable to the effects of ETS than adults because their bodies and lungs are developing and they differ from adults in their physiology. Lung growth is not complete until the end of adolescence making infants and children especially susceptible to toxicants. Exposure to toxicants, such as tobacco smoke, may alter normal development leading to effects that could persist into adulthood [3].

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R.R. Watson et al. (eds.), *Nutrition in Infancy: Volume 1*, Nutrition and Health,
DOI 10.1007/978-1-62703-224-7_19,

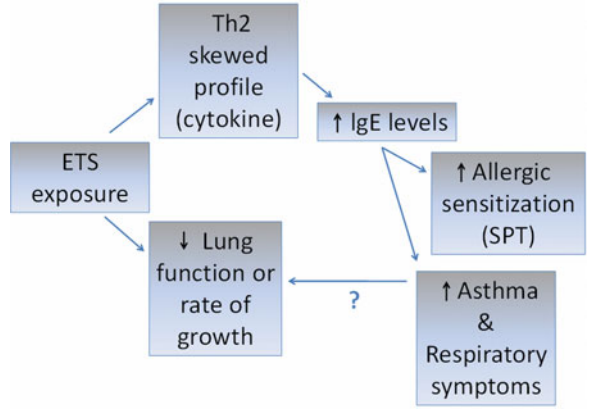

Fig. 19.1 Conceptual model describing possible relationship between immune system, IgE levels, allergic sensitization, asthma, respiratory symptoms, and lung function

Children exposed to ETS have an increased risk of health problems compared to children in smoke-free environments [1]. Adults are also affected by ETS and have increased risk of heart disease and lung cancer. The report concluded that there is no risk-free level of ETS exposure [1]. The Environmental Protection Agency, National Toxicology Program and the International Agency for Research on Cancer have classified secondhand smoke as a human carcinogen [1].

In infants and children, exposure to ETS is associated with an increased risk of sudden infant death syndrome, more severe asthma symptoms, respiratory symptoms such as breathlessness, phlegm, wheeze and cough, lower respiratory infections like bronchitis and pneumonia, and ear infections. The evidence that ETS has many negative health affects during childhood is clear [1].

This chapter focuses on the effects of ETS exposure in early life on the related health outcomes of asthma, allergy, Immunoglobulin E (IgE) levels, lung function, and other respiratory symptoms. A conceptual model describing the possible relationship between these health outcomes is presented below (see Fig. 19.1) and explained throughout this chapter. Primarily, health outcomes in infancy will be addressed with evidence of long-term health effects of ETS exposure in infancy.

Environmental Tobacco Smoke

ETS is classified as a Group A carcinogen, i.e., it is known to cause cancer in humans, by the Environmental Protection Agency [4]. Cigarette smoke contains thousands of chemicals including nicotine, carbon monoxide, formaldehyde, hydrogen cyanide, polycyclic aromatic hydrocarbons, heavy metals like lead. Many of these chemicals are known to be carcinogenic, mutagenic, and cytotoxic [5]. These chemicals affect health outcomes by acting as irritants, immune modulators, and mutagens [6].

ETS differs from actively inhaled smoke. ETS is a combination of 15% mainstream and 85% sidestream smoke. Sidestream smoke is smoke emanating from the end of a lit cigarette and mainstream smoke is the smoke inhaled and then exhaled [7]. The difference in composition of actively vs. passively inhaled smoke may be a factor in epidemiological studies showing a difference in the strength of association between tobacco smoke and health outcomes [6].

ETS exposure during the prenatal period, infancy and childhood has been assessed using parent report and/or cotinine measured from blood, urine, saliva, hair or meconium [8–11]. Parent report assessments of ETS exposure can be used to cover a range of time, e.g., exposure in utero or exposure from the ages of 0 to 5. Cotinine, a metabolite of nicotine, is used as a biomarker to assess level of exposure to tobacco smoke, either passive of active. Cotinine provides a quantitative, objective exposure

to tobacco within the last 24–72 h and is increasingly considered the gold standard. However, while parent report is a method subject to underreporting bias, there is concordance between the two [8, 12, 13].

Children are primarily exposed to ETS in the home [14, 15] and it is still relatively common for pregnant women to smoke. In 2002, 22% of women in the U.S. smoked during pregnancy [16]. There are likely critical windows in development when ETS exposure is particularly harmful and there may be a cumulative effect of exposure over time. Evidence suggests that exposure to ETS at different ages has different and sometimes independent effects [17]. Moreover, these age windows of increased vulnerability to the harmful effects of ETS exposure may differ between males and females.

Asthma and Other Respiratory Symptoms

In the United States, 22 million people are affected by asthma and this chronic disease is very common to childhood [18]. Asthma is characterized by airway hyper-responsiveness, inflammation and remodeling. Airway hyperresponsiveness refers to an exaggerated response, e.g., inflammation, to a trigger like an allergen. Inflammation in the airways of the lungs and recurring attacks of wheezing, shortness of breath, and coughing are typical of asthma. During an asthma attack the airways swell and narrow, produce mucus, and air flow is restricted in and out of lungs making breathing difficult. The seriousness and regularity of attacks varies by person [18–20]. Airway remodeling refers to structural changes in the lungs from repeated asthmatic episodes [21]. The US Department of Health and Human Services put forth this working definition of asthma in their 2007 Expert Panel Report for the Diagnosis and Management of Asthma [18] (p. 13):

> Asthma is a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role: in particular, mastcells, eosinophils, T lymphocytes, macrophages, neutrophils, and epithelial cells. In susceptible individuals, this inflammation causes recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night or in the early morning. These episodes are usually associated with widespread but variable airflow obstruction that is often reversible either spontaneously or with treatment. The inflammation also causes an associated increase in the existing bronchial hyperresponsiveness to a variety of stimuli. Reversibility of airflow limitation may be incomplete in some patients with asthma.

Classic risk factors for asthma include viral lower respiratory infections, family history of asthma and allergy, and persistent allergic sensitization [22]. Asthma can be atopic or non-atopic, meaning it is either allergy-induced or not allergy-induced. The type of asthma triggered by an allergic reaction is called allergy-induced asthma, atopic asthma or allergic asthma. Common allergens triggering asthma attacks include cat or dog dander, house dust mites and pollen. In cases where asthma attacks are not triggered by allergic reactions, the reasons for the attack are unclear [20] but could involve substances like tobacco smoke and chemical irritants. Atopy is present in approximately 80% of asthmatic children and 60% of asthmatic adults [23].

Asthma is classified into four main categories based on severity [20, 24] (Table 19.1). Most children with asthma have symptoms, like wheeze, before age 5 yet diagnosing asthma between 0 and 5 years can be difficult since asthma symptoms can be similar to those of other childhood

Table 19.1 Asthma severity

Type of asthma	Signs and symptoms
Mild intermittent	Mild symptoms no more than 2 days per week with nighttime symptoms less than two nights per month
Mild persistent	Symptoms 3–6 times per week but not more than once per day
Moderate persistent	Symptoms daily with nighttime symptoms more than once a week
Severe persistent	Symptoms continual throughout the day and frequently at nighttime

conditions. Furthermore, children that wheeze at young ages do not necessarily have asthma, especially when wheeze occurs concurrently with a cold or respiratory infection [25].

Wheeze early in life can indicate developing asthma. Recurrent episodes or severe and sudden episodes of cough, wheeze, shortness of breath, and chest tightness are commonly evaluated to diagnosis asthma and assess asthma severity. Also taken into account is whether these symptoms occur at certain times of the year, on exposure to particular things like animals or tobacco smoke, and if symptoms occur or worsen at night. Lung function tests such as spirometry are also used to diagnose asthma and other lung diseases and assess severity of disease [18].

Asthma can be worsened through active or passive smoking. ETS exposure may actually cause the onset of asthma or only exacerbate symptoms and severity in children that would already develop asthma regardless of ETS exposure. Whether ETS exposure causes or exacerbates asthma in childhood may have to do with the window of exposure during infancy. There is some uncertainty regarding when in the child's life passive smoking is most harmful and the importance of exposure through different times in a child's life [6, 26]. Overall, children exposed to ETS have a higher prevalence and severity of asthma than unexposed children [27].

Maternal smoking during pregnancy is strongly and consistently associated with wheeze in early infancy, indicating that it could be causal in the development of asthma [28–30]. Prenatal exposure to ETS is associated with asthma itself [3, 31]. It is unknown whether ETS exposure that occurs in later childhood after infancy can cause asthma [6].

Studies examining the postnatal period of ETS exposure during infancy find varying effects on asthma and other health outcomes and these vary depending on whether the child is exposed to maternal or paternal smoking. Maternal smoking has a greater effect on asthma symptoms, respiratory infections or atopy [32–34] while another study found that paternal smoking may have a greater effect [35]. Variability of health outcomes by source of ETS exposure, especially when dealing with postnatal exposure, probably has more to do with which parent smokes more and spends more time with the child.

There is a high correlation between in utero exposure to maternal smoking and postnatal ETS exposure and both need to be assessed when quantifying adverse health outcomes [36]. This association between ETS exposure and adverse health effects appears strongest for maternal smoking during pregnancy compared to postnatal exposures [37, 38], but postnatal exposures have their own independent associations [39]. There is evidence that maternal smoking during pregnancy exposes the fetus to tobacco toxicants 30- or even 100-fold higher than exposure to postnatal ETS exposure (passive smoking) [40]. This saturated exposure may partially account for stronger associations between adverse health outcomes and prenatal ETS exposure compared to exposure during other periods in an infant's or child's life.

Atopy

Atopy is "a personal or familial tendency to produce IgE antibodies in response to low doses of allergens, usually proteins, and to develop typical symptoms such as asthma, rhinoconjunctivitis, or eczema/dermatitis" [41] (p. 816). It is the strongest predisposing factor for asthma development [18]. Atopy, also referred to as allergy, and asthma frequently occur together [20]. There has been a rapid rise in the incidence and prevalence of allergy, suggesting an environmental as well as genetic component [42].

Atopy is measured objectively through skin prick testing [35]. Skin prick testing can measure allergic reaction to as many as 40 substances, such as mold, pet dander, dust mites, grass, pollen and foods. The test is usually conducted on the forearm of adults or the upper back on children. Potential allergens are dropped onto skin surface and then slightly "pricked" into skin using a small lancet.

Histamine and glycerin or saline are used as controls. Histamine will cause a reaction in most people so if there is no reaction it is likely that individual will not test positive for any allergen even if allergic. Glycerin or saline will usually not cause a reaction in people so if there is a reaction it is likely that an individual has sensitive skin and may test positively to many allergens even if not allergic [43]. Results of the skin prick testing are evaluated after about 15 min. If a person is allergic to a specific allergen then the skin will rise into a red, itchy wheal [43].

The relationship between allergic sensitization, as frequently measured by skin prick testing, and ETS exposure is quite conflicted. Some studies find ETS exposure to be a risk factor for allergic sensitization [44–46] while others in fact show a protective effect [35, 37]. ETS exposure may have a different effect for different allergens [48] and is especially detrimental to children with a family history of allergies [45, 49].

There are two competing theories for ETS exposure as a risk factor or protective factor for the development of allergy. As nicotine is immunosuppressive, ETS exposure will inhibit the development allergic sensitization, which is an overactive response of the immune system [50]. The other theory is that ETS exposure skews the ratio of immune cells that promote proinflammatory cytokines leading to the development of allergic sensitization [51].

A meta-analysis conducted on 36 studies [52] found many of the large studies did not find an association of maternal smoking on total serum IgE or atopic disease but also did not control for numerous potential confounding factors. The majority of studies in this meta-analysis examined skin prick test positivity and similarly showed no overall adverse effects of ETS exposure [52]. However, some more recent studies that do control for potential confounders have found an effect and interaction with other risk factors, like cat allergen and daycare attendance [53, 54].

Genetic predisposition towards atopy, frequently assessed through family history, may modify the effect of ETS exposure on allergic sensitization. Thus, ETS exposure may have a measurable effect on the development of allergic sensitization in children with a genetic predisposition but not on children without. Association between ETS exposure and allergic sensitization is seen in children with a family history of atopy [45, 46, 49] and in children with no family history of atopy [44].

However, studies restricted to children with a family history of atopy still provide conflicting evidence of ETS exposure's effect on sensitization. Children at risk of allergy exposed to maternal smoking during the prenatal period led to decreased risk of allergic sensitization at 1 year but not at 4 years [55]. In direct contrast, maternal smoking during pregnancy appeared to be protective against allergic sensitization in early childhood [56]. The effect of early life ETS exposure on allergic sensitization is equivocal. It is seemingly influenced by window of exposure, duration of exposure, family history of atopy, specific allergen, and interaction with other risk and protective factors like daycare and cat or dog ownership.

Role of Immune Response

Early life exposure to ETS, either in utero or in infancy, alters aspects of immune functioning [22, 57, 58]. There has been a strong interest in the role of the adaptive and innate immune response in the development of inflammation, asthma and allergy. The innate immune system responds to pathogens in a generic, nonspecific way by causing inflammation. Macrophages, dendritic cells, epithelial cells and neutrophils in the lung are innate immune cells [22]. The adaptive immune system is flexible and responds to pathogens in a specific way. Lymphocytes including T-cells and B-cells, produce antibodies to specific pathogens that are retained for a sort of immunological memory [22]. The innate and adaptive immune arms interact [59, 60].

T helper cells are a subgroup of lymphocytes. There is a balance between the ratio of T-helper (Th) 1 cells and T-helper (Th) 2 cells with Th1 cells responding to infection and Th2 cells mediating allergic

inflammation [18]. A Th2 phenotype will yield a higher production of proinflammatory cytokines leading to the release of IgE from B lymphocytes for narrowing of airways, sensitization to allergens, and other asthmatic symptoms. In contrast, individuals with a Th1 phenotype will produce cytokines that will not yield a strong proinflammatory response [51]. The development of a Th2 phenotype and sensitization may precede asthma. This T-cell priming appears to happen in early life, possibly even beginning in utero and is influenced by environmental factors like ETS and infections [57, 61, 62]. Maternal smoking is shown to alter innate and adaptive immune arms in infants [57] with effects that may last into adulthood [63].

Total Serum IgE

Immunoglobulin E (IgE) is a class of antibody that is naturally occurring in the body and plays an important role in atopy and in the development and perseverance of inflammation [18]. IgE mediates allergic response by stimulating the release of inflammatory agents like histamine on exposure to allergens. An atopic individual will make more IgE in response to inhaled allergens, such as cat dander, pollen or dust mites. Atopic individuals have higher levels of total serum IgE than do non-atopic active smokers [64–66]. Besides environmental factors, age and gender affect IgE levels. Peaks occur in the first and second decades of life and slowly decrease over time, making older adults more likely to have lower levels of IgE than younger adults and males might have higher IgE levels than females [64, 67].

The mechanism of tobacco smoke modulation of IgE levels is not well understood [64, 68]. There could be indirect and direct actions of tobacco smoke on IgE levels [69]. An indirect action could increase the likelihood of developing sensitivities to inhaled allergens. In fact, smoke increases permeability in the lungs possibly facilitating and enhancing penetration of allergens. Tobacco smoke could have a direct action on IgE levels through immune system cellular regulation changing the function of T-lymphocytes [70]. Th2 lymphocytes regulate IgE production. Thus, newborns with smoking parents have higher cord IgE levels regardless of parental atopy than newborns born to non-smokers [71].

Total serum IgE levels and specific IgE levels are related to each other and influenced by smoking, gender and age [67]. Individuals with high levels of total serum IgE have 4–13 times higher prevalence of allergen specific IgE [67]. As with total IgE, specific IgE declines in both men and women with increasing age. However, in one study total IgE declined only in women suggesting that factors other than specific IgE, like smoking, influence total IgE [67].

Very recently, it has been proposed that children undergoing assessment for possible allergy should not receive allergen specific IgE testing when total serum IgE concentrations are very low [72]. Children with low total serum IgE rarely have allergen specific IgE present. High total serum IgE levels are more likely to be associated with specific IgE and atopy symptoms [73].

Children with early persistent wheeze and sensitization to aeroallergens were shown to have high levels of total IgE before symptoms developed. Thus, it appears that high IgE levels, developed in response to environmental factors, precedes allergic sensitization, i.e., specific IgE [74]. This study did not assess the effects of ETS exposure [74]. In general, asthmatics have higher total serum IgE levels even when they test negative for specific IgE [75–77]. Even in non-atopic individuals there appears to be an interrelationship between total serum IgE and asthma. There is a possibility that non-atopic individuals are in fact allergic but are not tested for the correct allergen [75].

Active smoking in adults is consistently associated with elevated total serum IgE levels [64, 66, 78, 78] and current smokers have higher levels than ex-smokers [68]. IgE levels are the same among ex-smokers as for never smokers [68] but others found that they remained high in ex-smoking males from a Norwegian population [67]. The authors suggest that males have higher cumulative exposure

to tobacco smoke than younger men and women. Beyond active smoking, ETS exposure's effect on total serum IgE levels has yielded mixed results [68, 71, 80–82].

Exposure to maternal smoking in utero had an especially pronounced effect on total serum IgE and subsequent development of allergic sensitization in infancy in one study. This effect held true even in children considered "low risk" with no parental history of atopy [71]. However, others found no effect of maternal smoking during pregnancy on serum IgE levels either at birth or 9 months later [82].

Total serum IgE is affected by numerous factors including sex, age, environmental exposures like smoking, and specific IgE levels. The role of active smoking on increasing total serum IgE levels in adulthood is consistent through the literature. The effects ETS exposure either in utero, in infancy, or in adulthood are inconsistent.

Lung Function

The development of the human respiratory system is highly complex and lungs develop over a continuum spanning from embryogenesis to early adult life [83]. Lung development in utero and during early infancy, especially the first year of life affects respiratory health through the life course as this time is a critical period for growth and development of respiratory function [3]. Other toxic exposures and conditions in early life can affect lung function and growth [83]. The fetal period appears to be especially critical for lung development. Exposure to ETS during the fetal period and early infancy is associated with greater respiratory risk through childhood [84].

Lung function is measured using an array of pulmonary function tests that assess airflow and can be used to diagnose lung disease such as asthma, emphysema, bronchitis and chronic obstructive pulmonary disease. Some common lung function tests include FEV_1 (forced expiratory volume in 1 s) and FVC (forced vital capacity). The type of lung function test used depends on resource availability, age of the patient, and what is being diagnosed such as a specific disease or the efficacy of new medication. Because it is difficult to do lung function tests in children under 5, asthma diagnoses prior to this age are made relying on family history, child's medical history and physical exam [25].

As we age there is a natural decline in lung function. Lung function peaks around the second decade of life, plateaus between late adolescence and early to mid-30s and gradually declines thereafter [3]. Environmental factors, like ETS exposure in early life, can affect this normal growth and decline a number of ways. It may accelerate the rate of decline, plateau at a lower level than normal, or prevent lungs from reaching developmental potential. Lung function over the life course is influenced by numerous other factors including height, BMI, history of severe respiratory illness in childhood, childhood asthma and TB, socioeconomic status, gender, pack years smoking, and duration of breastfeeding [85].

For children, the effect of ETS exposure on lung function is dependent on dose, age at exposure, source and appears to vary by child's sex and asthma status [36, 86]. Thus, the effect of ETS exposure on lung function has been reported for females [86]. Maternal smoking appears more detrimental to lung function in infants than other household member smoking. As with asthma, the relationship between maternal smoking during pregnancy and lung function deficiencies during infancy is consistent and strong [34, 87, 88]. In a systematic review of 22 cross-sectional studies, there were small decreases in FEV_1 in children exposed to ETS, especially by the mother [89]. Current, postnatal ETS exposure in childhood is associated with lower FEV_1 which becomes stronger with prenatal exposure [90]. Lung function deficiencies from ETS exposure tend to manifest in lung function measurements of flow and volume.

Pulmonary health is necessary for achieving an overall good quality of life. FEV_1 was is an important predictor of all-cause mortality, including ischemic heart disease, lung cancer, and stroke [88, 91].

Even in lifelong never smokers, FEV_1 predicts total cause mortality as well as respiratory and cardiovascular mortality [92]. Avoidable early life exposures like maternal smoking that accelerate lung function decline, become increasingly important to examine and prevent [34].

Do Health Effects Track into Adulthood?

ETS exposure in utero or early infancy has many negative health outcomes during early childhood [1, 27, 29, 53, 54, 93]. Evidence for these effects lasting into adulthood is relatively scarce [95]. If the effects of ETS exposure can permanently alter the course of respiratory and immune system development, as has been postulated by clinicians and researchers, some of these effects should be measurable in adulthood. However, results are conflicted [94–104].

The adverse respiratory problems in childhood associated with ETS exposure decline with age and it is not clear why. It may be that children spend less time at home with parents as they grow older and therefore ETS exposure decreases [84]. There may be "catch up" phase in development during later childhood where some measures of respiratory health are recouped. However, the effects of early life exposure to ETS appear in health outcomes in infancy and track into adulthood. ETS exposure during early life may alter normal lung development such that there are permanent changes that lead to poorer respiratory health throughout the life course [103–106].

In a large questionnaire based cross-sectional study, adult non-smokers that were exposed to ETS by parents before age 18, had increased odds of chronic dry cough and phlegm between the ages of 45 and 74 years [95]. They found a dose–response relationship between respiratory symptoms in adulthood and the number of household smokers during childhood. Women had increased odds of having doctor diagnosed asthma if they had been exposed to at least one smoker prior to age 18 though this association was not found in men [94]. Studies with similar design assessing other respiratory outcomes such as emphysema, asthma, wheeze, and lung function, also indicate a dose–response relationship that can vary by sex [94, 97, 99, 103, 107].

However, not all studies found an association between early life exposure to ETS and adverse respiratory outcomes in adulthood [96, 98]. The effect of ETS exposure on allergic sensitization/atopy may be protective in adulthood [50]. This mirrors studies noted earlier that found a protective effect of ETS exposure in utero or infancy on the development of atopy [55, 56].

Children with parents that smoke are more likely to become smokers themselves [108, 109]. There are most likely both physiological and social reasons for this. For lung function there is evidence that the effects of maternal smoking and personal smoking in later life are synergistic [110]. The negative effects of maternal smoking on child lung function happen at least three different ways. First, maternal smoking lowers child's lung volume. Second, it is associated with more smoking in the offspring and less likelihood of quitting once smoking has begun. Third, maternal smoking and personal smoking synergistically increases airflow limitation in adults [110].

Cross-sectional studies are helpful in looking for associations between early life exposure to ETS and later health effects but more longitudinal studies will help determine causality and look at changes across time.

Conclusions

There is consistent and strong evidence that ETS exposure during pregnancy or early infancy has deleterious health effects in early childhood. Consistency of findings, dose–response relationships, and the strength of association between ETS exposure and health outcomes is suggestive of a causal relationship

between the two. The actual biologic mechanism of tobacco smoke's effect on asthma, respiratory symptoms, allergic sensitization, lung function and total serum IgE is still being explored and is not entirely clear at this time [6]. Evidence for ETS exposure's effect on total serum IgE and allergic sensitization remains conflicted but is clearer and stronger for asthma, respiratory symptoms and lung function. The strongest associations of adverse health outcomes relating to asthma, lung function and allergy are found when ETS exposure occurs during the prenatal period and early infancy.

Data from the US National Health and Nutrition Examination Survey III [12] showed that the most important predictor of cotinine, i.e., ETS exposure, in children was the reported number of cigarettes smoked in the home. However, the age of the child, race/ethnicity, parental education, family income, and home size were also predictive of cotinine levels [12]. All these factors can be taken into account when designing interventions for groups of children most at risk.

The measures of effect from ETS exposure on respiratory health outcomes can sometimes be small, like it is for lung function. However, considering most children in the US and many other countries in the world are exposed to some level of ETS, there is a substantial population attributable risk in children [6] and this is a considerable public health problem. ETS exposure is an entirely avoidable risk factor.

Policy Implications

In the last decade or two there has been a rise in industrialized countries implementing smoking bans in public places to protect everyone from the effects of ETS exposure. Many less developed countries have also implemented smoking bans but with less success due to lack of enforcement and resources. Children constitute a vulnerable group that needs extra protection.

On a more individual scope, clinicians can screen parents and intervene if they smoke, especially if inside the home or car. Parents or clinicians could be incentivized, through insurance costs for example, for low or reduced cotinine levels in children [111]. Service providers and settings catering to pregnant women or children can be staffed to screen, identify and refer smoking parents to cessation programs. If parents will not consider quitting smoking they can be educated to reduce exposure of children through smoking outside the home or car. Community-level interventions with a strong theoretical framework focusing on home ETS reduction are most effective [111].

Future efforts to protect children will need to focus on getting parents to stop smoking, preventing individuals from starting to smoke, and education on how to protect infants and young children from ETS among those parents that do not stop smoking.

Future Research

While there is general consensus among public health and healthcare professionals that ETS exposure negatively impacts health, there are areas that need further study [6, 84, 111, 112]. Limiting smoke exposure through infancy and childhood should target all children. However, gene-environment interactions should be examined to

1. Identify children at highest risk of respiratory problems due to ETS exposure
2. Elucidate causal associations
3. Determine ages when exposure causes most damage

Ages of exposure separating prenatal from postnatal ETS exposure especially need to be further explored, though this will be difficult since many mothers smoking during pregnancy continuing after

birth [3]. There is a need to discover the mechanisms of ETS exposure damage which could lead to better treatments and therapies mitigating the harmful effects of ETS. Longitudinal study designs should be used to track changes over time; changes in lung function, asthma status, respiratory symptoms, and allergic response looking also at levels of ETS exposure that can also change across time. As all children should be protected from ETS exposure, there is a need to explore intervention strategies to reduce or mitigate ETS exposure among children. Public education, clinical interventions, advocacy statements, and community-level interventions are all possible modes of ETS exposure reduction or elimination [14].

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Chapter 20
Smoking Mothers and Breastfeeding

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Key Points

- Breastfeeding has been indicated as the most important protector against many negative consequences of life.
- Pregnancy and childbirth are good occasions for quitting smoking.
- Second-hand smoking in homes where women and children are exposed through the smoking of other family members.
- Maternal smoking has been negatively associated with breastfeeding duration.
- Smoking interferes with the release of oxytocin.
- Public health policymakers have already banned smoking in many public places but there is a need to work harder towards increasing breastfeeding rates.

Keywords Breast milk • Smoking and pregnancy • Tobacco • İnfant health

Introduction

Breastfeeding confers short-term and long-term benefits on both child and mother [1], including helping to protect children against a variety of acute and chronic disorders. The long-term disadvantages of not breastfeeding are increasingly recognized as important [2, 3].

Reviews of studies from developing countries show that infants who are not breastfed are 6–10 times [4, 5] more likely to die in the first months of life than infants who are breastfed. Diarrhea [6] and pneumonia [7] are more common and more severe in children who are artificially fed, and are responsible for many of these deaths. Diarrhoeal illness is also more common in artificially fed infants even in situations with adequate hygiene. Prolonged breastfeeding has been shown to reduce the risk of allergic and respiratory diseases. Artificially fed children have an increased risk of long-term diseases with an immunological basis, including asthma and other atopic conditions [8].

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R.R. Watson et al. (eds.), *Nutrition in Infancy: Volume 1*, Nutrition and Health,
DOI 10.1007/978-1-62703-224-7_20,

Breast milk is the communication vehicle between the maternal immune system and that of the infant; while conferring multiple means of protection from pathogens, breast milk actively directs and educates the immune, metabolic, and microflora systems within the infant [9]. Breastfeeding is a key child survival strategy; Edmond et al. [10] showed a marked dose response of increasing risk of neonatal mortality with increasing delay in initiation of breastfeeding from 1 h to day 7. Furthermore, when mothers abandon breastfeeding, infants run a higher risk of morbidity [11] and mortality in developed countries [12], which is further aggravated in poor ones. According to the WHO (World Health Organization) [13] breast milk substitutes cause irreparable damage to infants.

Despite, breastfeeding promotion programs should emphasize early initiation as well as exclusive breastfeeding; anyone who works closely with new mothers and infants recognizes the many complexities associated with infant feeding. Human lactation is not strictly physiological; social and emotional factors play a role in how it is conducted. To reach the WHO goals for duration of breastfeeding, health workers must recognize and use the variables associated with breastfeeding duration and initiation.

Even though pregnancy and childbirth are good occasions for quitting smoking, an alarmingly large percentage of women who reduce or quit smoking during pregnancy resume smoking within 1 year after giving birth. Rates of relapse in the postpartum period are reported to be as high as 80% among women who quit smoking during pregnancy, with up to 60% relapse occurring in the first 6 months postpartum and up to 80% within 12 months [14–16]. Among the pregnant women less education, living with a smoker spouse, under stress, part-time employment rather than unemployment, low income, age under 30 years and breastfeeding <6 months have been found related to smoking during pregnancy and after childbirth and after initial cessation, more likely to relapse [17, 18].

The objective of this review is to present breastfeeding and maternal smoking connection and to investigate whether infants born to smoking parents are better protected by breastfeeding than by formula feeding.

Tobacco Smoking

According to the WHO data, there are approximately 250 million women worldwide who are regular smokers. Only 3% of smoking women can succeed in quitting each year [19]. Addictive effects of smoking can be strong as heroin addiction so quitting smoking seems not easy.

Tobacco smoking, now and in the past, has been a custom and addiction primarily of men, leaving women and children as the majority of the world's passive, or involuntary, smokers. However, tobacco addiction is increasing in young girls in women in developing countries. In that countries the main target of tobacco industry is women (pregnant or reproductive age). Although by 2008, 160 million people worldwide had been covered by comprehensive smoke-free laws, nearly 90% of the world's population is not protected, and laws do not limit exposure to second-hand smoking (SHS) in homes where women and children are exposed through the smoking of other family members [20].

Tobacco industry is a "vector that spreads disease and death throughout the world" [21]. The actions of the tobacco industry to forestall meaningful legislation on tobacco control and to adapt to changing circumstances in order to protect its interests [22]. The tobacco industry uses sophisticated strategies, such as working through the movie industry, to create a favorable environment to promote smoking [23].

Exposure to SHS is strongly associated with a number of adverse effects on children, involving, in particular, the respiratory tract. In a 1999 report on SHS and children's health, WHO stated "The vast majority of children exposed to tobacco smoke do not choose to be exposed. Children's exposure is involuntary, arising from smoking, mainly by adults, in places where children live, work, and play." Given that more than one billion adults smoke, WHO estimates that approximately 700 million, or

almost half, of the world's children are exposed to SHS [24]. In European homes there is at least one smoking person [25]. Every year 150,000–300,000 infants have been diagnosed as upper respiratory infection related to SHS. 7,500–15,000 infants have been hospitalized every year because of acute respiratory infections. Attack frequency and severity of bronchial asthma increases because of passive smoke exposure of 200,000–1,000,000 children. In Europe 300,000–500,000 infants experience acute respiratory tract infection due to passive smoking. The signs of chronic respiratory disease' such as cough, sputum production, wheezing, etc., are more frequent in children having smoking parents [26].

Young parents of poor socioeconomic background (especially vulnerable mothers) may not be capable of overturning such an unfavorable situation and quit smoking. It is more realistic to see the vulnerable (young, uneducated, poor, and frustrated) mother falling for the "conveniences" of a "cleaner" milk formula in lieu of her "contaminated" milk. This image of "contamination" can be indirectly passed on by the baby food industry and, perhaps unwittingly, by health professionals [27].

Cigarette Smoke as a Toxic Substance

The composition of smoke changes depending on the type of tobacco, loosely or tightly packing of cigarette, degree of humidity, type of its paper and its thickness and whether it has a filter or not [25]. The smoke that is coming out of the tip of cigarette, pipe, or cigar is called the side stream smoke. This smoke represents 85% of the smoke in the room. The smoke that is exhaled from the lungs of the smoker is called the main stream smoke and represents 15% of the smoke in the room. Many of the toxic gases in the side stream smoke have a higher concentration compared to the main stream smoke. There are nearly 4,700 chemical toxins in tobacco smoke, that occur as a result of burning of tobacco and most of which are carcinogenic [28]. When nicotine, water, and carbon monoxide are separated from the tobacco smoke, the rest is called the tar phase of the smoke. Tar phase includes nitrosamines, aromatic amines, and polycyclic hydrocarbons (for example, chemicals like benzopyrine and 2-OH benzopyrine with high carcinogenic potential). Among these, the substances with highest contribution to the carcinogenic potential of the cigarette smoke are thought to be the tobacco specific N-nitrosamines. These substances occur from nicotine and other tobacco alkaloids during tobacco processing and cigarette smoking. Tar phase of cigarette smoke also includes irritant and toxic organic compounds like ammonium, hydrocyanic acid, furfural, acrollein, nitric oxide, nitrogen dioxide, and phenol derivatives. Some of these compounds are severely irritant especially to the respiratory tract, while around 60 of them are known or suspected carcinogens. Because of the cyanide (CN) in the cigarette smoke, its metabolite thiocyanate (SCN) is determined in the blood of smokers. Cigarette smoke also includes metals like nickel, radioactive polonium-210, and arsenic oxide [28].

Smoking and Lactation

Maternal smoking has been negatively associated with breastfeeding duration. Women who smoke are less likely to breastfeed their children than non-smokers. Horta et al., found that mothers smoking cigarettes more than 20 in a day; have a possibility of exclusive breastfeeding time less than 6 months, approximately two times less than mothers not smoking [29]. Same investigators found that smoking mothers started complementary feeding 1.93 times more than not smoking mothers in a meta-analysis study. They concluded their results because of poor let-down reflex in smoking mothers [30]. In our study, we made a cox regression analysis and demonstrated that smoking mothers started to complementary feeding more than 4.62 times than non-smoking mothers in 4 months [31].

Simard et al. [32] determined that smoking in the postpartum period led to an 8 weeks shorter breastfeeding period. Interestingly, only women who smoked continuously through their pregnancy and postpartum were at most risk for early weaning. Liu et al. [33], Ratner et al. [34], Scott et al. [35] found smoking to be strongly associated with the discontinuation of breastfeeding by 10 weeks.

The effect of maternal smoking on breastfeeding is still controversial. Early weaning in smoking mothers may be related to both physiological and psychosocial problems. Nicotine in the mother's blood may reduce prolactin secretion. Reduced prolactin inhibits the let-down reflex. This may cause a decrease in milk supply [29]. However, this hypothesis was not proven by measuring serum prolactin levels in smoking mothers. On the other hand, smoking mothers may have significantly less motivation to breastfeed. Furthermore, the health care community may not support breastfeeding of smoking mothers because of their belief that nicotine in breast milk would be harmful to the infant.

Evidences for a Physiological Mechanism

For many decades it was known that nicotine was present in the breast milk of smoking women [36, 37]. The milk-to-plasma ratio for nicotine is 2.9, indicating that nicotine levels in breast milk are almost three times higher than in the mother's blood [38]. Gossain et al. [39] indicated for the first time lower prolactin levels in humans exposed to cigarette smoke. However, it appears that the difference between smokers and non-smokers is not significant and they appear to have used the incorrect statistical tests [40].

Andersen et al. [41] investigated prolactin levels in pregnant women. However, the mean daily cigarette use was recorded at their first antenatal visit, although the samples were collected at 36 weeks gestation. Although a small difference was found between smokers and non-smokers, the range in prolactin levels varied widely in both groups, and the clinical significance of this difference is uncertain [41]. Quigley et al. [42] found no acute change in prolactin levels when pregnant women smoked a cigarette under experimental conditions.

Basal prolactin levels were also lower in postpartum smokers than non-smokers, however, the rapid increase in prolactin during feeding was not affected by smoking [43]. Widstrom et al. [44] systematically sampled women who had a normal pregnancy and vaginal delivery and found higher somatostatin (an inhibitor of prolactin) [45] in smokers on day 4, but no difference at 3–4 months postpartum. However, the higher somatostatin found in smokers may correlate with the smokers' lower motivation to breastfeed, meaning that the hormonal differences may be secondary to smokers' breastfeeding behavior, rather than a primary physiological cause.

Another widely accepted belief is that smoking interferes with the release of oxytocin, the hormone responsible for the milk ejection reflex (or let-down) [46]. Smoking did not have any effect on oxytocin release in rats [47] or humans [43]. The milk volume of smokers was significantly less than non-smokers [48]; however, only ten women were sampled in each group; both groups were exclusively breastfeeding, but it was not documented if the groups spent equivalent time breastfeeding.

Smokers are more likely to perceive that they have low milk supply [49, 50] however, there is no sign of poor infant weight gain. Perceived low milk supply is the most common reason women give up breastfeeding and is not necessarily correlated with a documented low milk supply [51]. Similarly, the increased use of artificial feeds in hospital for infants of smokers could be a reason for low milk supply in hospital [52], but could also be a response to increased irritability in these infants due to nicotine withdrawal or a reduced maternal desire to breastfeed exclusively.

Smoking appears to alter breast milk by altering taste [53], by lowering Vitamin C [54] and Vitamin E [55] content of breast milk and by increasing oxidant levels [56]. In one of our study we found that the infants of smoking mothers had significantly lower serum vitamin A, E, and C levels compared to those of non-smoking mothers. However, we couldn`t make the assessment of mothers' milk vitamin A, E, and C levels [31]. Future research will probably identify further differences between the breast milk of smokers and non-smokers.

Evidences for a Psychosocial Mechanism

Several studies have found a dose–response relationship between the number of cigarettes smoked each day and breastfeeding intention, initiation, and duration that persists after adjusting for confounding factors [40]. Women who smoke seem to have significantly less motivation to breastfeed: they are less likely to intend to breastfeed [57, 58] and less likely to initiate breastfeeding [59, 60]. The dose–response relationship between the number of cigarettes smoked and women's intention [61] and initiation of breastfeeding [62] indicates the importance of social factors in women's infant feeding decisions; this association is clearly behavioral, not physiological.

In most developed countries, women who smoke and women who artificially feed their infants tend to be younger, less educated and have lower income than non-smokers and women who breastfeed [63]. Women who smoke and artificially feed their infants are less likely to have planned the pregnancy to follow antenatal classes and to respond to surveys related to infant nutrition [64, 65]. Smoking is usually associated with depression [66], however, evidence of a link between smoking and anxiety/depression in the postpartum population is absent [67]. Smokers are less likely to seek help with breastfeeding difficulties than non-smokers. Furthermore, smokers are more likely to feel that their milk supply is insufficient and their infant is unsettled than non-smoking women [68]. So smokers could be more susceptible to anxiety about their milk supply. And also, nicotine-affected infant may demonstrate irritability, which is interpreted as hunger or colic [69]; the stressed mother may increase the number of cigarettes she is smoking in response to her child's irritability [70].

Women who quit smoking during pregnancy and restart smoking in the postpartum period are more likely to stop breastfeeding [71] For some women, breastfeeding gives a reason not to smoke, while others resume smoking after birth and wean early [72], possibly because of a fear of the toxic effects of nicotine and other substances in the milk on their infants [71]. Smokers are "less health conscious" than non-smokers [71, 73]. Women see smoking as a luxury and a leisure activity, a quiet adult time or a coping strategy with anxiety, anger, and depression [74].

Health-related beliefs and practices in the mothers' social network are also potential social handicaps [75]. The infant's father has an important influence on infant feeding decisions [76]. There is a strong relationship between smoking pre-pregnancy, during pregnancy and postnatally, and the father's smoking status [77]. As the number of cigarettes smoked by the woman's partner increased, the woman was less positive about breastfeeding [78]. Non-smoking mothers have been found to be more likely to give up breastfeeding if they have a smoking partner even after adjusting for education and social support [75]. The reduction in breastfeeding when the father smokes was attributed by some to the effects of environmental tobacco smoke [29, 79]. However, the partner's attitude to breastfeeding is more relevant than the effect of passive smoking. Men who smoke may be less knowledgeable and enthusiastic about breastfeeding than non-smoking partners [75].

Maternal alcohol intake was associated with smoking during pregnancy. Being emotionally prepared for the pregnancy and making important choices for the care of the baby, such as feeding method, is possibly another factor in the continuation of maternal smoking and important area for education [80].

How Can We Determine Tobacco Exposure?

Exposure to passive smoking may differ within seasons, days, and even hours, It is unknown whether prenatal exposure or lifetime exposure or exposure in days or hours should be measured when considering the effects of passive smoking on some diseases such as otitis media. There is no threshold level about the hazardous effects of passive smoking. For example, exposure level not causing otitis media, may be enough to cause bronchial asthma [81].

Studies relying on questionnaires to determine tobacco smoke exposure are not reliable because cotinine has been determined in urine of babies of mothers not reporting any passive smoke exposure [82]. But there are epidemiological studies indicating that questionnaires and diaries may be helpful to document environmental tobacco smoke exposure [82, 83]. However, the distance of the passive smoker to the smoking source, exposure duration, and the magnitude of ventilation are important factors related to the amount of absorption of toxic substances into the body. Therefore, we need methods to objectively document the amount of absorption of tobacco smoke into the organism [84].

Several biological markers have been proposed for assessment of the importance of direct or passive exposure to tobacco smoke. The most widely used markers are carboxyhemoglobin in blood; carbon monoxide in expired air; SCN and nicotine in saliva, plasma, or urine; and cotinine, a major nicotine metabolite, which can be determined not only in urine but also in plasma and saliva [83, 84]. Some markers may be influenced by environmental sources other than tobacco smoke, namely, diet for SCN and road traffic or domestic emissions for carbon monoxide and carboxyhemoglobin. Therefore, these markers have been progressively replaced by nicotine and cotinine, which are more specific for tobacco smoke exposure. Because of the longer urinary half-life of cotinine as compared with nicotine (19 vs. 2 h) and of the absence of ambient contamination during sample acquisition (the unique source of cotinine is nicotine metabolization), cotinine is currently considered the marker of choice [85, 86]. Furthermore, cotinine concentration can be measured in fetal plasma, amniotic fluid, and breast milk [87].

Nicotine metabolism and pharmacokinetics can be different between children, so the same amount of nicotine can affect children differently. It has been suggested that nicotine, one of the many toxic substances found in cigarette smoke, may not be responsible for health hazards caused by passive smoking [88].

Smoking and Infant Health

Smoking during pregnancy is associated with multiple adverse fetal outcomes, including low birth weight, preterm delivery, stillbirth, congenital abnormalities increased risk for neonatal respiratory distress, etc. [89, 90]. Low birth weight was first reported in 1957 to be associated with maternal cigarette smoking during pregnancy [91] and the association is now considered to be causal [89]. Tobacco smoking is the single most important factor affecting birth weight in developed countries [92]. Martin and Bracken demonstrated a strong association between maternal smoking and growth retardation in their 1986 study [93] and several more-recent studies provide support for their findings [94, 95].

SHS exposure in early postnatal period may affect infant's physical development negatively. There are some studies which have conflicting results on growth parameters of breastfed infants who have smoking mothers. A cross-sectional study on 254 6–7-month-old infants was carried out by Yılmaz et al. [96]. In this study mother's smoking led to significant decrement in weight and head circumference of 6-month-old infants, whereas there was no significant effect on height of babies. Little et al. found better weight gain in 1-year-old breastfed babies of smoking mothers, when compared to those of breastfeeding and non-smoking mothers and smoking and formula-feeding mothers [97]. Nafstad et al., however, did not find any negative impact on growth of babies of smoking mothers in a multivariate analysis of factors on growth of 1-year-old infants; in that study, breastfed infants gained less weight when compared to formula-fed infants [98]. Berlenga et al. determined that 3-month-old infants of smoking mothers were significantly shorter than those of non-smoking mothers [99].

Iodine is essential for thyroid hormone synthesis and, accordingly, is required for normal development, growth, and metabolism. Worldwide, iodine deficiency is one of the main causes of preventable brain damage and mental retardation [100]. Lack of iodine for thyroid hormone synthesis during the fetal stage and/or the first years of life may lead to developmental brain damage. During the period of

breastfeeding, thyroid function of the infant depends on iodine in maternal milk. The protective effect of breastfeeding on thyroid metabolism is well documented [101]. Breastfeeding was beneficial in most cases of neonatal hypothyroidism [102] in spite of studies having conflicting results [103, 104]. Compared to formula-fed, exclusive breastfed infants showed the greatest reduction in spontaneous thyroid volume development during the first 3 months of life [105]. According to the results of another study serum T-4 and T-3 levels were significantly higher in breastfed compared to formula-fed infants [106].

SCN is an antithyroid substance derived from CN [107]. SCN inhibits competitively the function of the sodium-iodide symporter localized in the basolateral membrane of the thyroid gland. This transporter accumulates iodide in the thyroid gland for hormone synthesis [108].

The main environmental source SCN is CN detoxification, either as a breakdown product of food cyanogenic-glucosides or derived from tobacco smoking [109, 110]. Smoking origin SCN's half-life is longer (approximately 2 weeks), absorption is faster and more toxic than plant origin CN [109].

Meberg et al. [111] reported that the mean breast milk SCN levels of smokers was not significantly different from non-smokers (9.0 and 10.5 mg/L respectively). Comparatively, in the USA the breast milk SCN concentration of smokers (4.2 mg/L) was fourfold higher (0.92 mg/L) than of non-smokers [112]. Studies that address breastfed infants' thyroid status and maternal smoking are rare. Laurberg et al. [113] examined impaired iodine transport into breast milk if the mother was a smoker. Smoking during the period of breastfeeding dose dependently reduced breast milk iodine content to about half and, consequently, exposes the infant to increased risk of iodine deficiency [113].

Smoking modulates the dietary pattern of women, causing a significantly lower intake of essential nutrients [114], especially iodine [115]. This is one of the possible mechanisms of the iodine deficiency in the smoking mothers. Breastfeeding mothers should not smoke, but if they do, it is important that they obtain sufficient iodine from diet or from iodine containing supplements [113].

The non-enzymatic antioxidant system is functioning to protect the human body from dangerous effects of oxidants. It is composed of vitamins A, C, and E [31]. There are only few studies investigating the effect of passive smoking on serum antioxidants of children [116–118]. Nutrition of infants who are exposed to tobacco smoke is very important in order to protect them from oxidative stress. In one of our study multivariate analysis revealed that independent factors determining the serum vitamin A, C, and E levels of infants as breastfeeding and maternal smoking. Despite the lowering effect of tobacco smoking on these vitamins, breastfeeding seemed to compensate this loss of antioxidant capacity and decrease the oxidative stress in infants [31]. Although Korchazhkina et al. [119] found that antioxidant capacity of both breast milk and formulae is sufficient to prevent significant lipid peroxidation in a limited number of healthy premature infants, in a study on 54 healthy term infants, it has been demonstrated that breast milk provides a better antioxidant power than does formula [120]. Apparently, if SHS exposure of infants cannot be prevented, continuation of breastfeeding may help to prevent decrements in vitamin levels and antioxidant capacity [31, 54, 55, 120].

The effect on neurologic development of infants of nicotine absorbed through gastrointestinal tract is not clearly elucidated. However, in animals with chronic exposure to nicotine and in smokers, upregulation of nicotinic acetylcholine receptors in brain is observed together with increase in receptor functions. Similar to findings observed for fetuses [121] and adults after chronic exposure, nicotine exposure via maternal milk upregulated nicotinic receptor expression in neonates [122]. Such neonatal nicotine exposure during sensitive periods of development can produce long-term behavioral and learning deficits [81]. Negative influence on cognitive development of children of tobacco smoking is observed in non-breastfed children of mothers who smoked especially during early months of pregnancy. Even if the mother smokes, breast milk provides healthy brain development with the help of its high maternal hormones and high unsaturated long chain fatty acid concentration. Therefore, nicotine dependent mothers should be encouraged to breastfeed their babies [123].

Lately, it is emphasized that nicotine and other harmful metabolites that are digested via breast milk effects nicotinic receptors in early period of life which may result with tobacco addiction in

adolescent period [122, 124]. A study on causal factors of smoking in adulterant period has revealed that increase of saliva cotinine concentration with exposure to SHS is the most important independent factor [81, 124]. Another study on smoking adolescents showed that the level of cotinine in saliva that are obtained 6 year before is a factor to begin smoking [124].

Smoking is associated with sleep disturbances in adolescents [125] and adults [126]. Mennella et al. [127] reported that an acute episode of smoking by lactating mothers altered their infants' sleep/wake patterning. Infants spent significantly less time in active and quiet sleep and woke from their naps sooner. These changes are attributed to nicotine exposure. Nicotine directly suppresses pontogeniculooccipital spike activity, a factor important initiating and maintaining active sleep [128] and indirectly inhibits sleep promoting neurons in the ventrolateral preoptic area [129].

Postnatal exposure to nicotine via breastfeeding may perform various effects on autonomic cardiovascular control and vital functions of the infants. A Study with limited number of case on physiologic measurement of infants are performed just before breastfeeding and 20 min later. After breastfeeding, infants of smoking mothers had a significant change in respirations and oxygen saturation while infants of non-smoking mothers had a significant change in pulse only [130]. Results of another study on comparing heart rate variability and blood pressures of infants of smoking and non-smoking mothers showed that heart rate variability decreased, with increasing milk nicotine, ingested by the boys but not the girls. The differences of mean arterial pressure between sleep states in the infants were significantly lower in the smoke group compared to the nonsmoke group [131].

Infantile colic (IC) is a syndrome characterized by paroxysms of irritability, inconsolable crying, and screaming accompanied by clenched fists, drawn-up legs, and a red face [132]. The available evidence suggests that IC has multiple independent causes. IC has been attributed variously to infants' difficulty self-regulating, type of feeding, exposure to cow's milk proteins (especially α-lactalbumin) in formula or breast milk, exposure to tobacco smoke, and maternal depression or anxiety [132]. Several studies have presented somewhat conflicting results on a potentially etiological role of parental smoking. Matheson and Rivrud showed that breastfed infants of smoking mothers have colic more frequently [69]. Said et al. found an association with parental smoking independent from the type of feeding [133]. Haggart and Giblin reported no association between colic and parental smoking [134]. In a population-based, retrospective study conducted in the Netherlands between 1997 and 1998 [135]. Results of this study showed that maternal smoking and colic are associated but that breastfeeding weakens this association rather than reinforcing it. According to results of another population-based prospective study [136], compared with infants of non-smokers, infants of mothers who smoked during pregnancy had a twofold increase in their risk of IC. Infants of mothers who smoked after birth but not during pregnancy were also twice as likely to have colic. Surprisingly, infants of mothers who smoked both during pregnancy and after the birth were only 50% more likely to have colic, compared with infants of non-smokers.

If exposure to cigarette smoke increases the risk of colic, then this would provide additional incentives to parents to abstain from smoking [137]. However, further research is needed to assess whether this association is indeed causal [135].

It is shown that mother's taking excessive dose of nicotine in a short time may cause vomiting, severe irritability, and even apneic attacks, in breastfed infants [138]. Besides it is expressed that the infants whose mothers smoke more than 15 cigarettes in a day may result with nicotine toxicity via GIS [138].

While, many researches are realized on infections related to SHS, not much is known about infections caused by toxic metabolites transmitted via breast milk [139]. It is known that cigarette smoke consists of ciliatoxins toxic to the ciliae of nose, paranasal sinuses, middle ear, pharynx, larynx, and lungs. In children who are exposed to cigarette smoke, motility of the cilia deteriorates and this leads to excessive mucus accumulation. Hence, this situation predisposes the children to upper respiratory tract infections (URTI), lower respiratory tract infections (LRTI), and otitis media. During childhood

the frequency and severity of URTI, LRTI, sinusitis, otitis media, and bronchial asthma increases due to exposure to toxins within tobacco smoke [140, 141]. It has been found that tobacco smoke has a negative impact on infant health, especially within the first year of life [142]. İnfants who have smoking mothers are subjected to infections more than two times compared to ones having non-smoking mothers at their first year. There is a dose–response relationship between the amount of cigarettes that mother's have smoked and these infections [142, 143]. In case both parents smoke, incidence to respiratory tract infections increases by 72% [26]. Infections at early stages of life may cause to chronic obstructive pulmonary diseases.

Exposure to environmental tobacco smoke worsened the symptoms and the prognosis of bronchiolitis, while breastfeeding seemed to have a protective effect even in children exposed to environmental tobacco smoke [144]. Recent cross-sectional study by Yılmaz et al. [96] reached a conclusion that SHS exposure, through maternal, paternal or other people's smoking, is an independent risk factor for increased infection rates (otitis media, URTI, or LRTI). Furthermore, according to the multivariate analysis results, breastfeeding significantly decreased the risk of infections independently: 3.3-fold for LRTI, fivefold for URTI, and 5.4-fold for otitis media. According to the present results, the route of exposure tobacco smoke is significantly important for infections. Nonexposed infants are significantly protected against infections when compared to exposed ones. Passive exposure to tobacco smoke leads to significantly more common infections in infants when compared to breast milk exposure. When the passively exposed group is breastfed, the infection rate drops many fold. Thus, breast milk may have a prophylactic effect on the harmful influences of tobacco smoke. This finding was also confirmed by Rylander et al. [145], Pisacane et al. [146], and Beaudry et al. [147]. For the tobacco smoke to increase the risk of respiratory infections, sidestream smoke has to be inhaled [148]. Thus, tobacco smoke toxins diffusing into the breast milk may not increase the risk of respiratory infections in breast milk exposed infants as much as expected. Prolonged breastfeeding has been shown to reduce the risk of allergic and respiratory diseases [149]. The immunomodulatory constituents of breast milk, such as secretory immunoglobulins and oligosaccharides, and antioxidants in the breast milk might be responsible for the protective effect of breastfeeding against the tendency towards respiratory infections caused by SHS exposure of infants. But because these factors operate only as long as they are present on the mucosal surfaces, such a protective effect will not persist for very long after discontinuation of breastfeeding [146]. This is the reason why prolonged breastfeeding must be encouraged.

Fatal effect of SHS exposure in postnatal period is sudden infant death syndrome (SIDS) and this dramatic effect results from exposure to a number of components of cigarette smoke, including nicotine and carbon monoxide both prenatally and postnatally. The California Environmental Protection Agency (EPA) report estimates that 10% of SIDS deaths are attributable to SHS exposure [150]. The relationship between SHS and SIDS is independent from birth weight and gestation [141]. The evidence accumulated by the time of the 2006 US Surgeon General's report was found sufficient to reinforce the conclusion that SHS exposure is a cause of SIDS [89] The 2005 California EPA report [150] also concluded that a causal relationship exists between SHS exposure and SIDS. The reports noted not only the epidemiological evidence, but also the findings of animal models that indicate potential mechanisms [151]. Smoking mothers' infants have twofolds higher risk for sudden infant mortality. In pregnancy if both parents are smoke than the risk of sudden infant mortality is eight times higher compare to non-smoker parents. SHS exposure of the infant increases the risk for SIDS, whereas breastfeeding is protective for SIDS among non-smokers, but not smokers [152]. In another study on SIDS, the influence of breastfeeding was evaluated by comparison of the nicotine concentrations in breastfed and non-breastfed infants from smokers and non-smokers. Fivefold higher nicotine concentrations were determined in non-breastfed infants of parents who smoked as compared to all other groups. According to the results of this study it is concluded that in terms of the etiology of the SIDS nicotine intake by passive smoking is much more important than by breastfeeding [153].

Should Smoking Mothers Breastfeed Their Infants?

In infancy period, exposure to cigarette smoking can be both in utero and by passive exposure to environmental tobacco smoke. Breastfeeding is one form of passive exposure.

What are the harmful and beneficial effects of maternal smoking on breastfeeding mother and their infants? This question has not been fully answered. In the previous edition of American Academy of Pediatrics (AAP) Statement [154–156], the Committee on Drugs placed nicotine (smoking) in the "Drugs of Abuse-Contraindicated During Breastfeeding." The reasons for placing nicotine and, thus, smoking in this group were documented decrease in milk production and weight gain in the infant of the smoking mother and exposure of the infant to environmental tobacco smoke as demonstrated by the presence of nicotine and its primary metabolite, cotinine, in human milk [87, 138, 157, 159, 168]. Although, there is controversy regarding the effects of nicotine on infant size at 1 year of age [96–99], there is no clear evidence to document whether this amount of nicotine presents a health risk to the nursing infant. The Committee on Drugs therefore has not placed nicotine (and thus smoking) in "Drugs of Abuse-Contraindicated During Breastfeeding." but hopes that the interest in breastfeeding by a smoking woman will serve as a point of discussion about smoking cessation between the pediatrician and the prospective lactating woman or nursing mother [160].

The level of nicotine and cotinine passing to the child by means of the mother's milk has been shown to be dependent on the personal smoking habits, smoking frequency before breast feeding and the interval between the last time of smoking and the time of giving milk. Shorter the time between the last time of smoking and the time giving milk, greater the amount of nicotin and cotinine acquired with milk by the baby. Also, the amount of nicotine acquired with milk by the baby depends on the strength of inhalation of the smoke by the mother. The nicotine concentration in the milk of a mother with smoking habit is between 0.5 and 120 ng/mL. The amount of nicotine acquired by a 6-kg-baby who is fed only by the mother's milk has been calculated to be between 1.4 and 750 ng/h/kg if the baby is breastfed with an amount of 150 mL and a frequency six times a day. These measurements vary at a large extent depending on the baby's being a second-hand smoker and the amount of nicotin acquired. However, these levels are less than 1/20th of the level of nicotin acquired by an adult having a smoking habit [138].

Luck and Nau [138] demonstrated that the significant serum concentrations and urinary excretion rates of nicotine in the breastfed infants of smoking mothers suggested that nursing contributed to the nicotine exposure of these neonates. Becker et al. [161] directly measured breast milk cotinine and found a mean concentration as high as 495 ng/mg of creatinine, with a range of 347–707. Mascola et al. [162] found urinary cotinine levels 2–8-fold higher in all of their smoking exposure categories than in previous reports. They explained this situation by the difference in the sensitivity of methods used to detect urinary cotinine levels, failure to adjust for urine creatinine levels and difference in the smoking rates of different communities.

Even if a smoking mother does not smoke next to her child, she still causes a significant amount of exposure by breastfeeding. Usually, smoking mothers and sometimes health care providers think that avoiding passive smoke exposure is enough to prevent the hazardous effects of tobacco smoke exposure. The major concern about the presence of nicotine in mother's milk is whether or not gastrointestinal absorption of this toxin is hazardous to infants. In adults, gastrointestinal absorption of nicotine is reduced possibly because of first-pass elimination effect of the liver. However, in infants, this first-pass effect and absorption could differ from adults. In this stage of life, there is an immaturity in first-pass elimination [49]. In the case of infants, age may be important. Cotinine elimination half-life in neonates is two to three times that in adults, and it is not known whether it is days, weeks or even months before infants develop the capacity to metabolize nicotine fully. Some studies have shown that inhaled nicotine is more hazardous than ingested nicotine [49]. However, acute nicotine intoxication due to ingested nicotine has been reported [138]. On the other hand, cotinine is pharmacologically inactive, and it is unlikely that cotinine in breast milk has any adverse effects on an infant's health.

It is only a quantitative indicator of intake of other harmful metabolites [84]. Further investigations are needed of other harmful toxic substances in mother's milk, including their concentrations and their toxic effects.

Children from homes with high rates of tobacco use, such as poor families in developing countries and younger mothers with less education (in industrialized societies) may, through breastfeeding, gain an important asset to attenuate Health inequities [163]. Minchin [70] reviewed the associations between cigarette smoking, breastfeeding, and infant health, and concluded that it is far from ideal to smoke and breastfeed, but it is worse to smoke and not breastfeed. We should build into our anti-smoking programs specific concern for these vulnerable groups, i.e. pregnant women and lactating mothers. If we cannot stop smoking during pregnancy, it is fundamental not to miss the chance to encourage and support breastfeeding. Maternal support and infant feeding advice to smoking mothers must incorporate the additional risks of switching from breastfeeding to formula feeding. It is important to balance the risks of not breastfeeding vs. the risks of maternal smoking during breastfeeding. The breastfed infants of smoking mothers, although exposed to attenuated levels of breast milk SCN and nicotine, receive additional breastfeeding protection; non-breastfed infants of smoking mothers are also exposed to SHS "passive smoking" carrying tar, nicotine, carbon monoxide, acrolein, acetonitrile, as well as CN and other antithyroid compounds [164], but without the protective effects of breast milk.

Infants born to smoking parents are better protected by breastfeeding than by formula feeding. Therefore, if public health policies cannot stop addicted mothers from smoking during pregnancy it is fundamental not to miss the chance of encouraging and supporting breastfeeding. The food and health inequalities of socially disadvantaged groups demand well-crafted public health policies to reduce the incidence of diseases and of morbidity: these policies need to make it clear that breastfeeding is better and safer [27].

Prevention and Smoking Hygiene

Women who stop smoking by the first trimester give birth to infants with weight and body measurements comparable with those of infants of non-smokers, indicating a necessity for early intervention [21]. A woman is more likely to quit smoking during pregnancy than at any other time in her life [22], however smoking cessation interventions are not always available during pregnancy.

Public health policymakers have already banned smoking in many public places but there is a need to work harder towards increasing breastfeeding rates. Smoking cessation therapies can double the chance of quitting smoking, therefore, they can be proposed to smoking parents in the context of their child's health care visit [165]. The nicotine replacement therapy in addition to psychological support is proposed during the breastfeeding period [166]; gums or 2 mg of nicotine tablets (with a short half-life) can be taken after breastfeeding [167].

Although breastfed infants of a smoking or snuff-taking mother are exposed to nicotine in breast milk, the enterohepatic system is a better barrier than their lungs, inactivating most of nicotine reaching the liver. Both passive smoking at home and snuff-taking were associated with measurable nicotine levels in milk [168]. However, if we consider the toxic effect of many constituents in the cigarette smoke (carbon dioxide, tar, nicotine, and cyanide), the use of nicotine patches in breastfeeding women is safer than continued smoking. Besides there being no significant influence of nicotine-patch-using mothers on milk intake by the breastfed infant, the absolute infant dose of nicotine decreases by about 70% when using patch compared to smoking [169].

Health professionals have to work towards targeting smoking mothers to initiate and to continue breastfeeding. Traditional smoking cessation materials may not be sufficient for cigarette-addicted mothers. Furthermore, smoking parents have a low rate of receiving smoking cessation prescriptions. Smoking hygiene precautions can be implemented at that time [170].

Smoking hygiene has been shown as a promise in helping mothers who smoke and breastfeed to reduce infant respiratory illness. If women are unable to quit smoking, they must be advised to reduce the number of cigarettes smoked and to smoke away from the infant. Using an air purifier inside home, never smoking near infant or car is very important. Advising mothers to smoke only immediately after breastfeeding and at least 90 min prior to breastfeeding can reduce the toxicity of maternal smoking [171].

Health professionals should promote, protect, and support breastfeeding in communities with a high rate of tobacco use [163]. The most effective way to improve infant health is to promote breastfeeding. Maternal exposure to tobacco smoke during pregnancy compromises fetal development and infant health, which in turn can be aggravated by formula feeding. Longer breastfeeding was associated with lower risk of the infant dying in the post neonatal period [12], it is worth promoting full breastfeeding in addition to antismoking campaigns.

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Chapter 21
Exposure to Breast Milk in Infancy and Risk of Adult Breast Cancer: A Summary of the Evidence

Lauren A. Wise and Linda J. Titus

Key Points

- While there are many established short-term benefits of breastfeeding for infant nutrition and health, the potential long-term benefits regarding chronic disease and cancer morbidity in adulthood, including risk of breast cancer, are still unclear.
- In this chapter, we review the epidemiologic evidence regarding the association between being breastfed in infancy and risk of short-term and long-term health outcomes, focusing specifically on adult breast cancer.
- Few studies have investigated the relation between feeding practices in infancy and adult health. No overall association has been found for incidence of all cancers or any individual cancer type. The existing data on infant feeding practices in relation to breast cancer risk are not sufficient to confirm or refute any protective or harmful effect of having been breastfed on breast cancer risk, and additional studies are needed. Published studies have suffered from several methodological limitations including recall bias, misclassification of exposure, lack of control for confounding, small numbers, and limited variation in exposure.
- Until more definitive studies are conducted, health professionals should avoid informing their patients about a possible link between infant feeding and breast cancer while continuing to stress the many established benefits of breastfeeding for both infant and mother.

Key words Breast cancer • Lactation • Breastfeeding • Menopausal status • Risk factors

Abbreviations

RR Relative risk
CI Confidence interval
US United States

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R.R. Watson et al. (eds.), *Nutrition in Infancy: Volume 1*, Nutrition and Health,
DOI 10.1007/978-1-62703-224-7_21, © Springer Science+Business Media New York 2013

Introduction

There has been considerable interest in the health-related benefits of breastfeeding for the infant. While there are many established short-term benefits of breastfeeding for infant nutrition and health [1], the potential long-term benefits regarding chronic disease and cancer morbidity in adulthood, including risk of breast cancer, are still unclear. In this chapter, we review the epidemiologic evidence regarding the association between being breastfed in infancy and risk of short-term and long-term health outcomes, focusing specifically on adult breast cancer. We also present the results of a meta-analysis of published studies on breastfeeding in infancy and risk of adult breast cancer, updating a 2005 meta-analysis on this topic [2]. Finally, we make recommendations for improving future epidemiologic studies that investigate the effects of exposure to breast milk in infancy on longer-term health.

Most pediatric and nutritional organizations in the US recommend exclusive breastfeeding[1] for the first 6 months of life, and breastfeeding with nutritionally adequate and complementary foods for at least 12 months [3]. The World Health Organization (WHO) recommends extending the latter time period for *up to 2 years of age or beyond* [4]. The prevalence of breastfeeding in the US is lower than in Western Europe and other nations. In the US, ~33–36% of infants are breastfeeding at 6 months of age, and 17–20% of infants are breastfeeding at 12 months of age whereas worldwide, 79% of infants are still breastfeeding at 12 months [3].

Most literature on the health effects of being breastfed in infancy pertain to short-term health effects and illnesses in childhood. In a 2007 review [1] of published literature regarding the effects of breastfeeding on child health outcomes, exposure to breast milk in infancy was associated with a reduced risk of acute otitis media, nonspecific gastroenteritis, necrotizing enterocolitis, respiratory tract infections, atopic dermatitis, early-onset asthma, childhood obesity, type 1 diabetes, childhood leukemia, and sudden infant death syndrome (SIDS) [1]. There was no conclusive evidence for an effect of breastfeeding on infant mortality or cognitive performance [1], and subsequent studies have continued to produce inconsistent results [5–13]. None of the studies explicitly examined the difference between "direct breastfeeding" (infant suckling at mother's nipple) and "feeding of expressed breast milk." Moreover, definitions of "exclusive breastfeeding" varied widely in the literature. Almost all studies were nonexperimental (observational), which are susceptible to confounding and several biases, and there was a wide range in data quality across the different studies [1]. In addition, publication bias could not be ruled out. In contrast to the findings from observational studies, a recent cluster-randomized trial in Belarus—the Promotion of Breastfeeding Intervention Trial (PROBIT)—showed a positive influence of prolonged and exclusive breastfeeding on childhood cognitive performance [14], but no effect on asthma and allergy [15] or childhood obesity [16], when infants were followed up until age 6.5 years. Furthermore, no differences were observed for child behaviors (e.g., conduct problems, hyperactivity, peer problems) or mothers' satisfaction with interpersonal relationships, though mothers in the intervention group were more likely to breastfeed their next child [17].

The inconsistent results across observational and experimental data suggest that bias and residual confounding due to socioeconomic factors may explain some of the findings in previous observational studies. However, experimental data are not without their own limitations, including potential for bias due to nonadherence; confounding and chance variation (when samples are small); reduced generalizability (when confined to specific groups based on age, ethnicity, and geography); and inappropriate intervention (e.g., inaccurate or narrow range of exposure) [18]. Thus, differences between experimental and observational data do not necessarily reflect the limitations of observational studies [18].

Few studies have investigated the relation between feeding practices in infancy and adult health. Meta-analyses and systematic reviews of observational studies indicate that having been breastfed may reduce total cholesterol levels [19] and diastolic blood pressure [20], and lower risk of type 2

[1] WHO defines "exclusive breastfeeding" as no other food or drink, not even water, except breast milk (including expressed milk or milk from a wet nurse), but allows the infant to receive oral vitamins, minerals, and medicines.

diabetes [21] and obesity [22] in adulthood. No overall association has been found for incidence of all cancers or any individual cancer type [2]. However, with respect to infant feeding practices and risk of adult breast cancer, the results are less clear.

The characteristics of published studies assessing the association between exposure to breast milk in infancy and breast cancer are presented in Table 21.1 [2, 23–36]. Eleven of these studies—three cohort studies [2, 26, 28], seven case–control studies [25, 27, 30, 31, 33, 35, 36], and one cross-sectional study [32] were included in a meta-analysis of reports published before 2006 [2]. Penrose et al. [29] was omitted from meta-analysis because it compared odds of familial vs. sporadic breast cancer among exposed and unexposed women. The authors concluded that being breastfed in infancy was unrelated to overall risk of breast cancer and to risk among postmenopausal women, but was inversely associated with *premenopausal* breast cancer (RR = 0.88, 95% CI = 0.79–0.98) [2]. Most studies relied on the long-term recall or reporting of infant feeding practices among participants who were questioned *after* the diagnosis of breast cancer, introducing potential for recall bias. However, the three cohort studies, which used prospectively ascertained exposure information or used mothers' reports about breastfeeding to validate exposure data, found no evidence of an association overall or by menopausal status [2, 26, 28]. Since 2006, three additional case–control studies have been published on this topic [23, 24, 34]. Two of these newest studies supported an inverse association overall [23, 24]; one found a stronger inverse association among premenopausal women [24], and the other did not examine differences by menopausal status [23]. The third new study, based on a substantially larger number of cases, showed little evidence of an association overall or by menopausal status [34].

We updated the inverse-variance fixed-effect meta-analysis of published studies on infant feeding practices and risk of breast cancer (through August 2011) using the same search criteria as Martin et al., [2] and the "metan" command in STATA (Figs. 21.1, 21.2, and 21.3) [37]. The I^2 statistic was computed to estimate the degree of heterogeneity between studies that is not dependent on the number of studies, where an I^2 value of 0% indicates no between-study heterogeneity [37]. Consistent with Martin et al., [2] the updated meta-analysis showed a weak inverse association among all women (RR = 0.94, 95% CI: 0.89, 0.99) (Fig 21.1), an inverse association among premenopausal women (RR = 0.88, 95% CI: 0.78, 0.98) (Fig 21.2), and no association among postmenopausal women (RR = 0.98, 95% CI: 0.91, 1.05) (Fig 21.3). The I^2 tests indicated no statistically significant between-study heterogeneity in parameter estimates, albeit the studies among premenopausal women displayed a much higher degree of heterogeneity (premenopausal: $I^2 = 53.9\%$, $p = 0.07$; postmenopausal: $I^2 = 18.4\%$, $p = 0.30$). Thus, the published reports to date indicate a possible inverse association with premenopausal breast cancer, and no evidence of an association with postmenopausal breast cancer. However, given that the largest and most methodologically sound studies to date produced null results—a US prospective cohort study that used maternal reports to validate breastfeeding [28], a British prospective cohort study that also relied on maternal reports provided on average 7 years after birth [2], and a large case–control study of more than 3,700 cases [34]—it seems premature to conclude that having been breastfed reduces the risk of premenopausal breast cancer.

The exact mechanism(s) by which early life exposure to breast milk might influence adult breast cancer risk is unclear. Breast milk contains the optimal balance of fats, proteins, and carbohydrates for infant nutrition, as well as various immunologic and growth factors, providing benefits for child immunity, growth, and development [38]. However, breast milk also contains environmental toxicants (e.g., organochlorines and heavy metals) due to inadequately controlled pollution [38–41]. Initial interest in a viral etiology for human breast cancer was generated by animal studies showing that mammary tumors in certain strains of mice could be caused by a tumor virus transmitted via breast milk [42]. Early studies hypothesized that viral transmission through breastfeeding explained the elevated risk found in women whose mothers had developed breast cancer [25, 29, 32]. More recent reports of an inverse association between exposure to breast milk and breast cancer led to the hypothesis that anti-apoptotic milk proteins (e.g., α-lactalbumin) [43], progesterone and gonadotropin-releasing hormones [44], or reduced cytochrome P4501A activity may mediate the association [45]. Breast milk

Table 21.1 Characteristics of published epidemiologic studies of breastfeeding in infancy and risk of invasive breast cancer

Study design	Investigators	Enrollment date (case–control) or follow-up period (cohort)	Participants' birth year	No. cases	No. person-years (p-y) or controls	Method of exposure ascertainment	Coding of exposure	Estimated relative Risk (95% CI)[a]	Control variables
Cohort	Ekbom et al. [26]	1874–1954	1874–1954	458 <50 y: 212 ≥50 y: 246	1,197 <50 y: 600 ≥50 y: 597	Record-linkage. Hospital records completed by midwives/nurses on average 10 days after delivery	Exclusive or partly BF vs. no	*All women*: 1.03 (0.46, 2.27) ≤50 year: 0.96 (0.37, 2.49) ≥50 year: 1.23 (0.39, 3.85)	Maternal age at delivery, childhood socioeconomic status, duration of hospital stay, maternal age at menarche, parity, age at first birth, menopausal status
	Michels et al. [28]	1991–1997	1921–1964	Total: 1,073 Premeno: 413 Postmeno: 660	695,655 p-y	Self-report via questionnaire (validated using maternal reports: r=0.74)	Ever vs. never; duration	*All women*: 1.05 (0.91, 1.21) Duration: <9 month: 0.95 (0.80, 1.14) ≥9 month: 1.19 (0.93, 1.53) *Premenopausal*: 0.97 (0.71, 1.20) Duration: <9 month: 0.85 (0.66, 1.10) ≥9 month: 0.88 (0.52, 1.49) *Postmenopausal*: 1.12 (0.92, 1.37) Duration: <9 month: 1.06 (0.83, 1.36) ≥9 month: 1.30 (0.98, 1.72)	Age, birth year, preterm birth, family history of BRCA, height, BMI at 18, weight change since 18, history of benign breast disease, age at first birth, energy intake, alcohol
	Martin et al., 2005	1948–2003	1918–1939	74 <50 year: 13 ≥50 year: 61	94,610[b]	Maternal report via questionnaire (average 7 years after birth)	Ever vs. never; duration	*All women*: 1.62 (0.89, 2.94) ≤50 year: 2.50 (0.55, >4.00)[c] ≥50 year: 1.50 (0.78, 2.85)[c]	Age, survey district, social class of father, per capita weekly household food expenditure in childhood, birth order

Case–control	Bucalossi et al. [25]	1928–1956	Early 1900s	2,969	836	Self-report or proxy report by relatives via interviews or questionnaires	Ever vs. never	1.09 (0.72, 1.64)	None
	Henderson et al. [35]	1971–1972	>1906	Total: 308 <40 year: 69	308 <40 year: 69	Self-report via in-person interview	Ever vs. never	*All women*: 1.27 (0.79, 2.05) ≤40 year: 1.18 (0.53, 2.63)	Date of birth, race, socioeconomic status
	Brinton et al., 1983	1973–1977	1919–1932 (median)	1,192	1,080	Self-report via in-person interview	Ever vs. never	0.86 (0.7, 1.1)	Age
	Freudenheim et al. [27]	1986–1991	1901–1951	Total: 528 Premeno: 229 Postmeno: 299	Total: 528 Premeno: 229 Postmeno: 299	Self-report via in-person interview	Ever vs. never	*All women*:0.74 (0.56, 0.99) *Premenopausal*: 0.76 (0.52, 1.12) *Postmenopausal*: 0.73 (0.47, 1.13)	Age, education, BMI, family history of BRCA, age at menarche, parity, age at first birth, menopausal status, history of being breast disease, duration breastfed own children, fat and carotenoid intake, height
	Weiss et al. [33]	1990–1992	1946–1972	<45 year: 508	<45 year: 471	Maternal report via questionnaire	Ever vs. never	≤45 year: 0.74 (0.6, 1.0)	Age, BMI, family history of BRCA, previous breast biopsy, alcohol, number of mammograms, age at menarche, age at first birth, parity
	Titus-Ernstoff et al. [31]	1992–1995	1911–1945	Total: 4,008 Premeno: 205 Postmeno: 3,803	Total: 4,291 Premeno: 220 Postmeno: 4,071	Self-report via telephone interview	Ever vs. never	*All women*: 0.93 (0.83, 1.04) *Premenopausal*: 0.65 (0.41, 1.04) *Postmenopausal*: 0.95 (0.85, 1.07)	Age, state, education, religion, family history of BRCA, BMI, age at menarche, parity, age at first birth, age at menopause

(continued)

Table 21.1 (continued)

Study design	Investigators	Enrollment date (case–control) or follow-up period (cohort)	Participants' birth year	No. cases	No. person-years (p-y) or controls	Method of exposure ascertainment	Coding of exposure	Estimated relative Risk (95% CI)[a]	Control variables
	Sanderson et al. [30]	1994–1996	>1944	<45 year: 506	<45 year: 433	Maternal report via questionnaire or telephone interview	Ever vs. never; duration	≤45 year: 1.0 (0.8, 1.3) Duration: <3 month: 1.0 (0.7, 1.4) 3–5 month: 1.1 (0.7, 1.6) ≥6 month: 1.0 (0.7, 1.5)	Age. birth year, BMI, family history of BRCA, menopausal status, age at menarche, parity, age at first birth, infertility, use of OCs, birth weight, maternal age, birth order, maternal smoking
	Barba et al. [24]	1996–2001	1916–1966	Total: 845 Premeno: 270 Postmeno: 575	Total: 1,537 Premeno: 543 Postmeno: 994	Self-report via in-person interview	Ever vs. never	*All women*:0.82 (0.68, 0.99)[d] *Premenopausal*: 0.56 (0.38, 0.83) *Postmenopausal*: 0.86 (0.67, 1.11)	Age, education, race, BMI, history of benign breast disease, family history of BRCA, lactation, age at menarche, parity, age at first birth, age at menopause
	Nichols et al. [23]	2002–2006	1933–1986	1,648	773	Self-report via telephone interview	Ever vs. never	*All women*: 0.83 (0.72, 0.96) *First-born women*: 0.97 (0.74, 1.29)	Age, age at menarche, age at first birth, parity, menopausal status, postmenopausal hormone use, family history of BRCA, height, weight at age 20, weight gain, mammography use

	Wise et al. [34]	1997–2001	1922–1976	Total: 3,779 Premeno: 1,760 Postmeno: 1,985	Total: 4,433 Premeno: 1,531 Postmeno: 2,395	Self-report via telephone interview	Ever vs. never; duration (19% of women only)	*All women*: 0.99 (0.90, 1.09) *Premenopausal*: 0.94 (0.80, 1.10) *Postmenopausal*: 1.01 (0.89, 1.15) *All women, duration*: <3 month: 0.90 (0.70, 1.15) 3–6 month.: 0.77 (0.58, 1.02) >6 month: 1.05 (0.74, 1.48)	Age, state, education, religion, family history of BRCA, BMI, age at menarche, parity, age at first birth, menopausal status, age at menopause
Cross-sectional	Tokuhata [32]	1950–1966	1910–1939 (median)	13	1,314	Interview or questionnaires to mothers' relatives	Ever vs. never	0.88 (0.20, 3.94)	None
Case-series	Penrose et al. [29]	Early 1900s	Late 1800s-early 1900s	79	360	Self-report via in-person interview	Ever vs. never familial vs. sporadic BRCA	2.22 (0.85, 5.77)	None

[a]Relative risk (odds ratio, risk ratio, or incidence rate ratio) and 95% confidence interval comparing any or exclusive breastfed vs. bottle-fed, or breastfeeding duration category relative to bottle-fed. *BF* breastfeeding

[b]Estimated based on data reported on total person-years (N = 185,458) and proportion of women in sample (51%)

[c]Based on Figures C and D (no exact estimates provided) [2]

[d]Crude estimate based on numbers of cases and controls provided in Table 2 of text [24]

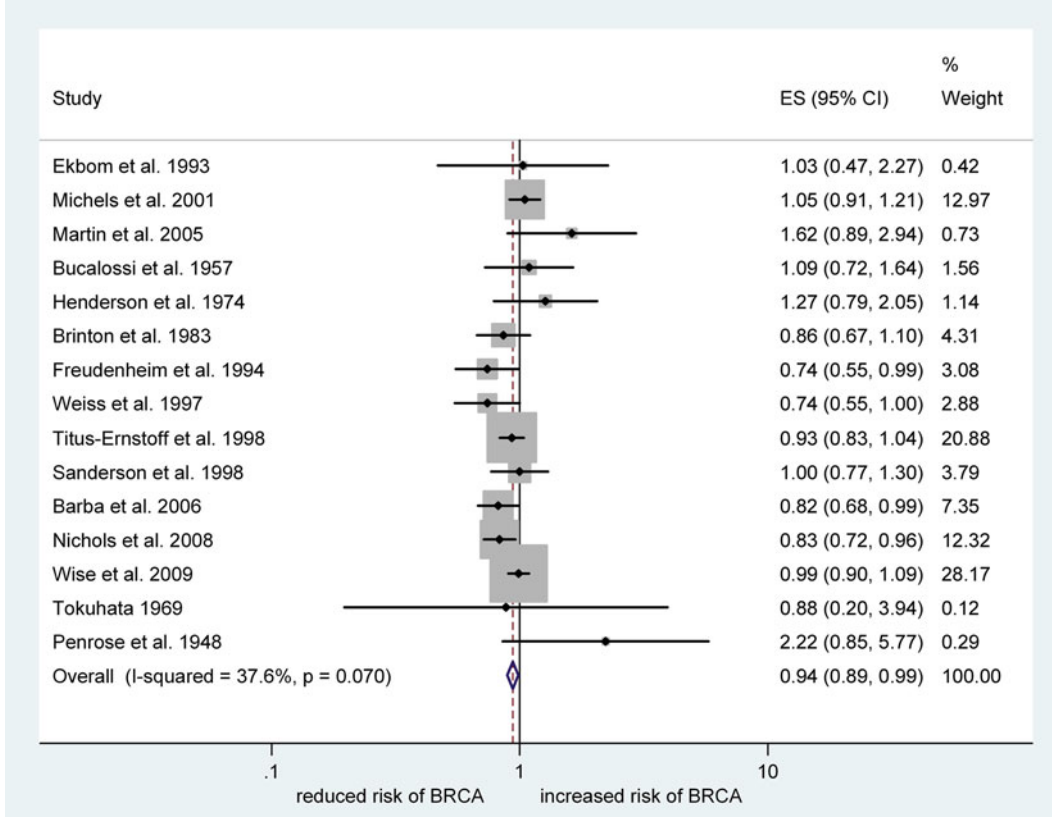

Fig. 21.1 Forest plot displaying an inverse-variance weight fixed-effect meta-analysis of studies on breastfeeding in infancy and risk of breast cancer: all women. Relative risks (ES) and 95% confidence intervals (CI) for breast cancer incidence, comparing women who were ever versus never breastfed in infancy. The study author and year of publication are indicated on the y-axis (ordered by type of study and year of publication). The box for each study is proportional to the inverse of the variance; horizontal lines show 95% CIs for each study-specific RR. The pooled estimate is shown at the bottom by a dashed vertical line (RR) and diamond (95% CI)

likely contains both chemo-protective and harmful agents, making it difficult to identify its direct influence on breast cancer risk.

In summary, the existing data are not sufficient to confirm or refute any protective or harmful effect of having been breastfed on breast cancer risk, and additional studies are needed. Published studies have suffered from several methodological limitations and future studies could be improved by using a prospective design (to avoid recall bias); collecting detailed exposure data on breastfeeding patterns (e.g., duration of breastfeeding, exclusivity of breastfeeding, and type of feeding: suckling vs. expressed milk); collecting data on a wide range of potential confounders including infant and parental characteristics; enrolling a large sample with sufficient numbers of premenopausal and postmenopausal cases; enumerating a study population with wide variation in the prevalence of breastfeeding; and conducting validation studies of breastfeeding reports using both participant and maternal data. For example, family studies of siblings with different breastfeeding histories would be particularly useful to adjust for confounding by social, environmental, and familial factors. Over a longer period of time, experimental studies that can rule out confounding such as PROBIT—albeit expensive to implement—could answer a broad range of questions about the long-term health benefits of breastfeeding [1]. In addition, the inclusion of new breastfeeding questions on the 2003 National Immunization Survey

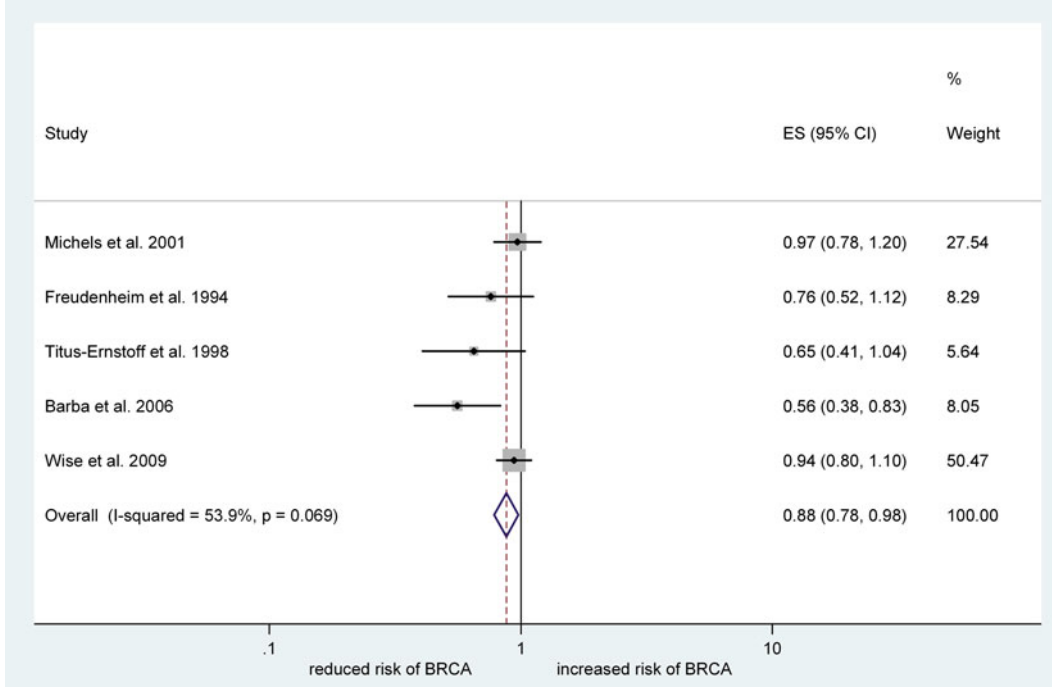

Fig. 21.2 Forest plot displaying an inverse-variance weight fixed-effect meta-analysis of studies on breastfeeding in infancy and risk of breast cancer: premenopausal women

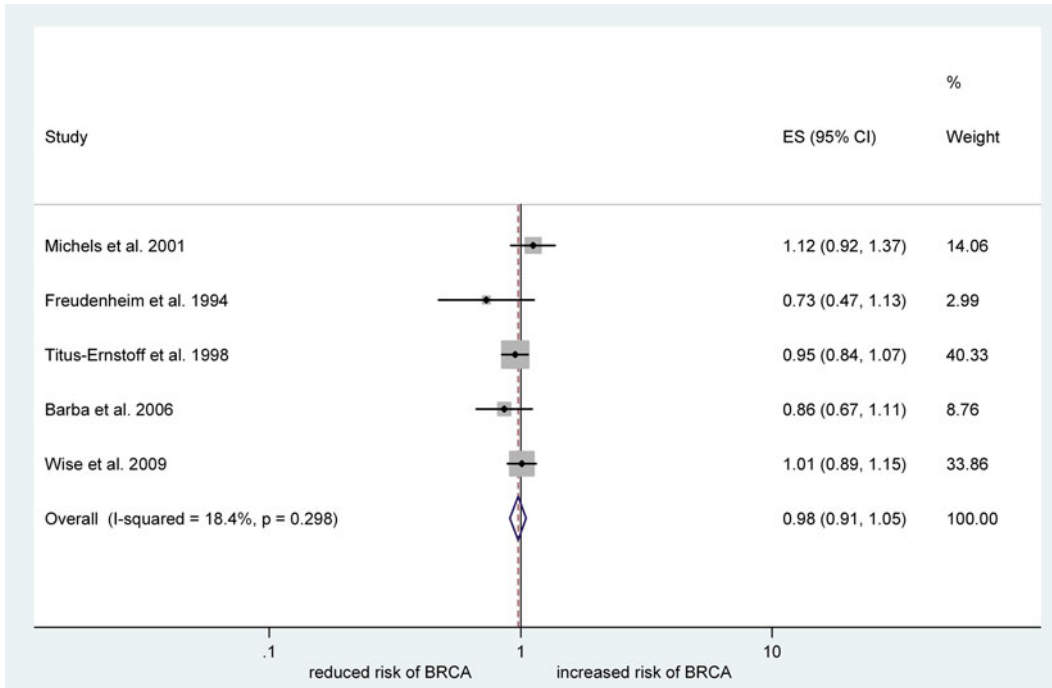

Fig. 21.3 Forest plot displaying an inverse-variance weight fixed-effect meta-analysis of studies on breastfeeding in infancy and risk of breast cancer: postmenopausal women

[46] (on initiation, duration, and exclusivity of breastfeeding) could provide useful data not only on breastfeeding trends, but also on the long-term health effects of being breastfed.

Health care professionals continue to play an important role in promoting breastfeeding by providing up-to-date information to pregnant and postpartum women, removing institutional barriers to breastfeeding, and advocating for policies that support breastfeeding as the norm for infant feeding [3]. Until more definitive studies are conducted, health professionals should avoid informing their patients about a possible link between infant feeding and breast cancer while continuing to stress the many established benefits of breastfeeding for both infant and mother.

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Chapter 22
Storage of Human Breast Milk

James Friel, Sandra Castillo San-Juan, and Milana Abramovich

Key Points

- Many infants are fed expressed human breast that has been stored frozen.
- The establishment of appropriate storage conditions is extremely important for keeping mother's milk safe, nutritious, and functional.
- Expressed human breast milk should be stored at a minimum of −20°C and protected from light, placed in glass or hard plastic containers or special breast milk freezer bags.
- The importance of proper storage of human breast milk should be emphasized to infant caregivers by healthcare professionals.

Keywords Breast milk storage • Shelf life • Pasteurization • Microwave • Thawing • Storage containers • Oxygen limitation • Refrigeration • Freezing

The Importance of Feeding Human Breast Milk

Numerous advantages for infants, their mothers, families, and society from breastfeeding and the use of expressed human milk have been documented by extensive research. These benefits extend beyond the infant's health and development by contributing to the mother's wellness and that of families and the general community by raising healthier individuals [1]. Consumption of human milk is advantageous to the environment, as manufacturing and transport of infant formulas demands energy and produces waste. There are appreciable cost savings from a reduction in formula purchasing [2–4].

Breastfeeding is sufficient to support optimal infant growth and development for approximately the first 6 months of life. Many health organizations recommend exclusive breastfeeding for the first 6 months of life, defined as the consumption of human milk with no supplemental food of any type, while allowing vitamins, minerals, and medications [2, 5]. The World Health Organization [WHO] [2002] recommends continuing partial breastfeeding into the second year of life.

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R.R. Watson et al. (eds.), *Nutrition in Infancy: Volume 1*, Nutrition and Health,
DOI 10.1007/978-1-62703-224-7_22, © Springer Science+Business Media New York 2013

Breast milk is recognized as an ideal source of nutrients for term and preterm infants, benefiting host defenses, digestion and absorption of nutrients, gastrointestinal function, and neurodevelopment [6]. Numerous studies have shown that inadequate early nutrition and/or growth may have an adverse long-term influence on development, including neurodevelopmental impairment, abnormal adipose tissue distribution, insulin resistance, glucose intolerance, and higher blood pressure later in life [7–10].

Why Human Breast Milk is Stored

Not all babies can be fed human milk directly from the breast. Illnesses, abnormalities, separation from the mother, and other reasons may interfere with breastfeeding; therefore, these babies are fed expressed milk from a bottle. Mothers may express their milk (1) for their own comfort in situations of sore nipples or postpartum breast engorgement, (2) in order to increase milk supply, (3) to leave milk for later feeding if they are away from their baby, and (4) in situations of adoption or surrogacy [11–17]. Some mothers working out of home express their milk, which is later fed to their infants from a bottle [18, 19]. Expressed breast milk, often supplemented with nutrients, is also widely used in hospitals for feeding of premature, small for gestational age, and also term infants who may be ill and cannot suckle [20, 21]. Expressed breast milk can be donated to milk banks, where, following pasteurization and screening, it is distributed for the feeding of infants with medical conditions, including formula intolerance, feeding issues related to prematurity, for adopted infants, and for those who are not able to receive their own mother's milk [22]. Breast milk can be expressed by hand or using an electric, battery operated or manual Breast Pump [23].

Expressed Human Breast Milk Shelf Life

It is extremely important to emphasize that expressed human milk is a food product, and, as such, it has a limited shelf-life. Shelf life of a food can be defined as the period of time during which it remains safe for consumption and also preserves a sufficient level of sensory acceptability for its target consumer population. The shelf life of any food is defined by the relationship between four critical factors: formulation, processing, packaging, and storage conditions [24]. As to date only limited processing procedures have been developed for expressed human milk, the key factors that impact the shelf life of expressed human breast milk are packaging and storage temperature. Therefore, these two parameters must be carefully determined.

Expressed human milk is susceptible to regular food degradation processes, thus its quality decreases with passage of storage regardless of the preservation methods used and the control of storage conditions [25]. However, the rate of the decrease in quality can be slowed down. As many oxidized products of rancidity not only contribute to the development of off-flavors, but are also considered to be unhealthy [26], it is important that storage of this precious food preserves its protective, digestive, inductive, and nutrient carrier properties as much as possible in order to keep it safe, nutritional, and functional. These numerous factors must be considered and prioritized when establishing storage parameters, as some of them demand contradicting conditions. Thus, the intention to use expressed human milk poses many challenges during the selection of the two key shelf life factors, which are storage temperature and the packaging.

Table 22.1 Current official protocols for storage of expressed human milk for healthy full term infants

Institution	Storage temperature				
	room temp. (19–25°C)	4°C	−15°C	−18°C	−20°C
Winnipeg Public Health—Government of Manitoba [52]	N/A	8 day	2 weeks	6 month	12 month
City of Toronto Public Health [53]	6–8 h	5 day	2 weeks	3–6 month	6–12 month
Government of British Columbia [54]	4 h	3 day	1 month	6 month	6–12 month
Government of Nova Scotia [55]	4–6 h	8 day	2 weeks	3–4 month	>6 month
La Leche League International [34a]	6 h	8 day	N/A	12 month	12 month
Academy of Breastfeeding Medicine [56]	6–8 h	5 day	2 weeks	3–6 month	6–12 month
American Dietetic Association [57]	N/A	48 h	N/A	3 month	12 month
Children's Hospital Central California [58]	10 h	7 day	2–4 weeks	3–4 month	>6 month
Lucile Packard Foundation for Children's Health [59]	10 h	7 day	2–4 weeks	3–4 month	>6 month
Florida Department of Health: Hernando County Health Department [60]	5 h	5 day	N/A	3–4 month	>6 month
Australian Breastfeeding Association [61]	6–8 h	3–5 day	2 weeks	3 month	6–12 month
Government of Western Australia, Department of Health [62]	4 h	48 h	N/A	3 month	12 month
South African Paediatric Association [63]	2 h	48 h	N/A	N/A	3 month
Palo Alto Medical Foundation [64]	27°C: 4 h 21°C: 10 h	5 day	2 weeks	3 month	6 month
Israel Ministry of Health [65]	19–22°C: 10 h 22–25°C: 4 h	8 day	2 weeks	3–4 month	>6 month

Low-temperature Storage of Expressed Human Breast Milk

Expressed human milk is susceptible to food degradation processes, thus requiring research and development of handling procedures [20, 25]. Similarly to any food, low-temperature storage, such as refrigeration or freezing, may retard microbial growth and delay some degradative changes in the physiochemical character of human milk [18]. This principle leads to the publication of various storage condition protocols. Official recommendations for the storage temperature and time, applicable to unpasteurized expressed human milk, can be found in Table 22.1. As can be seen, current storage recommendations vary, making it not clear which protocol should be followed.

Official recommendations have been established with the purpose to assure that by the time expressed human breast milk is ready for feeding, its bacteriological safety is not compromised [27]. Many studies have been conducted in order to question the appropriateness of current recommendations for other factors which may have an influence on the quality of stored human milk, such as bacteriostatic activity preservation, nutrient content, and more. A review of the studies can be found in Table 22.2.

Normally, the lower the temperature at which food is stored, the better preservation effect can be reached for its constituents. However, some studies show that this statement might not apply to some of the components of expressed human milk, such as vitamin C, antioxidant activity, inhibition of bacterial growth, and white blood cell count [28–31].

Thawing of human milk should be done in the refrigerator, with subsequent warming by placing the container of expressed milk into a container of warm water, followed by shaking to mix any separated layers [32–34]. Thawed milk should be used within 24 h [23].

Table 22.2 Storage condition studies for expressed human milk—literature review

Storage temp.	Recommended storage time	Component studied	Findings
4°C	8 days	Vitamin C, riboflavin, LA, ALA, DHA, ARA in untreated, in pasteurized and in stored with limited oxygen human milk	The four fatty acids and riboflavin, but not vitamin C, maintained general stability during refrigeration, frozen storage and Holder pasteurization. Oxygen limitation using nitrogen gas and −80°C temperature had only occasional beneficial effect on some of the studied components
−20°C	Preferable temperature for storage of unpasteurized human milk for 4 weeks		Pasteurized and non-pasteurized human milk can be stored at 4°C for 8 days; oxygen limitation is redundant
	Also preferable for storage of unpasteurized and pasteurized milk for 6 months		During 4 weeks storage, unpasteurized human milk benefited from −20°C compared with −80°C temperature [in pasteurized milk the opposite effect was observed]. After 2 weeks of storage at both temperatures, vitamin C level dropped significantly, leading to a recommendation of supplementation of the infant, if fed exclusively this milk. Oxygen limitation was not beneficial
−80°C	Preferable temperature for storage of pasteurized human milk for 4 weeks		During storage for 6 months, −20°C was beneficial for unpasteurized human milk [but not for the pasteurized]; oxygen limitation had a positive effect at this temperature [28]
25°C	4 h	Bacterial growth	Bacterial growth was restricted mainly to nonpathogens, was minimal at 15°C throughout the 24 h of storage, was low at 25°C for the first 4–8 h, and was considerably higher at 38°C even during the relatively short period of 4 h [66]
4°C	72 h	Bacterial growth	Breast milk contaminated with various bacteria can be safely stored at 4°C and at 6°C for at least 72 h. Even longer storage periods at 6–8°C pose a minimal risk for growth of potential pathogens [39]
4°C	24 h	Bacterial growth	Mean bacterial count [no heavy contamination] at any time during the 24 h was not significantly different from that at the beginning of the storage in the refrigerator [67]
4°C	8 day	Bacterial growth	Refrigeration has a significant inhibitory effect on bacterial growth, while freezing does not [30]
−20°C	1 month	Bacteriostatic activity, nutrients contents	Loss of bacteriostatic activity was detected. There was no change in levels of IgA, IgM, IgF, lactoferrin, lysozyme, concentrations of amino acids, and fatty acids [68]
4–6°C	48 h	Bactericidal activity	Degree of bacteriolysis was measured. Bactericidal activity persisted after refrigeration for 48 h and after freezing for 10 days [69]
−20°C	10 days		
−20°C	3 month	Bactericidal activity	Up to two-thirds of the original bactericidal activity level was maintained. Bactericidal activities of refrigerated samples diminished rapidly during 24 h storage, but compensated for by enhanced bacteria sequestration activity (greatly enhanced during the first few days, whereas in frozen samples—gradually lost) [70]
4–6°C	48 h	Bactericidal activity	Refrigeration for 48 h did not cause significant modifications, whereas storage beyond 72 h significantly lowered the degree of bacteriolysis versus fresh milk [71]
4–6°C	24 h	Bioavailable vitamin C	During storage for 1 month in a freezer or for less than 24 h in a refrigerator, 2/3 of the initial vitamin C can be preserved [27]
−16°C	1 month		

4–6°C −4°C to 8°C	24 h 1 week	Vitamins A, C, E, total protein, fat, lactose, zinc	Refrigeration (4°C) caused a statistically significant decline in levels of vitamins C and A during 24 h of storage. Freezing (−4 to −8°C) for 1 week resulted in a significant decline in the vitamins A, C, and E levels; however, the mean and the range of values remained within the international reference ranges. Other nutrients showed a statistically nonsignificant decline at the mentioned storage conditions [72]
4°C	48 h	Antioxidant activity	Freezing of HM is not recommended, as it resulted in a greater decrease in antioxidant activity compared with refrigeration [29]
Room −19°C	6 h 14 day	Bacterial growth	Streptococcus colony count increased more rapidly at 0–4°C compared to storage at −19°C [73]
<38°C	24 h	Digestive enzymes [amylase and lipases]	The digestive enzymes of human milk were not affected during storage for 24 h at temperatures up to 38°C, even though pH decreased sharply [74]
−20°C −70°C	5 month	FFA levels, lipoprotein lipase (LPL) and bile salt-stimulated lipase (BSSL) activity	Lipase activity levels were unaffected by rapid freeze-thawing followed by storage for 1 month at −20°C or −70°C. LPL and BSSL remained fully active during frozen storage. Milk fat was hydrolyzed at −20°C but not at −70°C [20]
15°C 25°C	24 h 4 h	pH, proteolysis, lipolysis, bacterial growth	Human milk pH decreased 2 units by 24 h of storage at all temperatures tested. Proteolysis was minimal during milk storage. Lipolysis was rapid, starting in the first hours of storage. Bacterial growth was restricted mainly to non-pathogens, was minimal at 15°C throughout the 24 h of storage, was low at 25°C for the first 4–8 h, and was considerably higher at 38°C during 4 h. Milk should not be stored at 38°C [74]
−20°C	N/A	Glutathione peroxidase [GPx], malondialdehyde [MDA] concentration	Refrigeration storage during 48 h and freezing storage during 10 days lead to a significant decrease in GPx enzymatic activity. MDA concentration significantly increased during 48 h of refrigeration, but the increase was nonsignificant during frozen storage for 10 days. Frozen storage is preferred to refrigeration for preservation of mother's milk quality [75]
4°C	48 h	Macrophages, B- and T-lymphocytes, neutronphils	Storage in glass containers for 48 h at 4°C resulted in a significant decrease in cell viability and macrophage and neutrophil concentration, but not lymphocytes. Freezing of human milk had only minimal effect on its antibody content, but altered cellular stability. Refrigeration for short periods of time offers an effective means of supporting milk cells in storage [76]
4°C	96 h	Bacterial colony counts, white blood cell counts, osmolality, pH, sIgA, lactoferrin, protein, total fat, FFA	Declines in pH, white cell counts, total protein, gram-positive colony counts and a rise in free fatty acid concentrations were detected. No significant changes in osmolality and concentration of sIgA, lactoferrin, total fat and total, and gram-negative colony counts were observed. Despite the decline in white blood cell counts, more cells remain after storage up to 96 h than after freezing or pasteurization. Thus, integrity of fresh HM is not affected by 5 days storage in the refrigerator [31]
4°C −18°C	48 h 28 days	Triglycerides, carotenoids	Triglyceride and carotenoid concentrations remained stable, with the exception of lutein concentration which decreased during storage at 4°C and during freezing [77]

(continued)

Table 22.2 (continued)

Storage temp.	Recommended storage time	Component studied	Findings
−20°C −80°C	60 days	MDA, GPx activity	MDA content of HM remained stable for 30 days during storage at both temperatures. This stability was lost during storage for another 30 days. GPx content remained stable for 30 days at −80°C, but dropped during storage for an additional 30 days. GPx content of HM stored at −20°C decreased during storage for 60 days. The advisable storage temperature is −80°C for a maximum duration of 30 days [78].
0–38°C	72 h	Microorganisms	Storage duration for expressed HM should not exceed 24 h at 4–10°C, 8 h at 15–27°C and 4 h at 30–38°C. Although 0–4°C seemed safest for HM storage, it is not recommended due to the hazards of the thawing process [79]

The microwave oven is not an appropriate device for thawing and warming of frozen human milk for feeding. This is because there is a danger of hot spot creation, which may harm the baby and because of the possible destruction of milk components such as IgA and lysozyme, caused by the excess heating effect. The growth of *E. coli* has been shown to increase following microwave heating, probably due to the loss of the anti-infective factors [18, 33, 35].

Storage of Expressed Human Milk with Reduced Oxygen Availability

Reduction of oxygen availability may slow down spoilage reactions, including lipid oxidation [24]. However, this factor may affect some of the constituents of expressed human milk, such as vitamin C and possibly DHA [28]. In addition, off-flavors may develop under these conditions due to the accumulation of ethanol, acetaldehyde, and other volatiles [36], which might result in infant's aversion to stored milk [37]. Limiting oxygen can be achieved using vacuum packaging or nitrogen gas flushing [24].

Storage of Pasteurized Human Breast Milk

International best practice requires pasteurization of donor human milk prior to feeding to recipients [38]. The only purpose of pasteurization is to destroy pathogenic microorganisms [18], as freshly collected breast milk is rarely sterile and normally contains bacteria which are transferred from the maternal skin and nipple duct microflora. Generally, the risk of infection to the infant originating from these microorganisms is not expected [39]. However, potential pathogens also may be found, which can produce lipases, proteases, and decarboxylases causing damage to antimicrobial proteins or converting free amino acids into toxic amines [39].

Conditions commonly used for the pasteurization of human milk are 62.5°C for 30 min—a process named "Holder pasteurization" [40, 41]. This treatment achieves a good compromise between maintaining microbiological safety and the nutritional and biological quality of breast milk. Holder pasteurization has been shown to destroy the pathogens in milk, including *M. tuberculosis* and vegetative cells of *Bacillus cereus*, as well as some viruses, such as HIV, HTVL 1–2, Cytomegalovirus, Herpes Simplex, and Rubella. These results are not achievable at lower pasteurization temperatures [4]. Rapid pasteurization at 72°C for 5 or 15 s has been shown to reach a better compromise between maintaining microbiological safety and the nutritional and biological quality of human milk; however, the required special equipment is currently available only at the industrial level [41].

The Holder pasteurization process maintains partial bactericidal activity of breast milk against *E. coli*. Key nutritional factors (oligosaccharides, lactose, LC-PUFAs, fatty acids, gangliosides, proteins, sulfur amino acids), vitamins A, D, E, B_2, B_{12}, biotin, niacin and pantothenic acid, other biological factors (amylases, EFG) and also absorption of nitrogen, calcium, phosphorous, and sodium have been shown not to be affected by this treatment [18, 28, 41–46].

Despite its indisputable advantages, heat treatment has an adverse effect on some of the milk components. Studies show that Holder pasteurization inactivates milk lipoprotein lipase and BSSL (an enzyme of major importance to the infant, assisting in the hydrolysis and absorption of milk fat in the small intestine), resulting in a reduced absorption of fat in preterm infants [18, 46]. Levels of vitamin C, folic acid, vitamin B_6, and thiamin decrease [18, 45, 46]. Some biologically active, immunologic, and anti-infective factors are affected. Reports exist about the reduction in IgA levels and activities, IgG, lysozyme, lactoferrin levels and activities, lymphocytes, growth factors, cytokines, lipase level, and the activity and destruction of IgM [41, 47].

Recently, a home-made high temperature heat treatment method, named the "Flash-heat treatment method," has been suggested for HIV-positive mothers in developing countries. According to this method, 50 mL of breast milk are poured into an uncovered glass peanut butter jar, which is placed in an aluminum pan containing 450 mL of water. This apparatus is heated over a flame until the water reaches 100°C and is at a rolling boil. The milk is then immediately removed from the water. Typically, the milk reaches the temperature of 72.9°C in this process [48].

Although the effect heat treatment has on breast milk composition has been the objective of extensive research, milk stability during subsequent storage has not been well studied. According to guidelines for the operation of human milk banks established by Arslanoglu et al., (2010), if human milk has been pasteurized using Holder pasteurization, it should be stored at −20°C. There is no general consensus for the best storage time for expressed human milk based on current research. Storage for less than 3 months has been recommended for pasteurized milk targeted for feeding of preterm neonates. If the pasteurized milk is refrigerated at 4°C, the maximum storage period has been set at 24 h by Arslanoglu et al., (2010); however, Abramovich and Friel (2011) have extended the acceptable storage time for pasteurized human milk to 8 days.

Storage Containers for Expressed Human Breast Milk

Expressed human milk should be stored in proper containers in order to minimize the potential harm to milk nutrients and to eliminate the possibility of contamination. Modern plastics offer a variety of materials for the manufacturing of storage containers, some of which are more and some of which are less suitable for expressed human milk.

Polyethylene bags should not be used to store expressed human milk because of the potential for contamination, loss of cellular components, sIgA specific for *E. coli* polysaccharides, and also loss of fat, which adheres to the walls of the bag [49]. Polyethylene bags do not withstand the expansion of milk during freezing and frequently leak upon thawing. They are fragile, easily punctured, and may leak through the seals [11].

Polypropylene and stainless steel containers may become scratched, accumulating milk in the scratches, thus enhancing the possibility of potential bacterial contamination [50]. In addition, storage in polypropylene bottles has been shown to result in some loss of lactoferrin and lysozyme (over 24 h period), loss of cellular components, and some loss of vitamin C [45, 49].

Much controversy and debate surround the use of polycarbonate for baby bottles. This plastic material contains bisphenol A, a substance which is suspected to pose a health risk. Polycarbonate baby bottles that contain bisphenol A have been prohibited by the Government of Canada since March 11, 2010 [51], followed by several other countries.

Glass containers or hard plastic bottles with tight-fitting lids for prevention of leakage and oxidation of components are preferred for storage of expressed human milk. They should be opaque, to prevent photo degradation of nutrients in milk [50]. However, there have been reports of greater loss of leukocytes in glass containers, compared with plastic, as a result of cells adhering to the walls of the container [49]. Special freezer bags for breast milk have been also made available [23].

Recommendations for Expressed Human Breast Milk Storage to be Provided to Infant Caregivers

Breastfeeding is undeniably the best practice for the delivery of all breast milk nutritional and functional factors to the infant. If feeding of stored milk is required, it is crucial that appropriate storage conditions are followed in order to allow the optimal amounts of the beneficial components to reach

the infant through breast milk without any compromise on safety. However, as can be seen from the variation in storage recommendations summarized in Table 22.1, the selection of appropriate storage conditions is not an easy task.

In general, the most appropriate guidelines for storage of breast milk would be the ones published by the mother's local health authority. These recommendations take into account local climate, culture, population general behavior, and equipment availability. It is extremely important to take into account also the mother's readiness to follow the provided advice, to assist her in making the right choices, in following the provided guidance and to adjust it to her individual capabilities. No recommendation can be beneficial, if it cannot be followed. In case local health authority recommendations are not available, international guidelines, such as those provided by The WHO or La Leche League, should be followed with the incorporation of the necessary adjustments, as described above.

It is important to bear in mind that during storage of breast milk, some nutrient contents gradually decrease, therefore supplementation of the infant should be considered, if fed by significant amounts of stored breast milk [28].

Appropriate handling practices guidance must be provided to the caregiver, as improper handling can negate all efforts for safe and nutritious milk delivery to the infant. An emphasis must be put on (1) washing hands before milk expression, (2) proper cleaning of the equipment and the containers, (3) clear labeling, (4) immediate and stable placing into the refrigerator of the freezer, and (5)consumption of the oldest stored milk first. The best choice for storage containers would be glass or hard plastic (but not polycarbonate) bottles with tight-fitting lids or special breast milk freezer bags. The containers of choice must be opaque or protected from light.

Human breast milk is by far the first and the most important food in life of every human being in any part of the world. Great effort must be put into assuring that this amazing liquid provides its best qualities to the young and vulnerable infant.

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Part IV
Micronutrients and Healthy Infant Nutritional Status

Chapter 23
Consequences of Micronutrient Deficiency and Interventions to Improve Micronutrient Status

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Key Points

- Infants are at a high risk for micronutrient deficiencies due to high demands for micronutrients to sustain growth.
- Concurrent deficiency of several micronutrients are likely, and should be considered the norm rather than the exception.
- For normal birth weight infants, breast milk provides enough micronutrients for the first 6 months of life.
- Low birth weight infants need extra micronutrients for catch-up growth.
- Complementary foods in developing countries often are low in quality, having an energy density which is too low, and providing too little micronutrients per intake.
- Improving nutrition status of pregnant women could help building stores in the fetus, thereby improving nutritional status of the newborn.
- Preconception micronutrient status could be an effective strategy to improve nutritional status of both mother and infant.

Keywords Iron • Zinc • Vitamin A • Growth • Deficiency • Complementary foods • Breast feeding • Infancy • Supplementation • Fortification

Introduction

Infants are prone to micronutrient deficiency and indeed millions of infants worldwide are deficient in at least one micronutrient [1], although most infants are deficient in several micronutrients at the same time [2]. An important reason why micronutrient deficiencies often occur concurrently is that the same causal factors to some degree underlie deficiencies of many different nutrients. Monotonous and unbalanced diets, lack of animal-based food products in the diet, and anti-nutritional or absorption-inhibiting factors in the diet will all reduce the nutritional value of a diet [3]. For instance, potent

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R.R. Watson et al. (eds.), *Nutrition in Infancy: Volume 1*, Nutrition and Health,
DOI 10.1007/978-1-62703-224-7_23,

Table 23.1 Recommended daily nutrient intakes (RDI) from the World Health Organization (2004) for adults and 7–12 months old infants and RDI expressed per body weight

	RDA adult	RDA infant	RDA adult/kg[a]	RDA infant/kg[a]
Iron (mg/day)[b]	19.6–58.8 (females) 9.1–27.4 (males)	6.2–18.6[a]	0.3–1.0 (females) 0.1–0.4 (males)	0.6–1.9
Zinc (mg/day)[b]	3.0–9.8 (females) 4.2–14.0 (males)	2.5–8.4	0.05–0.2 (females) 0.06–0.2 (males)	0.3–0.8
Magnesium (mg/day)	260 (male)	54	3.7 (male)	5.4
Vitamin A (μg RE/day)	600 (male)	400	8.6 (male)	40
Vitamin B1 (mg/day)	1.2 (male)	0.3	0.02 (male)	0.03
Vitamin B12 (μg/day)	2.4 (male)	0.7	0.03 (male)	0.07
Vitamin D (μg/day)	5 (male)	5	0.07 (male)	0.5

[a]Assuming a body weight of 60 kg for a female adult, 70 kg for a male adult and 10 kg for an infant
[b]Recommended intakes for iron and zinc depend on bioavailability from the diet, hence the range signifies recommended intakes from a high bioavailable diet and a low bioavailable diet

cation-binding substances such as phytates, which are commonly found in cereal diets, make those diets have a particularly low bioavailability for iron as well as for zinc [3, 4]. Such dietary flaws are associated with poverty, and will result in nutritional deficiencies, even when basic energy and protein needs are met, which is often not even the case. As a result, infants and children are at risk for deficiency of not just a single micronutrient but often a whole range of micronutrients to varying extents, the exact combinations determined by the general dietary pattern (e.g., rice-based or maize-based) and the gaps between intake and requirement.

However, other factors also contribute to the high risk for micronutrient deficiency in infants. First of all, infants have significantly higher requirements for nutrients to be able to sustain the high growth rate during the first year of life. Although this might not be apparent when looking at absolute requirements for micronutrients, when expressed as the daily requirement per body weight, one realizes that infants need to absorb much more micronutrients per serving of food compared to adults (Table 23.1).

As portion size is a limiting factor in infants, it follows therefore that infants need foods which have a high energy density, containing micronutrients that are highly bioavailable. The best example of such a food is of course breast milk. Indeed, as is also reflected in the recommendations of the World Health Organization (WHO), for the first 6 months, infants should preferably receive nothing else but breast milk as this is the safest and surest way of meeting all their nutritional requirements [5]. It is recognized now that breastfed infants have many health advantages over bottle fed infants, both in the short-term, allowing optimal growth and development, and in the long-term, promoting optimal immune function development and psycho-motor development and reducing risk for allergy and metabolic dysfunction (e.g., diabetes and obesity) [5]. However, concerns have been raised that suboptimal nutritional status of mothers might affect breast milk quality for some micronutrients such as vitamin A, although high concentrations of other micronutrients such as zinc are maintained in breast milk even though maternal status is low [6].

But poor maternal micronutrient status certainly contributes to micronutrient deficiency of newborns during the first year of life. A main factor affecting micronutrient status of the newborn is intra-uterine nutritional status. Infants are born with stores for many micronutrients to prepare for a period with high growth rates, tissue development, and a high metabolism. Poor micronutrient status during pregnancy will result in lower neonatal stores for example iron or vitamin A, and breast milk vitamin A content is related to maternal vitamin A status [2]. Furthermore, epigenetic programming in utero probably primes the metabolism of small for gestational age infants towards metabolic dysfunction later in life, and is also thought to determine biological growth potential to some extent [7].

And indeed, the nutritional status of the mother is not only very important during pregnancy, but even before conception. Several micronutrient deficiencies are known to have distinct effects on the development of the fetus, although many questions remain on precisely how preconceptual nutritional status affects growth and development of the fetus. The most well-known example is folic acid deficiency, which, when occurring during conception, increases the risk for cleft palate and neural tube defects. But pre-pregnancy micronutrient stores can also determine intra-uterine growth of the fetus. Birth weight for example is much more strongly correlated to anemia and iron stores of the mother in the first trimester than to those in the second or third trimester [8], and is intriguingly, also linked to preconception nutritional status [9].

After 6 months of age, infants should receive complementary foods (CF) to supplement the nutrients provided by the breast milk, although it is recommended to continue breast feeding until at least 2 years of age [10]. In this age period, breast milk is a valuable high-quality supplement to the diet, providing not only extra energy, high-quality protein and bioavailable micronutrients, but is also important for the continued transfer of protective immune factors, and the development of an optimal intestinal bacterial colonization.

The addition of complementary foods is needed to meet the increasing nutritional needs of the growing infant. Yet, in developing countries this is often the period when nutritional status deteriorates and growth falters. This is because unfortunately, CF used in many developing countries is poor in quality, lacking in essential nutrients, often with suboptimal bioavailability, resulting in a low (micro) nutrient density of the food. Furthermore, the intake capacity of infants is limited, especially when meal frequency is low, which is often the case in conditions of poverty where both time and resources for cooking are restricted. As a result, the CF part of the diet does not provide enough nutrients for the infant to meet the requirements, inevitably leading to deficiency if such feeding is sustained over a longer period. The situation is even more precarious when it is remembered that in developing countries infants are commonly born with suboptimal stores for certain nutrients (e.g. iron and vitamin A) because of suboptimal maternal nutritional status during pregnancy.

In addition to the potential nutritional inadequacy of CF, the exposure to food-borne pathogens also plays a significant role in the often detrimental effect of the weaning period on nutritional status and growth. With the introduction of CF to the infant also comes the introduction of infectious agents, especially when hygienic conditions are challenging and safe water not readily available, resulting in illness and diarrhea. Gastro-intestinal infections are especially detrimental to nutritional status in young children, as diarrhea reduces the absorption and increases losses of (micro) nutrients, while at the same time the infection and epithelial damage increases the requirements for nutrients. Moreover, appetite and intake are often reduced during illness.

Hence, infants in developing countries are facing the complex challenges presented by the need for relatively large quantities of macro- and micronutrients to be able to maintain the high growth and development of infancy, while commonly being born with suboptimal stores, being fed inadequate diets, and being challenged by numerous infectious agents, while at the same time their immune system is not yet fully developed and their intake capacity limited. All considered, achieving normal growth should actually be regarded as quite an accomplishment under these circumstances, and it is not surprising that in developing countries often 40–60 % of the children are to a more or lesser degree stunted.

Nutritional Status and Deficiencies in Infants: The Macro- and the Micronutrients

Undernutrition has many effects on the body, even more so in infants as they are growing and developing. Several important public health indicators such as growth, morbidity, and mortality are closely associated with nutritional status, either directly or interlinked with infection. These indicators measure

the outcome of undernutrition, resulting from a wide range of effects such as reduced immune-competence, catabolism, specific tissue, and metabolic dysfunction such as epithelial lesions and anemia. The body needs energy, protein, and a range of micronutrients (vitamins, minerals, and trace elements) in order to maintain normal metabolism and tissue function and thereby health and growth. Deficiencies are most often due to inadequate intake, although lack of stores and increased losses also play a role, especially in infants. Diets that are inadequate often lead to more than one micronutrient deficiency, and often also do not supply sufficient macronutrients, therefore deficiencies can be expected to occur in combination. Interventions that target only one deficiency are therefore unlikely to satisfactorily address the nutritional challenges, and unlikely to consistently improve health and growth in the long term. This is aptly illustrated in a general way by micronutrient interventions. These often have disappointingly small effects on growth, and the effects are often not sustained, simply because macronutrient restrictions and other micronutrients that are limiting are not being addressed.

Historically, protein and energy nutrition have always received most attention, but nowadays, partly because of better measuring techniques, the focus has shifted more to micronutrients. In fact so much so that in public health nutrition today the macronutrients tend to be rather overlooked. Therefore, in resource-poor settings it is recommended to scrutinize the quantity and quality of the energy and protein components of the dietary intake of infants as a first step, as optimal health and sustained growth and development are fundamentally unattainable if the diet does not meet the requirements for these principal nutrients. Micronutrient deficiencies usually have more specific, and therefore more visible effects, but these often appear only after a longer period of inadequate intake, or if requirements are suddenly increased, for example, by infection. Dietary intake data usually points towards a certain pattern of likely micronutrient deficiencies, and should sometimes be used to guide policy as measuring (marginal) deficiency states in infants may be difficult, as will be discussed below. A general tool which can help identify gaps in dietary intake is linear programming, for which several programs are now available [11].

Nutritional Status and Deficiencies in Infants: Type I and Type Il Nutrients

As micronutrients play many different roles in the metabolic pathways of the human body, the consequences of deficiency are also diverse. However, general patterns can be identified when using the concept of Type I/Type II nutrients as developed by Golden [12]. Type I nutrients can be considered as the "classic" nutrients, which have a specific biochemical function in the body. If a type I nutrient becomes deficient, specific symptoms develop. Examples include vitamin A deficiency leading to xerophthalmia and iron deficiency leading to iron-deficiency anemia (IDA). In contrast, type II nutrients are the "growth" nutrients, in that deficiency of these nutrients will foremost lead to growth faltering, as these nutrients are essential for all tissues. The body's reaction to deficiency of any of these nutrients is to slow or stop growth, and eventually switch to catabolism, breaking down tissue to recycle the lacking elements in order to safeguard basic essential metabolic processes. A mild deficiency of any type II nutrient will lead to stunting, whereas a more severe deficiency will lead to cachexia and wasting [12]. As can be appreciated from this concept, any deficiency of a type II nutrient will lead to growth retardation.

Reversing the effects of deficiency is also different between type I and type II nutrients. For type I nutrients, providing sufficient amounts of the nutrient which was deficient will automatically restore the biochemical function. So, in IDA, providing iron will result in an increase in hemoglobin concentrations and resolve the anemia. In contrast, to counter the growth impairment after a type II nutrient deficiency, one needs to provide all the type II nutrients to enable catch-up growth. So, requirements for magnesium and phosphorus for a zinc deficient child receiving zinc treatment are higher than for a normal child of the same age. Therefore, providing single micronutrient interventions might be

Table 23.2 Examples of micronutrient deficiencies and their consequences

Micronutrient	Type	Consequences
Iron	1	Iron deficiency anemia, cognitive impairment
Vitamin A	1	Xerophthalmia, nightblindness, immune function impairment
Vitamin B1 (Thiamin)	1	Beri-beri
Vitamin C	1	Scurvy
Zinc	2	Growth retardation, stunting, cognitive impairment
Magnesium	2	Growth retardation, stunting
Phosphorus	2	Growth retardation, stunting

effective for type I nutrients, providing that only one micronutrient is lacking, but will not be effective for type II nutrients. (Table 23.2)

It is beyond the scope of this chapter to outline in detail the consequences of deficiency of each micronutrient. Some micronutrients such as iodine (Chap. 15), vitamin D (Chap. 17), and vitamin A (Chap. 64) have been addressed in other chapters, and specific textbooks are also available [13]. However, as an example, iron will be discussed in more detail. There is a long history of scientific interest in iron deficiency in infants, generating a large body of evidence yet many issues remain unresolved. Therefore, iron makes an excellent case to illustrate micronutrient nutrition in infants.

Consequences of Micronutrient Deficiencies: Iron in Infants

Apart from causing anemia, it is now well established that iron deficiency has adverse effects on psycho-motor development of infants and children [14]. Although the extent of the effects of iron deficiency without anemia on cognitive development in humans is not well documented, animal models strongly suggest adverse effects even before the occurrence of anemia. Moreover, these adverse effects appear to be irreversible especially in the period before weaning. Hence, iron deficiency in infants and children <2 year of age might cause irreversible damage to cognitive development [14]. Infants are normally born with iron stores which will last for several months after birth. Exceptions are pre-term and low birth weight infants. In developing countries, low birth weight is very prevalent, affecting >50 % of the newborns in some parts of Asia and sub-Saharan Africa. Low birth weight is strongly associated with maternal undernutrition during pregnancy, as well as with growth impairment, morbidity, and mortality in the infants. In utero, iron is transported over the placenta through a process which is not well-understood yet, and which reaches a maximum rate of transfer during the last 2 months of gestation [15]. As this process is up-regulated in iron-deficient conditions, iron stores of infants born from iron-deficient mothers appear to be similar to those born from iron-replete mothers. Long-term follow-up suggests however that infants born from iron-deplete mothers have a higher risk of becoming iron deficient later in infancy [15]. After birth, two important factors affecting iron status are rapid growth and gender, with infants experiencing fast growth, such as the catch-up growth necessary in low birth weight infants and male infants being more at risk for iron deficiency [16]. As breast milk contains only low concentrations of iron, breastfed infants are at risk of becoming iron deficient after 6 months of life, even though the iron in breast milk is highly bioavailable. Unfortunately, high-quality complementary foods, containing sufficient amounts of bioavailable iron are either not available or not affordable in many developing countries. As a result, iron deficiency and IDA is highly prevalent in developing countries in infants 1 year of age [17]. Therefore, blanket supplementation with iron for infants has been considered. However, iron supplementation can have adverse effects, especially in malaria-endemic areas [18], and could in principle impair absorption of zinc, thereby compromising zinc status [17, 19]. Moreover, iron supplementation can strongly modulate the

immune balance of infants, driving the immune response towards a more Th1-biased response [20], and change the bacterial colonization of the intestinal tract. It is unclear at the moment what health effects these changes bring. Although iron fortification has been considered more safe, with less direct effects on morbidity prevalence and immune function indicators, a recent study showed that iron-fortified biscuits for school children also caused changes in bacterial gut flora [21]. Therefore, the current challenge is to find interventions to improve iron status of infants, thereby improving cognitive development and intellectual potential, without the risk for adversely affecting health, either directly or in the long term.

Interventions to Improve Micronutrient Status

As described above, infants are at high risk for developing micronutrient deficiency. And often, infants are deficient for several micronutrients simultaneously. Therefore, interventions to improve micronutrient status are likely to be more effective when addressing more than one micronutrient, and preferably the whole range of nutrients which are likely to be restricted, given the general dietary pattern and constraints. Surprisingly, most interventions to improve micronutrient status which are currently in place in many countries focus on one or two micronutrients only. Well-known examples include iron and folic acid supplementation for pregnant women, and half-yearly high dose vitamin A supplementation for children between 6 month and 5 year of age.

In general, strategies to prevent micronutrient deficiency in infancy can be grouped into three categories: (a) interventions before birth as a means to improve micronutrient stores after birth and possibly improve pregnancy outcomes such as birth weight, (b) interventions to treat an existing micronutrient deficiency and (c) interventions to prevent micronutrient deficiency. Below, examples of each will be discussed.

Interventions Before Birth to Improve Micronutrient Status of the Newborn

For many micronutrients, infants are born with stores which have been accumulated in utero, especially in the third trimester of pregnancy. The size of the stores is related to body weight and pregnancy duration. Therefore, pre-term and low birth weight newborns have less stores, for example, iron than normal newborns [22]. In addition, especially pre-term infants experience catch-up growth during the first months, making these infants even more vulnerable for micronutrient deficiency. Before entering pregnancy, women need an iron reserve of at least 300–500 mg to avoid becoming iron deficient after the first trimester [23, 24]. Most women in developing countries, and indeed, many women in developed countries, do not have such iron stores, and are at a high risk of becoming iron deficient during pregnancy. Indeed, anemia and iron deficiency are highly prevalent during pregnancy, and supplementation with iron and folic acid, often as a blanket program in which pregnant women are to receive 90 pills of iron and folic acid to cover the last months of pregnancy, are part of standard antenatal care programs. But there is uncertainty on whether providing iron and folic acid during pregnancy is beneficial for the newborn. Although iron supplementation trials have been demonstrated to be efficacious in vulnerable population groups, large-scale programs with iron supplementation are in general ineffective [25]. Moreover, recent studies in areas with endemic malaria have raised concern about the safety of iron supplementation [18]. A reason for the lack of effectiveness of large-scale programs could be that women are reached too late in pregnancy. Indeed, from a large study in China, it appears that iron supplementation during pregnancy is only beneficial during the first 12 weeks of pregnancy [26]. In contrast, Dibley and colleagues used National Health and Demographic survey data to show that infants born from mothers receiving iron and folic acid supplementation during

pregnancy in general had much lower rates of neonatal death than infants born from mothers not receiving iron and folic acid (RR: 0.53; 95 % CI: 0.36–0.77) [27], but other outcomes such as birth weight were not so much affected. And this beneficial effect of iron and folic acid supplementation in pregnant women was also present in countries with endemic malaria, provided that it is combined with intermittent malaria treatment [28]. Hence, currently there is uncertainty about the benefits of iron and folic acid supplementation during pregnancy to improve neonatal health.

One would expect that providing multiple micronutrients during pregnancy instead of only iron and folic acid would have more beneficial effects. Several large studies were conducted in recent years on the efficacy of multiple micronutrient supplementation during pregnancy. However, results have been confusing, partly because studies used different combinations of micronutrients, different amounts of micronutrients or looked at different outcomes. A Cochrane review (2006) concluded that the effect of multiple micronutrient supplementation was not different from iron and folic acid supplementation alone, with no effects on pre-term births or peri-natal mortality [29]. A more recent meta-analysis however concluded that prenatal multi-micronutrient supplementation was associated with a significantly reduced risk of low birth weight and improved birth weight when compared with iron–folic acid supplementation [30]. Moreover, some studies suggest that different combinations of micronutrients have different effects on the birth weight distribution curve, with some combinations (iron and folic acid) especially affecting the lower end of the distribution curve, whereas other combinations (multiple micronutrients) appear to shift the whole distribution curve [31], raising concerns for increased prevalence of obstructed labor after multiple micronutrient supplementation during pregnancy.

Besides providing micronutrients before or during pregnancy, another intervention, which is much simpler and which hardly requires any logistics is available. During birth, the umbilical cord is often directly clamped, preventing the continuation of blood flowing towards the newborn. By delaying this clamping of the umbilical cord by only 2 min, the placental blood flowing to the newborn delivers a bonus gift of many valuable nutrients including much needed iron in the form of hemoglobin. This simple and elegant strategy can reduce the need for example blood transfusions for anemia in preterm infants by 50 % [32]. Indeed, a 2-min delay in clamping the umbilical cord leads to significant higher iron stores at 6 month of age [33], and costs nothing more than a change of practice. Therefore, the World Health Organization strongly recommends delayed cord clamping, but regrettably this intervention is not yet practiced in many countries.

Interventions to Treat An Existing Deficiency

Interventions to treat an existing micronutrient deficiency in infants focus mainly on restoring the deficit. Most often, the diagnosis of deficiency is made clinically, for example by looking at the paleness of the skin or mucosa for anemia or by a history of stunting and chronic diarrhea for zinc deficiency. Such basic clinical assessment is often the only method available in resource-poor settings, but unfortunately has a low sensitivity and specificity. For type I nutrients, specific biochemical tests with a high sensitivity are available which give a good indication of body stores. For example, serum ferritin and soluble transferrin receptor concentrations give an accurate indication of body iron stores [34]. The changing metabolism and developing physiology of infants does make interpretation of biochemical indicators less straightforward however, and for many indicators there is some discussion about the thresholds to define deficiency in infancy. WHO cutoff values to define micronutrient deficiency are regularly refined to reflect this ongoing discussion. In contrast, for type II nutrients, we lack accurate indicators. So although serum zinc concentrations may indicate the prevalence of zinc deficiency on a population level [35], it tells us little about the zinc status of an individual.

In general, supplementation strategies are very effective in restoring Type I nutrient stores. So, daily iron supplements for a month can restore iron stores in an iron-deficient infant, and a single high

dose vitamin A supplement given to an infant with Bitot's spots rapidly reverses this serious condition which could have led to blindness.

Effects of supplementation with type II nutrients are much harder to measure. For example, zinc supplementation in individuals who are stunted and therefore likely to be zinc deficient, may [36] or may not [37] improve growth. As discussed above, availability of all Type II nutrients is required to allow catch-up growth to take place. Other, more specific outcomes however might respond to single type II nutrient supplementation. For example, supplementation with zinc after an episode with diarrhea has been shown to improve recovery, implying enhanced recuperation of the intestinal mucosa. However, as was shown by a large multi-country trial in SE Asia, zinc supplementation could not prevent progressive growth faltering in infancy. This so-called SEAMTIZI trial had study sites in Vietnam, Thailand, and Indonesia (two sites). Infants from around 5 months of age received iron (10 mg/day), zinc (10 mg/day) or both. Although the intervention improved iron and zinc status [17], at the end of the study, overall stunting prevalence was above 20 %, with a beneficial effect of zinc supplementation on growth only in infants who were anemic at baseline [37].

Interventions to Prevent Micronutrient Deficiency

Instead of trying to restore health only after deficiency has caused symptoms and thereby damage, such as growth faltering, illness, anemia, blindness, etc., it is of course much more sensible from a public health point of view, but also from a cost effectiveness view, to prevent these deficiencies from arising in the first place. However, adherence and motivation of subjects, providers and policy makers alike is harder to procure and sustain in the absence of concrete symptoms and damage. Likewise, effectiveness of such preventative interventions is also harder to measure and is often less spectacular than for instance healing (near) blindness is. Another consideration is that such interventions will almost always be less targeted, as there are no signs or symptoms, and therefore need to be safe for a wide range of subjects, and benefit as many of a population as possible. Targeting may not always be possible, but such interventions should certainly be tailored to the specific circumstances of the population, and regularly adjusted to accommodate for instance improvement in national socio-economic conditions.

Preventing micronutrient malnutrition in infants and young children requires an integrated approach that needs to integrate complementary actions to improve maternal, infant, and young child nutrition [38]. As the life cycle stages of preconception and pregnancy have been discussed above, below we will focus mainly on the period for complementary feeding (6–24 months). During the first 6 month of life, exclusive breast feeding is the most important intervention to prevent micronutrient deficiency, a topic extensively covered in Section B of this book. An estimated 13 % of infant deaths could be prevented by improved breastfeeding practices alone [39]! And an additional 6 % through improved complementary feeding practices [40]. Therefore, developing low-cost, high-quality (high nutrient dense) complementary foods should be a key target. Indeed, this was the aim of the FASEVIE project in Vietnam, a collaboration between the National Institute of Nutrition of Vietnam, the Institute for Research for Development (IRD, France) and "Groupe de Recherches et d'Echanges Technologiques" (GRET, France). Two products were developed: a ready-to-use micronutrient-fortified instant flour and a food complement containing amylases and micronutrients which could be added as a powder to the traditionally prepared rice gruels. The project showed that the provision of these products not only improved micronutrient status [41], but also prevented growth faltering during the intervention, even though growth faltering started again after the intervention [42]. Unfortunately, scaling-up of these low-cost, high-quality CF has not been very successful in Vietnam so far, and reasons for this should be investigated.

Conclusions

Micronutrient deficiency in infancy is a serious, highly prevalent public health problem. As a single micronutrient deficiency is less common than deficiencies of multiple micronutrients simultaneously, mono-micronutrient intervention are likely to have less impact on improving micronutrient status and health than integrated approached, targeting several micronutrients at the same time. Interventions to improve micronutrient status of infants should not focus only on the infant, but regard to the whole life cycle approach in which improving micronutrient status of women of reproductive age and pregnant women will benefit the newborn also. The expected benefits of improved micronutrient status of infants are many, including reduced morbidity and mortality, better anthropometrical status, and better cognitive development. Hence, it will provide the infant the much needed nutrients, enabling the development of the individual's full potential.

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Chapter 24
Maternal Nutritional Supplements: Effects on Infants

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Key Points

- Multivitamin–mineral supplements during pregnancy are likely to improve infant outcomes in developing countries, but there is no evidence supporting their routine use in developed countries.
- Iron supplements before and during pregnancy are likely to benefit infant outcomes, particularly in countries with high level of deficiency.
- Folic acid supplements during early pregnancy reduce risk of neonatal deaths and congenital malformations due to neural tube defects.
- Vitamin D supplements during pregnancy are likely to be beneficial to infant health where the mother is at high risk of vitamin D deficiency.
- Calcium supplements in pregnancy may reduce the risk of pre-eclampsia in the mother, and may have beneficial effects in relation to the developmental origins of hypertension.
- No evidence of benefit of vitamins E, C, A, or zinc supplements during pregnancy.
- Balanced protein-energy supplements may be beneficial to infant outcomes in areas with high prevalence of maternal under-nutrition.

Keywords Supplements • Micronutrients • Pregnancy • Infant • Birth outcome

Introduction

Poor maternal nutrition can have serious adverse effects on fetal and infant growth and development. Nutritional supplements during pregnancy are increasingly being promoted by national and international bodies to improve the nutritional status of pregnant women. However, they are not subject to the same rigorous safety and efficacy standards as prescription medications [1]. Although they may be associated with adverse events, there is little research into the associated hazards and risks [2]. They are considered relatively cheap, feasible, and having the potential to improve maternal nutrition when administered through national antenatal programs. However, the evidence regarding their benefit in relation to infant health is conflicting, and in many cases inadequate. This chapter will review the evidence examining the relationship between dietary supplements and infant outcomes, focusing in particular on multivitamin–mineral supplements and iron. More detailed reviews about other micronutrients such as vitamin D and iodine are included in other chapters of this book.

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R.R. Watson et al. (eds.), *Nutrition in Infancy: Volume 1*, Nutrition and Health,
DOI 10.1007/978-1-62703-224-7_24,

Multivitamins and Minerals

Multivitamins and minerals (MVM) supplements have been routinely recommended for pregnant women and those who might become pregnant in some developed countries such as the United States [3]. They are not routinely recommended during pregnancy by the World Health Organization (WHO), or in other developed countries such as the UK. These preparations are readily available over-the-counter, and heavily advertised and promoted to expectant mothers especially in Western countries. Multiple micronutrient deficiency is common among pregnant women in low-income countries [4]. However, pregnant women in developed countries are expected to have better baseline nutrient status compared to pregnant women in developing countries, and nutritional deficiencies are more likely to be restricted to specific micronutrients such as iron.

The benefit of MVM supplements in relation to infant health outcomes is supported by findings of randomized controlled trials (RCT) in developing country settings. Studies in Nepal, India, Indonesia, Guinea-Bissau, and Tanzania have shown positive effects on adverse birth outcomes such as infant mortality and low birth weight (LBW) [5–9]. However, other trials in Nepal, Mexico, and Zimbabwe have failed to demonstrate a significant effect on the incidence of LBW [10–13], and some have even demonstrated an increased risk of adverse outcomes [13, 14]. However, in relation to the incidence of neural tube defects (NTD), a direct comparison of folate vs. multivitamin supplementation indicated a significant reduction in the folate group suggesting that folate supplementation may be more useful that MVM considering this outcome [15].

According to a Cochrane systematic review, there was a favorable effect of MVM supplementation on the incidence of LBW and small for gestational age (SGA) compared to none or placebo supplementation. However, there was insufficient evidence to suggest replacement of iron and folate supplementation with multiple micronutrient supplements. The review, which included nine trials and around 15,000 women, recommended further research to quantify the degree of maternal or fetal benefit and to assess the risk of excess supplementation and the potential for adverse interactions between the micronutrients [16]. All the trials included in this review were conducted in low-income countries.

An updated review by the same authors published recently, including data from 17 studies all conducted in developing countries, showed a significant reduction of 9% in the risk of SGA compared to iron-folate supplementation (Fig. 24.1) [17]. Also, a recent meta-analysis by Shah et al. of 13 RCTs on the effect of MVM supplements on infant outcomes showed a significant reduction in the risk of LBW in women who received these supplements during pregnancy compared to placebo (RR = 0.8, 95% CI 0.7, 0.9). Mean birth weight was also higher as compared to women who took combined iron and folic acid supplementation [18]. There were no differences in the risk of preterm birth or SGA. One third of the women included were in the first trimester, half were in the second trimester and the rest in the third trimester during the trials. All, but one, of the included trials were conducted in a developing country. This review included a trial of HIV positive women, which the Cochrane review did not include.

There is scarce evidence examining the effect of MVM during pregnancy in developed countries. An RCT in France showed significant positive effects for micronutrient supplementation vs. placebo on the incidence of LBW [19]. However, this study had a relatively small sample size of 100. The supplements given in this study were iron-free, and thus differ from most of the currently available over-the-counter MVM preparations for pregnant women. The Camden study on the impact of multivitamin supplementation on pregnancy was conducted in a disadvantaged urban setting in the USA [20]. Risks of both LBW and preterm delivery were significantly reduced with supplement use in the first and second trimester. Analysis was restricted to data obtained by 28 weeks of pregnancy and did not report on the relationship between infant outcomes and supplement use in late pregnancy.

In a prospective cohort study in Leeds, United Kingdom, taking daily MVM supplements during any stage in pregnancy was not associated with birth weight, SGA, or large for gestational age at any

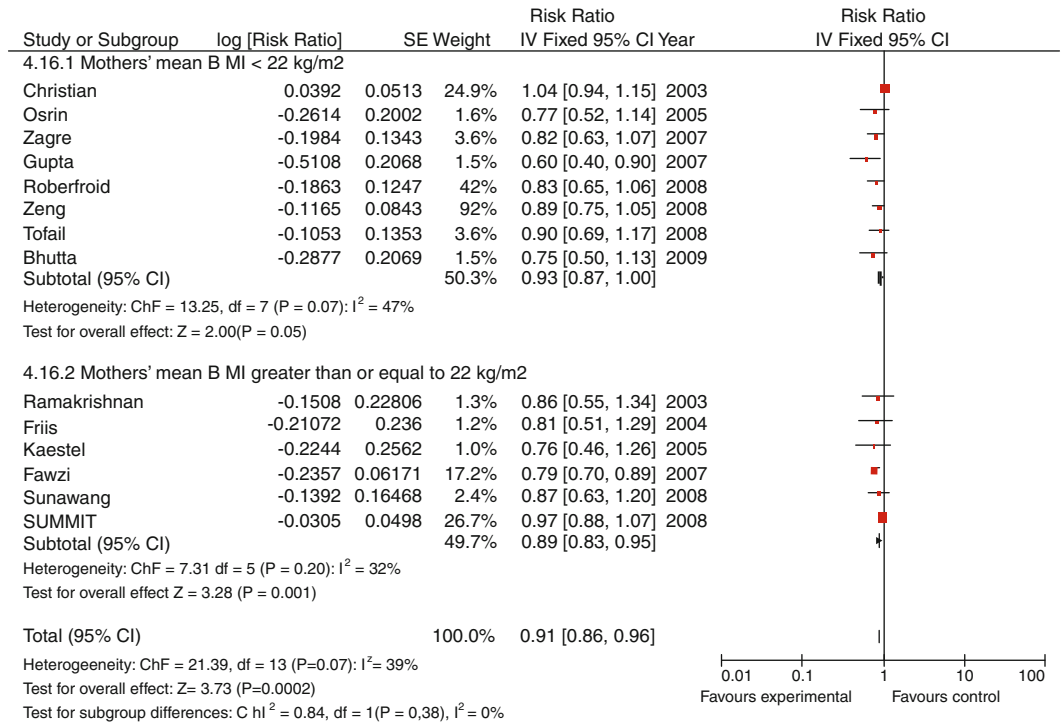

Fig. 24.1 Meta-analysis results of the effect of multiple micronutrients during pregnancy vs. iron-folate on SGA babies with subgroup analysis according to maternal mean body mass index (fixed model) (From [17])

stage in pregnancy [21]. However, taking MVM supplements in the third trimester was associated in this study with an increased risk of preterm birth, with this effect being more pronounced in primiparous women [21]. This study is observational so causality cannot be inferred from the findings. Women in this cohort were having adequate amounts of most micronutrients from their diet alone as assessed by the 24 h dietary recall, confirming the inverse supplement hypothesis, that women who least need supplements are most likely to take them [22]. Health value and susceptibility to illness are major predictors of supplement use by women, with dietary supplements acting as an insurance against possible ill health [23].

Interactions between micronutrients in the same supplement or in different supplements may provide an explanation to the inconsistent findings of population studies. Significant interaction may decrease the bioavailability of micronutrients and their transfer across the placenta. For example, copper overload induces iron overload, by interfering with the iron regulatory mechanism, and iron interacts with zinc affecting absorption [24, 25] [26]. A reduction in availability of micronutrients to the fetus, by interactions between the nutrients at maternal gut, liver, or in the placenta itself, may result in adverse outcomes for the baby, or ineffective interventions at best [21]. There is very limited evidence regarding the ideal doses of the micronutrients in the supplements that would prevent such undesirable effects. Preparations used in different studies are heterogeneous in type, ingredients, and dosage. Another possible explanation for the conflicting evidence results is the heterogeneity in the period of administration of MVM during pregnancy, as need and utilization of MVM may be substantially different in late compared to early pregnancy.

Clinicians and midwives in countries, where gross multiple micronutrient deficiencies are not common, should be cautious when recommending over-the-counter MVM supplements to nutrient-replete women. As in any clinical situation, they should weigh the potential risks and benefits when considering

prescribing such supplements. It may be better for the type of supplement recommended/prescribed to be more focused on the specific vitamin/mineral deficiency the woman has. However, this raises the issue whether screening for micronutrient deficiencies during pregnancy is a feasible and cost-effective option and there is little evidence examining this question.

Rigorous research is still needed to assess if routine MVM supplementation during pregnancy is required. There is no solid evidence that MVM supplementations have additional benefits over iron and folate alone in relation to the risk of infant mortality, though there is evidence of reducing the risk of LBW/SGA. There is no solid evidence to support the routine use of MVM supplements in developed country settings to improve infant outcomes. The WHO recommends further studies evaluating the effect of different combinations and dosages of the different micronutrients in the supplements [4].

Iron

Iron is used to synthesize hemoglobin during fetal life, and is essential in brain development. Iron deficiency (ID) is the leading single nutrient deficiency in the world [27]. In developing countries, 50% of pregnant women are anemic mostly due to ID. It is the only nutrient deficiency which is also significantly prevalent in industrialized countries [28]. The prevalence of ID in developed countries has been estimated to range between 25 and 40% of pregnant women [29–32], with an even higher prevalence in lower socioeconomic groups [33]. Iron deficiency anemia (IDA) is associated with an increased risk of LBW, preterm delivery, and perinatal IDA [34–41]. Perinatal ID can permanently impair intelligence, motor and behavioral development as well as increase risk of future IDA [39]. There is evidence from experimental studies that ID during pregnancy adversely affects the offspring's blood pressure, obesity levels, and other cardiovascular outcomes in the long term [42–46].

It has been suggested that the physiological iron requirement during the second half of pregnancy cannot be met through diet alone [47, 48]. Iron supplements are widely recommended and used during pregnancy worldwide [49, 50]. The WHO recommends weekly folic acid and iron (60 mg) supplementations to women of reproductive age in areas were the prevalence of anemia in this group is >20% (or >40% in pregnant women) [51]. WHO guidelines for pregnant women recommend a standard daily dose of 60 mg of iron for 6 months or 120 mg iron daily if taken for less than 6 months during pregnancy, as well as for the first 3 months postpartum [52]. In the USA, routine low-dose iron supplementation (30 mg/day) is recommended for all pregnant women [53]. European Union guidelines also recommend iron supplements in the second half of pregnancy [54].

However, the evidence that ID during pregnancy may be detrimental to infant health does not necessarily mean that administration of iron supplements during pregnancy is an effective way of dealing with this problem. Most RCTs of iron supplementation in pregnancy have shown positive effects on maternal iron status. One randomized controlled trial showed that a supplement of 40 mg/day from 18 weeks gestation onwards prevented ID in 90% of women during pregnancy and postpartum [55], but the evidence is inconsistent around the effects of iron supplementation on infant outcomes. A Cochrane review concluded that a mother is less likely to have IDA if taking iron supplements. However, with regard to infant outcomes, there were no significant differences in the incidence of perinatal mortality, preterm birth, SGA, or LBW between the supplemented and the unsupplemented groups. Higher infant ferritin concentrations at 3 and 6 months and birth length were found in the supplemented group [56]. The review recommends further trials to assess the effect of routine iron supplementation during pregnancy on clinically important infant outcomes.

A placebo-controlled RCT in Hong-Kong published after the Cochrane review showed favorable effects of taking iron supplements in the second trimester on birth weight and incidence of SGA [57]. We have shown a positive association between iron intake, from food and supplements, during the first trimester of pregnancy and birth weight in a cohort of around 1,300 British women [58]. However,

RCT evidence from Iran showed that iron supplementation in women with Hb>13.2 g/dL in the second trimester is positively linked to gestational hypertension, as well as an increase in the risk of SGA birth [59].

High-dose supplements (>100 mg/day) are associated with side effects such as nausea, vomiting, and constipation [60]. The United States' Institute of Medicine (IOM) has established an upper tolerable dose of 45 mg/day to minimize the risk of side effects [61]. There are potential drawbacks of taking routine iron supplements during pregnancy that need to be weighed against the benefits. In addition to gastrointestinal side effects, iron can inhibit the absorption of other minerals such as manganese and zinc [62–64]. Iron supplements can also reduce the absorption of dietary non-haem iron [65], and can potentially increase oxidative stress and the production of free radicals [66, 67]. It has also been shown that iron transfer to the fetus is better in non-iron-supplemented than in supplemented women [68].

Iron in supplements is found in two forms: ferrous and ferric. Ferrous iron supplements such as ferrous fumarate, ferrous sulfate, and ferrous gluconate are better absorbed than ferric iron [69]. The amount of iron available for absorption varies according to the supplement with ferrous fumarate having the highest amount of elemental iron available. As the dose of iron in the supplement increases, the amount of iron absorbed decreases so that if iron supplements are recommended they should be taken in two or three equally spaced doses.

Despite the inconclusive evidence on the benefit of routine iron supplementation during pregnancy, it is widely recommended on a national and international level. The assumption underlying this recommendation is that supplementation, even if not beneficial, would be harmless to mother and baby. However, Studying animal models suggest that glucose tolerance is reduced by iron supplementation [70]. Links have been made between iron intake and the risk of type II diabetes and gestational diabetes [71–73]. This link is mainly found for haem iron from meat sources, and therefore the relationship could be between meat consumption and diabetes risk rather than iron per se. Also this link was not supported by an RCT which found no link between iron supplements in the second trimester and GDM [57]. In other studies, multiple biomarkers of iron status were also elevated in pre-eclamptic compared to healthy pregnant women [74].

Although some studies suggest a link between maternal serum ferritin concentration during the second trimester and the risk of preterm birth [75, 76], it is important to note that serum ferritin is not a specific marker for iron status as it is an acute inflammatory marker and therefore the observed relationship may be due to inflammatory pathophysiological changes that are associated the risk of adverse pregnancy outcome. About 10–15% of Northern European population is heterozygous for the common mutations in the *HFE* gene that predisposes to iron overload [77]. Blanket routine supplementation may be harmful in women with this genetic predisposition [78].

Taking account of the above, some caution the administration of iron supplements to iron-replete women, especially those at risk of pregnancy complications such as pre-eclampsia and GDM [79]. It seems that any positive effects of iron supplementation on infant outcomes such as birth weight are enhanced the earlier iron supplements are taken in pregnancy [80]. In the UK, the National Institute for Clinical Excellence (NICE) does not recommend routine iron supplementation during pregnancy. Rather it recommends that hemoglobin levels less than 11 g/100 mL in the first trimester and 10.5 g/100 mL at 28 weeks are investigated and iron supplementation considered if indicated [81]. However, the problem arises when women who are not necessarily anemic have depleted iron stores which may still be detrimental to infant health. Individually tailored use of iron supplements according to blood indices for iron status such as serum ferritin can avoid any potential harms of mass supplementation [82]. It has been suggested that pregnant women with ferritin >70 mcg/L have no need for iron supplements [83]. However, there is a need for research into the effectiveness, cost-effectiveness, and feasibility of such selective supplementation policies in developed countries. Routine iron supplementation to all pregnant women seems to be the most effective option due to high levels of deficiency in developing countries.

Folic Acid

Daily folic acid supplementation from before conception to 6–12 weeks pregnancy has been judged to be effective in reducing the risk of NTD including anencephaly, spina bifida, and encephalocele [84]. In low-income countries an estimated 29% of neonatal deaths related to visible congenital abnormalities are attributed to NTD [85]. Meta-analysis of three RCTs of folic acid supplementation for women with a previous pregnancy with NTD indicates a 70% (95% CI: 35–86) reduction in recurrence (secondary prevention). For NTD primary prevention through folic acid supplementation, combining one RCT with three cohort studies suggested a reduction of 62% (95% CI: 49–71). A meta-analysis of eight population-based observational studies examining folic acid food fortification gave an estimated reduction in NTD incidence of 46% (95% CI: 37–54) [85].

A Cochrane systematic review of four RCTs including around 6,500 women also found a reduction of 72% in NTD with periconceptional folic acid supplementations (RR 0.28, 95% CI 0.13, 0.58) [15]. The reduction in risk included both women with a previously affected child and those without. There was no increase in risk of spontaneous abortion or ectopic pregnancy in the supplemented group [15]. Although some of the trials included in the review showed an increase in the risk of multiple pregnancies, the results were not statistically significant. A Chinese cohort of around 242,000 women found no association between folic acid supplementation and multiple pregnancy [86].

The neural tube closes, at about 21–27 days after conception [87]. Therefore supplements must be started before conception on in the first month of pregnancy, but many women do not realize they are pregnant by this stage. Weekly folic acid supplementation of 2.8 mg/day is recommended by the WHO to women of reproductive age in populations with anemia prevalence of >20% and with no folic acid food fortification programs and to all pregnant women [51, 88]. However, the evidence for the weekly dose is limited and is based on the weekly equivalent of the daily dose of 400 μg. WHO also recommends a daily dose of 400 μg throughout pregnancy and the first 3 months postpartum [49]. Fig. 24.2 shows the uptake levels of folic acid for women of childbearing age in the USA. In this 2007 survey, 40% reported taking daily folic acid supplements, 81% reported awareness of folic acid and 12% reported knowing that folic acid should be taken before pregnancy [89].

In the UK, women are recommended to take folic acid supplements at a dose of 400μg/day from before conception to 12 weeks of gestation [81]. It is possible to achieve this level of intake through taking supplements or fortified foods. However, achieving this intake through unfortified diet alone is difficult. Folic acid fortification could prevent 13% of neonatal deaths currently attributed to congenital abnormalities in low-income countries [85]. One study showed a reduction in the incidence of NTD since the folate food fortification program took effect in the USA in 1998 [90]. Folic acid supplementation has been recognized as one of the most effective existing interventions to improve neonatal survival on a global level [91].

Vitamins C and E

A systematic review which included and RCTs, involving 766 women showed no difference between women supplemented with vitamin C alone or combined with other supplements compared with placebo in birth weight, the risk of stillbirth, neonatal, or perinatal death, or intrauterine growth restriction. However, those who took vitamin C supplements alone or combined with other supplements were at increased risk of giving birth preterm (RR 1.38, 95% CI 1.04–1.82) [92]. Another Cochrane review on vitamin E supplementation in pregnancy stated that the data are too few to say if vitamin E supplementation either alone or in combination with other supplements is beneficial during pregnancy [93].

Other studies have suggested potential adverse effects of supplements containing antioxidant vitamins such as vitamins C and E, on pregnancy outcome when taken in women with adequate

Fig. 24.2 Percentage of women Aged 18–45 years who reported taking a supplement containing folic acid daily,* by survey year and selected sociodemographic characteristics—United States, 2003–2007†

Characteristic	2003 (N = 2,006) (%)	2004 (N = 2,012) (%)	2005 (N = 2,647) (%)	2007 (N = 2,003) (%)
Race				
White	34	43	36	40
Nonwhite	28	31	23	36
Ethnicity				
Hispanic	29	38	27	38
Non-Hispanic	33	40	34	40
Age group (yrs)				
18–24	25	31	24	30
25–34	34	39	36	47
35–45	35	46	37	40
Education				
Less than high school	21	19	20	29
High school	28	32	31	36
College (any)	37	48	35	48
Annual household income				
<$25,000	24	30	27	32
$25,000–$39,999	31	40	28	39
$40,000–$49,999	39	48	37	43
≥$50,000	38	46	38	43
Pregnancy status				
Pregnant	82	81	90	93
Not pregnant	30	37	31	37
Total	**32**	**40**	**33**	**40**

SOURCE: Gallup Organization.

* Based on response to an open-ended question, "What type of vitamin or mineral supplements do you take on a daily basis?"

† Statistical estimates were weighted to reflect the total population of women aged 18–45 years in the contiguous United States who resided in households with telephones. For total results based on this sample of women, the error attributable to sampling was plus or minus 2 or 3 percentage points (with 95% confidence). The 2006 survey included only women aged 18–35 years and therefore was excluded.

dietary micronutrient intake. Smedts et al., in a case control study of offspring with congenital heart disease (CHD), found that periconceptional use of vitamin E supplements with high dietary intake of the same vitamin was associated with up to ninefold increase in the risk of CHD [94]. Another study found that use of vitamins C and E supplements was associated with an increased risk of premature rupture of membranes [95]. In an RCT to assess the effect of vitamins E and C supplementation during pregnancy on the incidence of pre-eclampsia, Poston et al. found that more LBW babies were born to women who took these antioxidants than to controls [96]. A recent meta-analysis of seven studies concluded that combined vitamin C and E supplementation had no potential benefit in improvement of maternal and neonatal outcome and increased the risk of gestational hypertension in women at risk of pre-eclampsia [97].

Vitamin D

A Cochrane review into vitamin D supplementation in pregnancy concluded that there is not enough evidence to evaluate the effects of vitamin D supplementation during pregnancy [98]. Another Cochrane review into the prevention of rickets in term-born infants recommends vitamin D supplements

to groups of high-risk children, like infants and toddlers; living in Africa, Asia, or the Middle East or migrated children from these regions into areas where rickets is not frequent [99]. A more recent systematic review of 17 studies conducted between 1976 and 2004 concluded that there is no evidence that routine vitamin D supplementation of healthy pregnant women improves infant outcomes. However, it does improve vitamin D status and growth in the first year in South Asian babies [100]. There is a need for more evidence examining the effect of vitamin D supplementation in pregnancy and infant/child bone mass and skeletal health.

Findings from a UK prospective birth cohort suggest no association between maternal vitamin D status in late pregnancy and body size in infancy and childhood, child's intelligence, psychological, or cardiovascular health. This study found an increase in the risk of eczema at 9 months in women with high vitamin D concentration in pregnancy [101].

The national recommendation in England is for routine vitamin D supplementation for pregnant women in "high-risk" groups with a dose of 10 μg/day [102]. These include women of South Asian, African, Caribbean, or Middle Eastern origin, having limited exposure to sunlight including those who remain covered when outdoors, those who consume a diet low in vitamin D such as vegans, and those with body mass index above 30 kg/m [2]. In the United States, the Food and Nutrition Board at the IOM recommend vitamin D intake of 600 IU/day during pregnancy and lactation [103]. This is slightly higher than the conventional dose (400 IU) included in the prenatal multivitamins that are routinely recommended for all pregnant women in the USA. Although higher doses are needed to correct vitamin D deficiency, the American College of Obstetricians and Gynecologists does not recommend routine screening during pregnancy due to insufficient available evidence [104].

Vitamin D is suggested to have a positive effect on immunity [105]. Higher maternal vitamin D intake has been linked to reduced risk of wheezing in infancy, and asthma and allergic rhinitis in childhood [106, 107]. Vitamin D supplementation in infancy/early childhood may play a role in protecting against the development of type I diabetes [108]. However, this evidence is based on observational studies, and the evidence regarding the ideal timing of supplementation is limited.

The American Academy of Pediatrics (AAP) recommends vitamin D supplements to infants and children with 400 IU daily [109]. This was increased from its previous recommendation of 200 IU/day. In Australia and New Zealand recommendations state that pregnant women, especially those who are dark-skinned or veiled, should be screened and treated for vitamin D deficiency, and breastfed infants of dark-skinned or veiled women should be supplemented with vitamin D for the first 12 months of life. At-risk children are recommended to receive 400 IU vitamin D daily; if compliance is poor, an annual dose of 150,000 IU may be considered [110].

Vitamin A

Vitamin A deficiency is a serious public health problem in many parts of Africa. Although pregnant women are suspected to be at higher risk of this deficiency, there is limited data on vitamin A status during pregnancy in African countries [111]. A Cochrane systematic review, including 16 RCTs, concludes that there is no role for vitamin A supplementation in reducing maternal or perinatal mortality. The dose of vitamin A given, in combination with additional micronutrients and the duration of supplementation differed in the trials assessed in the review. The dose ranged between 5,000 IU and 10,000 IU for daily doses, around 200,000 IU vitamin A for weekly supplementation and 200,000 IU vitamin A at time of delivery [112].

High levels of vitamin A during early pregnancy may increase the risk of congenital malformation in the infant. The evidence is well established in experimental studies in animals, however, the dose

threshold in the epidemiological evidence is still unclear [113]. Some suggest a threshold of 10,000 IU, however this comes mainly from case–control studies [114].

The WHO recommends that high-dose vitamin A should be avoided during pregnancy because of the theoretical risk of birth defects. However, it recommends high-dose vitamin A supplementation to all postpartum mothers within 6 weeks of delivery, when the chance of pregnancy is remote, preferably delivered in combination of infant immunization programs in countries where vitamin A deficiency is a problem (where night blindness occurs) [115].

Calcium

Calcium supplementation during pregnancy reduces the risk of hypertension and pre-eclampsia especially for high-risk women and those with low dietary calcium intake [116]. The WHO recommends 1.5–2 g/day to pregnant women [117]. A Cochrane systematic review recommends at least 1 g of calcium daily during pregnancy to reduce the risk of gestational hypertension [118]. However, the review found no differences between the supplemented and the unsupplemented groups in the incidence of LBW, preterm birth, SGA, stillbirth, neonatal morbidity, or mortality.

Calcium is known to inhibit iron absorption in a dose-dependent fashion [119]. Therefore, the WHO recommends that the timing of taking calcium supplements should be separated from that of iron or iron + folic acid supplements [116]. It can also interact with zinc, magnesium, and phosphorus which are important micronutrients during pregnancy [119].

There is controversial evidence that calcium supplementation in pregnancy is associated with lower offspring blood pressure. A follow-up of a calcium supplementation trial in Argentina including 591 children at around age 7 concluded that systolic blood pressure is lower in the children of supplemented mothers, however, the effect was only statistically significant among overweight children [120]. Other follow-ups of supplementation trials in Massachusetts, USA, and The Gambia found no association with offspring blood pressure at 3 years and 5–10 years respectively [121, 122].

Zinc

A review including seven trials found favorable effect of zinc supplementation on the incidence of preterm birth, with no effect on birth weight or other infant outcomes measured in the trials. The review recommends further research [123].

Isolated zinc deficiency is rare as it frequently coexists with other micronutrient deficiencies such as iron in at-risk populations, and therefore should usually be tackled with multiple micronutrient supplements if present [124].

Magnesium

In a systematic review of seven trials involving 2,689 women, oral magnesium treatment from before the 25th week of gestation was associated with a lower frequency of preterm birth, LBW, and SGA compared with placebo. Of the seven trials included in the review, only one was judged to be of high quality. Poor quality trials are likely to have resulted in a bias favoring magnesium supplementation [125]. The review concludes that there is not enough high quality evidence to show that dietary magnesium supplementation during pregnancy is beneficial.

Balanced Protein-Energy

Poor nutritional status of the mother at conception and inadequate energy and protein intakes during pregnancy can have an adverse effect on fetal growth [126]. A systematic review of protein-energy food supplements including 13 trials found that the difference in birth weight and the incidence of preterm birth between supplemented and supplemented groups was not significant. However, there was a significant reduction in the incidence of SGA, as well as the incidence of stillbirth and neonatal death based on three trials. Most of the trials were based in developing countries. High-protein or balanced-protein supplementation alone was found not to be beneficial and may be harmful to the fetus [127].

Pooled results from another review of 11 studies showed that balanced protein-energy supplemented group had higher birth weight compared to controls (Mean difference 59.89 g, 95% CI 33, 87) [128]. This effect was more pronounced in malnourished women compared to adequately nourished women. There was 31% reduction in the risk of SGA. There was no statistically significant effect of balanced protein-energy supplementation on neonatal mortality (RR = 0.63, 95% CI 0.37, 1.06).

Intervening universally in areas with high prevalence of maternal under-nutrition with this type of supplementation during pregnancy has been argued to be more effective than targeted energy supplementation to women considered at risk of under-nutrition based on anthropometrical screening [129] (Table 24.1).

Table 24.1 Summary of the potential effects of maternal dietary supplements on infant outcomes with recommendation on use

Nutrient	Effects on infant	Supplement advised?
MVM	Likely to improve infant outcomes in developing countries	Possibly—where evidence of deficiency is present or the national prevalence of multiple micronutrient deficiency is high
	Possibility in well nourished women of reduced bioavailability of micronutrients due to interactions	
	No evidence to support routine MVM supplements in developed countries	
Iron	Likely to improve infant iron status	Yes—in developing countries with high levels of deficiency both during pregnancy and for women of childbearing age
	Positive effect on birth weight	
	High dose—side effects in mother: nausea, vomiting, constipation	
	Interactions with other minerals (e.g., Calcium) preventing absorption	Possibly—in developed countries
	Have been linked to pre-eclampsia and gestational diabetes in mother	
Folic acid	Reduce risk of neonatal deaths and congenital malformations due to NTD	Yes—daily during pregnancy up to 12 weeks gestation
		Yes—for women of childbearing age
Vitamin C and E	No evidence of benefit	No—could be harmful
	Possibly increase risk of hypertension in women at risk of pre-eclampsia	
Vitamin D	Possibly improve vitamin D status and growth in high-risk infants and toddlers	Yes—for those at high risk of deficiency
	May have beneficial effect in reducing risk of conditions such as asthma and type 1 diabetes	
Vitamin A	No evidence for reducing perinatal mortality	No—but provide high-dose supplement within 6 weeks of delivery where deficiency is common
	High doses in early pregnancy may cause congenital malformation	

(continued)

Table 24.1 (continued)

Nutrient	Effects on infant	Supplement advised?
Calcium	Reduce risk of pre-eclampsia especially in high-risk women and those with low intake May be linked to lower childhood blood pressure May inhibit iron absorption	Yes—Only with low calcium intake, separated from use of iron or other mineral supplements
Zinc	May reduce risk of preterm birth Deficiency usually in combination with other micronutrients	Not enough evidence
Magnesium	Low quality evidence shows improved birth outcomes	Not enough evidence
Balanced protein-energy	May reduce incidence of SGA, stillbirth, and neonatal death Birth weight may increase if supplements given to women who are malnourished	Yes—in areas with high prevalence of maternal under-nutrition.

Summary

Conclusive evidence is provided solely for periconceptional folate supplementation in the prevention of NTDs. A Lancet review in 2005 recommended 16 interventions to improve neonatal survival, out of which two were supplementation programs: folic acid to reduce NTD incidence and calcium to reduce pre-eclampsia and eclampsia incidence [91]. MVM supplements may be beneficial in women with poor nutrition and multiple micronutrient deficiencies. Adverse effects seen in some studies associated with MVM supplementation may be due to the detrimental effects of certain components such as vitamins C and E, and/or to the interaction between the multiple ingredients of the preparation. There is much less evidence on the need for supplementation in general during pregnancy in developed compared with developing countries.

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Chapter 25
Food Fortification

Christine A. Northrop-Clewes

Key Points

- Vitamins and minerals, also known as micronutrients, are critical components of good nutrition.
- All people should obtain all the energy, macro- and micronutrients from their diet for a healthy and productive life.
- Countries need to address the causes of micronutrient malnutrition intrinsic to poverty and unsustainable livelihoods
- Intervention strategies: supplementation, fortification, dietary diversity, nutrition education and public health practices.
- Food fortification is a sustainable method of improving dietary quality of a targeted group or population without changing dietary habits.
- Optimal feeding practices are critical, especially in the first 1,000 days (−9 to 24 months) of life.
- Fortified complementary foods are a cost-effective way to fulfill micronutrient needs of infants >6 months.

Keywords Malnutrition • 1,000 days • Vitamin A • Iron • Iodine • Food fortification • Complementary foods • Infant • Breastfeeding • Woman

Acronyms and Abbreviations

25OHD	25-Hydroxyvitamin D
ACC/SCN	Administrative Coordination Committee/Subcommittee on Nutrition
ADI	Acceptable daily intake
DALYs	Disability-adjusted years
EAR	Estimated average requirement
FAO/WHO	Food and Agricultural Organisation/World Health Organisation
$FeSO_4$	Ferrous sulphate
GAIN	Global Alliance for Improved Nutrition
GDP	Gross domestic product
HAZ	Height-for-age *z*-score
Hb	Haemoglobin

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R.R. Watson et al. (eds.), *Nutrition in Infancy: Volume 1*, Nutrition and Health,
DOI 10.1007/978-1-62703-224-7_25,

IDA	Iron deficiency anaemia
IDD	Iodine deficiency disorder
INCAP	Institute of Nutrition of Central America and Panama
IOM/FNB	Institute of Medicine Food and Nutrition Board
JECFA	Joint FAO/WHO Expert Committee on Food Additives
kcal	Kilo calories
KI	Potassium iodide
KIO_3	Potassium iodate
LNS	Lipid-based nutrient supplement
MDGs	Millennium development goals
MNP	Micronutrient powder
MSG	Monosodium glutamate
NaFeEDTA	Sodium iron ethylenediaminetetraacetate
NDNS	National Diet and Nutrition Survey
NTDs	Neural tube defects
PAHO	Pan American Health Organization
ppm	Parts per million
QC	Quality control
RDA	Recommended dietary allowance
RE	Retinol equivalents
RNI	Reference nutrient intake
SMHP	Sodium hexameta-phosphate
ULs	Tolerable upper intake levels
UN	United Nations
UNICEF	United Nations Children's Fund
USAID	Unites States Agency for International Development
USI	Universal salt iodisation
VAD	Vitamin A deficiency
VMNIS	Vitamin and Mineral Information Service
WHO	World Health Organisation

Introduction

The term malnutrition refers to both under-nutrition and over-nutrition and affects billions of people worldwide. Under-nutrition is a lack of the necessary energy, protein and/or micronutrients, while over-nutrition means too much energy, fat or specific micronutrients in the diet [1]. Traditionally, under-nutrition has been prevalent in developing countries, while over-nutrition and obesity has been widespread in developed countries. Recently, however, obesity has been increasing in developing countries, leading to a double burden of disease, especially in urban settings.

Data from The Lancet Series 2008 reported that stunting, severe wasting and intrauterine growth restriction were responsible for 2.2 million deaths and 21% of disability-adjusted life-years (DALYs) in children under 5 years of age [2]. Deficiencies of vitamin A and zinc also contribute to 0.6 million and 0.4 million deaths respectively, a total of 9% of global childhood DALYs [2] and, although iron and iodine deficiencies resulted in fewer child deaths, they were still responsible for about 0.2% of global childhood DALYs. Suboptimum breastfeeding was estimated to be responsible for 1.4 million child deaths equivalent to 10% of DALYs in children under 5 years of age [2]. Co-exposure of these nutrition-related factors were together responsible for about 35% of child deaths and 11% of the total global disease burden. The high mortality and disease burden resulting from these nutrition-related

factors make a strong case for the implementation of interventions to address the causes and improve the health of infants and young children.

Vitamins and minerals, also known as micronutrients, are critical components of good nutrition. In particular, vitamins A and D, folate, iodine, iron, zinc and other B vitamins including thiamin (vitamin B1), riboflavin (vitamin B2), niacin (B3), cobalamin (vitamin B12) and pyridoxine (vitamin B6) are important for healthy and productive populations. Without them, children develop birth defects, blindness and an inability to learn properly, among other long-term disabilities. In terms of the implications to national economies, countries may lose 2–3% of their Gross Domestic Product (GDP) as a result of iron, iodine and zinc deficiencies.

Without addressing malnutrition, the world community might not be able to achieve the Millennium Development Goals (MDGs), especially those related to health, hunger and poverty. During the United Nations (UN) MDGs Summit in September 2010, a new initiative, the '1,000 Days' campaign was launched, which highlights the importance of good quality nutrition in a child's first 1,000 days [3]. Progress to achieve the MDGs related to hunger, poverty, education, maternal and child health and infectious diseases will not be possible without international cooperation to improve nutrition. There is a critical window of opportunity to act between the fertilisation of the ovum and the child achieving 2 years of age, known as the first 1,000 days of life, when nutrition interventions can overcome the possible irreversible cognitive and physical setbacks of malnutrition during this important time of development. Optimal feeding practices for children aged 0–24 months include, exclusive breastfeeding until 6 months of age, and introduction and appropriate use of complementary foods from 6 months onwards. Where home-made complementary foods are poor in nutritional quality, new micronutrient powders (MNPs), such as 'Sprinkles™' are now available to sprinkle onto infant porridge. In addition, new fortified infant cereals can be purchased which are packaged in small sachets affordable to the poorer families.

History of Fortification

The scientific rationale, including technology, stability, interactions and effectiveness for fortifying staple foods was developed early in the twentieth century [4, 5]. In 1923, Switzerland was the first country to fortify salt with iodine to prevent goitre and cretinism because iodine deficiency was widespread throughout the alpine region. Also in 1923, the United Kingdom (UK) and the United States of America (US) began fortifying milk with vitamin D to prevent rickets, which were common at that time in the northern hemisphere due to the lack of sunshine in the winter months and poor socioeconomic conditions [6].

In 1944, the government of Canada started the fortification of white wheat flour with iron, thiamin (B1), riboflavin (B2) and niacin and margarine with vitamin A. Results were remarkable, and symptoms of vitamin A and B deficiencies were substantially reduced or eliminated. Beriberi was eliminated completely and infant mortality in Canada during the first year of life fell from 102/1,000 live births in 1944 to 61/1,000 in 1947 [4].

The introduction of polished rice into the Philippines at the turn of the twentieth century was associated with widespread beriberi. However, in October 1948 thiamin-fortified rice was distributed, which led, for example in Bataan province, to a spectacular reduction in death from beriberi from 194/10,000 in 1948 to 20/100,000 in 1950 [7].

Fortification of sugar with vitamin A in Guatemala in 1974 reduced the prevalence of low plasma retinol concentrations (<0.35 μmol/L) from 3.3 to 0.2% within 2 years. The Institute of Nutrition of Central America and Panama (INCAP) used sugar because there was no other staple food reaching all the target groups in the country [8].

In 1993, Venezuela began fortifying pre-cooked yellow and white corn flour with vitamins A, B1, B2, niacin and iron and wheat flour was fortified with B1, B2, niacin and iron. The two cereals represented 45% of the calorie intake of the population. Evidence of a reduction in the prevalence of iron deficiency from 37 to 19% and anaemia from 15 to 10% was shown in a study of 397 children [9].

In 1994, the government of Guatemala reviewed the fortification of wheat flour and included folic acid, because a high prevalence of deficiency of this vitamin existed and its potential importance in preventing anaemia was recognised. Columbia, Bolivia and Ecuador followed the example of Guatemala in 1996 and fortified their flour with folate. In 1998, the US also added folic acid to their wheat flour (1.54 mg/kg flour); however this was to reduce the number of births affected by neural tube defects (NTDs). The US Public Health Service recommends that women of childbearing age should eat at least 400 μg/day of folate to prevent NTDs [10]. Likewise in Chile, from January 2000, 2.2 mg/kg folic acid was added to wheat flour, to achieve a consumption of 400 μg folic acid/day from wheat products. NTD rates before fortification (1999–2000) and after fortification (2001–2002) were compared at nine public hospitals in Santiago (25% of all births) and total NTD rate declined from 16 to 10/10,000 live births (40% decline). The marked decrease in NTD rates after fortification supports the conclusion that folic acid fortification of wheat flour is an effective intervention for preventing many NTDs. Furthermore, it is estimated that the total cost of rehabilitation for one child affected with spina bifida in Chile from birth to 18 years of age is US$ 120,000, while the total cost of adding folic acid to wheat flour is US$ 0.15/ton of wheat flour or US$ 175,000/year. Hence, just two cases of NTD prevented in a year would have recovered the entire annual cost of fortification with folic acid [11].

Micronutrient Deficiencies

The World Health Organisation (WHO) has maintained a Vitamin and Mineral Nutrition Information System (VMNIS) since 1991, which contains databases, related to three micronutrients of public health significance globally: iodine, vitamin A and iron [12]. Part of the mandate for WHO is to assess the micronutrient status of populations, monitor and evaluate the impact of strategies for the prevention and control of micronutrient malnutrition, and to track related trends over time. The databases provide data on the micronutrient status of the population at the global and regional levels in an attempt to increase the awareness of the public health community and policy makers, and to evaluate the impact of interventions and measure progress towards the MDGs.

Vitamin A deficiency (*VAD*)—is a major nutritional concern in poorer societies across the world and the WHO used data from the VMNIS to compile summary tables for children <5 years and pregnant women. The cutoff identified by the WHO to classify those at risk of biochemical VAD is a serum retinol concentration <0.7 μmol/L in children 6–71 months [13]. As there is no WHO recommended cutoff for serum retinol concentrations in pregnant women, the same cutoff as for preschool children was used. Table 25.1 summarises the global prevalence of VAD in preschool children and pregnant women as identified by serum retinol concentrations <0.7 μmol/L and shows globally 190 million preschool children affected by VAD. The data shows a global reduction since 1994 when an estimated 254 million were VAD [14]. The figures are undoubtedly an over-estimate as inflammation also reduces plasma retinol concentrations, which was not taken into account in any of the estimates. Nevertheless, the figures suggest a serious problem with VAD.

Iron—anaemia is defined as an insufficient number of red blood cells to meet the oxygen-carrying capacity needed by the body. Iron deficiency is thought to be the most common cause of anaemia globally, but other nutritional deficiencies (folate, vitamins A and B12), acute and chronic inflammation, parasitic infections and inherited or acquired disorders that affect haemoglobin synthesis, red blood cell production or red blood cell survival, can all contribute to anaemia. Haemoglobin concentration alone cannot be used to diagnose iron deficiency, and so serum ferritin, transferrin receptors (sTfR),

Table 25.1 Prevalence of serum retinol concentrations <0.7 μmol/L and number of individuals affected by vitamin A deficiency in two population groups: preschool children (<5 years) and pregnant women, 1995–2005 (adapted from WHO [14])

	Preschool children		Pregnant women	
WHO region	Prevalence (%)	Nos. affected (millions)	Prevalence (%)	Nos. affected (millions)
Africa	44.4	56.4	13.5	4.18
Americas	15.6	8.68	2.0	0.23
South-east Asia	49.9	91.5	17.3	6.69
Europe	19.7	5.81	11.6	0.72
Eastern Mediterranean	20.4	13.2	16.1	2.42
Western Pacific	12.9	14.3	21.5	4.60
Global	33.3	190	15.3	19.1

Data from countries with GDP in 2005 <US$15,000

Table 25.2 Prevalence of low haemoglobin concentrations (<110 g/L) and number of individuals affected by anaemia in two population groups: preschool children (<5 years) and pregnant women, 1995–2005 (adapted from WHO [15])

	Preschool children		Pregnant women	
WHO region	Prevalence Hb <110 g/L (%)	Nos. affected (millions)	Prevalence Hb <110 g/L (%)	Nos. affected (millions)
Africa	67.6	83.5	57.1	17.2
Americas	20.0	23.1	24.1	3.9
South-east Asia	65.5	115.3	48.2	18.1
Europe	20.0	11.1	25.0	2.6
Eastern Mediterranean	46.0	0.8	44.2	7.1
Western Pacific	20.0	27.4	30.7	7.6
Global	47.7	293.1	41.8	56.4

Data from countries with GDP in 2005 <US$15,000

C-reactive protein (CRP), α-1 acid glycoprotein (AGP), vitamin A, folate and vitamin B12 are also being measured in an effort to understand the aetiology of anaemia. The prevalence of anaemia is an important health indicator, and when it is used with other measurements of iron status, the haemoglobin concentration can provide information about the severity of iron deficiency. Table 25.2 summarises the WHO global and regional prevalence of anaemia as measured by concentrations of haemoglobin using established cutoffs for each population group [15].

Iodine—Iodine deficiency disorders (IDDs) are a major public health problem for populations throughout the world, and particular at-risk groups are pregnant women and young children. The most devastating outcomes of IDD are increased perinatal mortality and child mental retardation, which are the primary reasons for the current Universal Salt Iodisation Program (USI) to eliminate IDD [16]. The main factor responsible for IDD is a low dietary supply of iodine in populations living where the soil has low iodine content as a result of past glaciation or the repeated leaching effects of snow, water and heavy rainfall. Table 25.3 shows the proportion and number of school-age children (6–12 years), globally and regionally, with insufficient iodine intake based on urinary iodine (UI) concentrations <100 μg/L [16]; school-age children are used to monitor IDD as they are a convenient population group to sample.

Other micronutrients—of increasing interest to the nutritional world are deficiencies of the B vitamins, vitamin D and zinc.

Vitamin D—Although different methodologies were used, studies by Woo et al. [17] and Islam et al. [18] both report women with values of 25-hydroxyvitamin D (25OHD) <25 nmol/L (16% in

Table 25.3 Proportion of school-age children population with insufficient iodine intake (<100 μg/L urinary iodine [UI]) [16]

	School children	
WHO region	Prevalence UI <100 μg/L (%)	Nos. affected (millions)
Africa	42.3	49.5
Americas	10.1	10.0
South-east Asia	39.9	95.6
Europe	59.9	42.2
Eastern Mediterranean	55.4	40.2
Western Pacific	26.2	48.0
Global	36.5	285.4

Dhaka; 18% in Hong Kong and 40% in Beijing, measured in spring time) and >90% of women had 25OHD <50 nmol/L. Such low concentrations are of concern because of potential adverse consequences for the women's own health and because poor vitamin D status in pregnant women is associated with decreased foetal and childhood bone mineral accretion, and an increased risk of rickets in their infants [19]. Furthermore, poor vitamin D status in women of childbearing age indicates that status is also likely to be poor in other age groups in the population. Based on a plasma 25OHD concentration <25 nmol/L, current evidence suggests that the risk of vitamin D deficiency is high in many parts of the world. However, no common definition exists for adequate vitamin D status but the Institute of Medicine (IOM) (2011) has suggested cutoffs of 30 nmol/L for nonpregnant women and 27.5 nmol/L for children [20]. Recent surveys have shown the risk of vitamin D deficiency to be a potential problem in nonpregnant women 15–49 years (prevalence 60%) and children 12–59 months (prevalence 20%) in Jordan (National Micronutrient Survey 2010). The National Diet and Nutrition Survey (NDNS) in the UK also provides evidence of low vitamin D status in most age groups in the UK population, especially older children and young adults, and in older people living in institutions [21]. Young women of childbearing age also have low vitamin D status and are likely to begin their pregnancies with low stores. Other evidence highlights a greater risk of vitamin D deficiency in population subgroups, particularly infants from black and ethnic minority groups. Cases of clinically apparent vitamin D deficiency in UK children, predominantly of Afro-Caribbean or South Asian origin, are widely reported but there is a lack of NDNS data to support the clinical data [22]. However, the US National Health and Nutrition Examination Survey (NHANES) (1999–2002) found that 10% of the US population had concentrations of 25OHD <27.5 nmol/L (10th percentile), with non-Hispanic blacks having the highest prevalence of low 25OHD concentrations [23].

Zinc—Zinc deficiency impairs the physical growth and increases the risk and severity of a variety of infections in children because of the critical structural and functional roles of zinc in multiple enzyme systems involved in gene expression, cell division and growth, immunologic and reproductive functions [24]. It is important to be able to assess zinc status and three main types of assessment have been considered: biochemical, dietary and functional methods. Serum or plasma zinc concentration is considered the best available biomarker of the risk of zinc deficiency in populations but it does have severe limitations. Inadequate dietary intake of absorbable zinc is one of the major causes of zinc deficiency and assessment of the adequacy of zinc intakes through the use of 24-h dietary recalls or weighed dietary records is an important component in evaluating the risk of zinc deficiency in a population. The percentage of children under 5 years of age with height-for-age *z*-score (HAZ) less than −2.0 SD with respect to the reference population has been recommended as the best functional indicator to assess the likely risk of zinc deficiency in a population but physical growth is influenced by many factors. However, this risk is considered to be elevated and of public health concern when the prevalence of low height-for-age is greater than 20%. The validity of these indicators and proposed cutoffs is still provisional, so they should be evaluated further when opportunities become available during national assessment surveys [24].

B vitamins—The B vitamins are a group of water-soluble vitamins that play an important role in cell metabolism and include: thiamin, riboflavin, niacin, pantothenic acid, pyridoxine, biotin, folate and vitamin B12. Recently both folate and vitamin B12 have increased in importance, mainly because of their roles in anaemia, and folate in preventing NTDs. Several other B vitamins are involved in folate metabolism, including riboflavin, pyridoxine (vitamin B6) and vitamin B12. In the absence of vitamin B12, folate is trapped as N5-methyltetrahydrofolate, and cannot be recycled back into the folate pool.

Folate is an essential vitamin and is involved as a coenzyme in the transfer of one-carbon units in amino acid inter-conversions and is essential for protein synthesis. It is necessary for the production of DNA and RNA and for the synthesis of red and white blood cells, as well as being needed for the integrity of the central nervous system, gastrointestinal system and growth of the foetus and child. Folate deficiency leads to megaloblastic anaemia, in addition, the folate status of women of childbearing age is a particular public health concern due to the risks of having a baby with NTDs as a result of folate deficiency. Red cell folate concentration is considered to be a better measure of long-term folate status than serum folate because it reflects body stores at the time of red cell synthesis; serum folate concentrations reflect recent dietary intake.

Vitamin B12 deficiency is most commonly caused by malabsorption associated with a lack of intrinsic factor (also known as pernicious anaemia), which is formed by the parietal cells and is necessary for the absorption of B12. It is important to diagnose B12 deficiency as it causes neurologic and psychiatric damage. Iron and folate deficiency can coexist with B12 deficiency.

Strategies for the Control of Micronutrient Malnutrition

The control of vitamin and mineral deficiencies is an essential part of the overall effort to fight hunger and malnutrition. Countries need to adopt and support a comprehensive approach that addresses the causes of micronutrient malnutrition and the often associated ‘hidden hunger’ which is intrinsic to poverty and unsustainable livelihoods. Actions that promote an increase in the supply, access, consumption and utilisation of an adequate quantity, quality and variety of foods for all populations groups should be supported. The aim is for all people to be able to obtain all the energy, macro- and micronutrients from their diet in order to enjoy a healthy and productive life. Policy and programme responses include supplementation, food-based strategies such as dietary diversification and food fortification, as well as nutrition education, public health interventions and food safety measures. These approaches should be regarded as complementary, with their relative importance depending on local conditions and the specific mix of local needs [25].

Supplementation through periodic administration of pharmacological preparations in the form of pills, capsules or syrups is an effective strategy whereby almost immediate benefits can be brought to the most at-risk groups. However, hard-to-reach ‘at-risk groups’, other household and community members who are not targeted to receive the supplement may not benefit. Supplementation usually requires a large foreign currency input for the procurement and purchase of the micronutrients in a pre-packaged form, and a distribution system. A high degree of compliance is a necessary factor for success (especially if supplements need to be consumed on a longer-term basis, e.g. iron tablets). A lack of supplies and poor compliance are consistently reported by many programme managers as being the main barriers to success. However, the vitamin A supplementation programme can be considered a success as it has been adopted in many countries as part of ‘national health days’ for children under 5 years, which often take place twice a year, hence the child gets a vitamin A capsule twice a year.

Fortification of foods with micronutrients that are insufficient in the daily diet has largely been responsible for the elimination of vitamin and mineral deficiencies in the Western World. Margarine containing no natural ‘fat-soluble A’, was the first ‘imitation’ food produced on a large industrial scale

to be fortified with vitamin A; now margarine is among those items of food most frequently fortified with vitamin A in the world [26]. In addition, fortification of margarine with vitamin D is thought to have rid Canada and Northern Europe of rickets in the early part of the twentieth century [27]. Fortification of refined flour with iron in Sweden and the US is said to have dramatically reduced iron deficiency anaemia (IDA), and in countries where iodisation of salt has been introduced, sustained reductions in the prevalence of IDD have been seen [28]. Enrichment of a staple food improves dietary quality long-term without a change of diet habits. Food fortification tends to have a less immediate but a much wider and more sustained impact. It should therefore be considered as an addition to dietary diversity, which takes the longest to implement [29].

The micronutrient gap can be addressed in children >6 months of age, when breastfeeding is no longer sufficient to meet nutritional requirements, by the feeding of specialised fortified foods to infants and young children, e.g.:

1. Fortified blended foods which describe any prepared porridge or cereal fortified with micronutrients.
2. Complementary food 'supplements' which can be added to other foods or eaten alone to improve both macro- and micronutrient intake, e.g. lipid-based nutrient supplements (LNS) such as fortified peanut spread.
3. Micronutrient powders (MNPs), which are pre-packaged sachets of micronutrients that can be added to local porridges and paps or family foods to improve micronutrient status of children older than 6 months [30].

Dietary improvement aims to increase dietary availability, regular access and consumption of vitamin- and mineral-rich foods in at-risk and micronutrient-deficient populations in developing countries. Such efforts require changes in dietary behaviour, which may necessitate changes in food supply and availability, hence may need a long time period to achieve success.

Public health interventions, in addition to the specific interventions outlined above, public health interventions are often needed to help prevent micronutrient malnutrition. Micronutrient malnutrition is often associated with a high prevalence of infection and so infection control (e.g. hand washing, immunisation, malaria and parasite control) and improvement of water and sanitation are an essential part of the health improvement package.

Nutrition education and other factors, such as the quality of child-care and maternal education, also need to be taken into consideration.

Developing a Food Fortification Programme

Definition and Requirements of a Food Fortification Programme

WHO/Food and Agriculture Organization (FAO) defines food fortification as the practice of deliberately increasing the content of essential micronutrients—vitamins and minerals (including trace elements)—in a food so as to improve the nutritional quality of the food supply and to provide a public health benefit with minimal risk to health [31]. The public health benefits of fortification may either be demonstrable, or indicated as potential or plausible by generally accepted scientific research, and include:

1. Prevention or minimization of the risk of occurrence of micronutrient deficiency in a population or specific population groups.
2. Contribution to the correction of a demonstrated micronutrient deficiency in a population or specific population groups.

3. A potential for an improvement in nutritional status and dietary intakes that may be or may become suboptimal as a result of changes in dietary habits or lifestyles.
4. Plausible beneficial effects of micronutrients consistent with maintaining or improving health.

Food fortification involves the addition of micronutrients to food in order to maintain or improve the quality of the food of a targeted group or population and to provide a public health benefit with minimal risk to health [31, 32].

The Codex: 'General Principles for the Addition of Essential Nutrients to Foods' defines 'fortification' or 'enrichment' as 'the addition of one or more essential nutrients to a food whether or not it is normally contained in the food, for the purpose of preventing or correcting a demonstrated deficiency of one or more nutrients in the population or specific population groups'. The Codex General Principles go on to state that the first-mentioned conditions for the fulfillment of any fortification programme 'should be a demonstrated need for increasing the intake of an essential nutrient in one or more population groups. This may be actual clinical or subclinical evidence of deficiency, estimates indicating low levels of intake of nutrients or possible deficiencies likely to develop because of changes taking place in food habits' [33].

Food fortification can be used to correct a demonstrated dietary deficiency, to restore nutrients lost during food processing (restoration), to increase the nutritional quality of manufactured food products used as a sole source of nourishment, or to ensure that when manufactured foods substitute for other foods the nutritional content remains constant. However, the fortified food(s) needs to be consumed in adequate amounts by a large proportion of the target individuals in a population. It is also necessary to have access to, and to use fortificants that are well absorbed, yet do not affect the sensory properties of foods. In most cases, it is preferable to use food vehicles that are centrally processed, and have the support of the food industry [25]. Fortification of food with micronutrients is a valid technology for reducing micronutrient malnutrition as part of a food-based approach when existing food supplies and limited access fail to provide adequate levels of the respective nutrients in the diet. Food fortification supports ongoing nutrition improvement programmes and should be regarded as part of a broader, integrated approach to prevent micronutrient malnutrition, thereby complementing other approaches to improve micronutrient status.

The important steps in the development of and the conditions for a successful food fortification programme are summarised in Table 25.4.

Selection of a Food Vehicle

Selection of the right food ingredient or food to act as a carrier (food vehicle) of the specific micronutrient (fortificant) is important for compliance. There are a number of criteria, which must be met for the food to be a vehicle [4, 34]:

- A high proportion of the target population must consume the food.
- The food should be eaten regularly, in relatively constant amounts and the upper and lower levels of intake for the population groups should be known.
- There should be little variation in consumption pattern between individuals and between regions.
- The normal serving size should meet a significant part of the daily dietary requirement.
- All the population should be able to afford to buy the food, i.e. the additional cost of fortification should be reasonable for the consumer.
- The probability of excessive intake is minimal (i.e. risk of toxicity is low).
- There should be no change in acceptability of the product or change in the quality of the product as a result of fortification.

Table 25.4 Development of a food fortification programme [34]

Steps in the development of a food fortification programme	Conditions necessary for the success of the food fortification programme
Determine the prevalence of the micronutrient deficiency or deficiencies	Get Political support and buy-in
Determine the micronutrient intake from a dietary survey	Get industry support and buy-in
Obtain consumption data for potential food vehicles	Get legislation in place to mandate for the food to be fortified
Determine the micronutrient availability from the typical diet	Train staff at industry, monitoring and marketing levels
Seek government support	Ensure the fortificant chosen has good bioavailability
Seek food industry support	Consider possible inhibitory effects from the typical diet
Assess status of potential vehicles, suppliers and the processing industry chain	Need adequate laboratory facilities for internal and external quality control
Determine the type and amount of micronutrient fortificant	Consider possible cultural or other objections to the fortified food
Develop relevant fortification technology in-country	Consumer acceptability
Study interactions, potency, stability, organoleptic qualities of the fortificant	Ensure adequate study design/statistical evaluations of the population
Determine the bioavailability of the fortified food	Consider other causes of deficiency e.g. parasitaemia, malaria or other non-dietary causes
Develop standards for the fortified food	Ensure constant supply of the fortificant
Develop legislation and regulation for mandatory compliance	
Develop internal and external quality control procedures	
Promote the fortified food to improve consumer acceptance	

Processing/Storage

Ideally a central processing plant should carry out the fortification process. It should be a simple process using low-cost technology. The vehicle and fortificant should be stable, with no micronutrient interaction and remain mixed even after storing.

Stability and Marketing

The nutrient(s) added should be sufficiently stable in the food using customary conditions of packing, storage, distribution and use. The product should be labelled according to the standards of the country. There should be an adequate turnover of the product. Oxygen, humidity, heat, acids, redox agents and light can affect vitamins, while other components can interfere with the stability, like heavy metals. Technology exists to prevent losses, but losses cannot be totally avoided. In order to ensure that when the food is ingested the vitamin content is as described on the label, the food industry should compensate for losses during processing and during storage of the finished product [4].

Selection of Fortificants

- The fortificant must have good bioavailability during the normal shelf life of the fortified food.
- It should not interact with the flavour, taste, texture, colour or cooking properties of the vehicle and should not shorten the shelf life of the vehicle.

- The fortified product should be offered at a price, which is affordable.
- The fortificant should be a suitable colour and have the right solubility and particle size for mixing with the vehicle.
- There should be a commercial source of the food-grade fortificant.
- It should be commercially possible to add the fortificant to the vehicle [4, 34].

Types of Fortification

1. *Mass fortification*—is the addition of one or more micronutrients to foods commonly consumed by the general public and includes staple foods such as cereals, condiments and oil [25]. Mass fortification is usually mandated by law, and is the best option available, when data collected from the general population indicates a public health risk of a significant number of the population becoming deficient in the specified micronutrients. In many instances the data may come from biochemical analysis of body fluids, e.g. plasma/serum, urine collected during national or subnational surveys, which indicates suboptimal levels of the micronutrient or from dietary intake data.
2. *Targeted fortification*—is the production of fortified foods for specific target groups, e.g. complementary foods for preschool children or special biscuits for lactating women. In some cases these foods may supply a substantial amount of the daily micronutrient requirement [31].
3. *Market-driven fortification*—is applied where a manufacturer uses a business-orientated initiative in which specific amounts of one or more micronutrients are added to their food product, usually a processed food, and the food is sold as a product with added benefits. This type of fortification is usually voluntary, but where fortification laws exist the level of fortification must be within the regulatory limits [25]. In the European Union (EU), fortified processed foods may be a substantial source of e.g. iron and vitamins A and D.
4. *Household fortification*—the transition from exclusive breastfeeding to family foods, referred to as complementary feeding, typically covers the period from 6 to 23 months of age, when malnutrition starts in many infants, especially in low-income countries and populations [35]. A recent WHO guideline on use of home fortification of foods for children 6–23 months recommends the home fortification of complementary foods with MNPs containing at least vitamin A, iron and zinc [35]. WHO recommend that the interventions with multiple MNPs should be implemented as part of a national infant and young child-feeding programme.

Biofortification—of staple foods by the breeding and genetic modification of plants to improve their nutrient content and/or absorption has been used on several staple foods, e.g. golden rice. The potential for plant breeding to increase the micronutrient content of various cereals, legumes and tubers exists; for instance, it is possible to select certain cereals (such as rice) and legumes for their high iron content, various varieties of carrots and sweet potatoes for their β-carotene levels, and maize for a low phytate content (which improves the absorption of iron and zinc) [25].

Fortification Technology

For most foods, technology is quite simple. For example, vitamins which are soluble in water can be dissolved in water and added to liquid foods like dairy products, fruit juices and beverages or in powder form, they can be mixed directly with foods like wheat flour, corn flour, corn starch and dry milk. The fat-soluble vitamins can be added directly to the oily phase of foods like margarine, cooking oil, mayonnaise and recombined milk. The industry can microencapsulate fat-soluble vitamins in

order to mix them with powders, water-soluble products or to protect them from oxygen and other harmful components [4].

Fortification of rice and sugar requires more complex technologies. Vitamin A in powder form is adhered with vegetable oil to the sugar crystals, by embedding a beadlet of retinyl palmitate, plus antioxidant, in a gelatin matrix that transforms the liposoluble and liquid vitamin into a dry water-dispersible powder. Rice is fortified by spraying the vitamins onto rice kernels and then coating with food-grade resins to avoid leaching when washing the rice before cooking [36]. Alternatively, rice-like material can be fortified with micronutrients that can be reconstructed to mimic grains of rice and then mixed with the authentic rice.

Fortification Costs

Compared to the social and health costs of micronutrient deficiencies, the direct cost of delivering nutrients in foods is remarkably low [4]. The cost of fortification includes the cost of the fortificant, labour costs for processing, packaging and labelling, transport and quality control (QC). In addition, depending on the type of food to be fortified, the level of fortification and the technology needed, the final cost of fortification can vary widely. The cost limit is defined as the highest increase in the cost of the food due to fortification that is acceptable to producers and consumers. Indeed, one of the most important criteria for a successful and sustainable food fortification programme in free trade economies is a low proportional increase in product price as a result of fortification. This is especially true of mass fortified products (Table 25.5) [25].

Dary and Mora compared the cost of fortifying different foods with vitamin A, considering food consumption patterns and losses of vitamin A during storage, transport and cooking [37]. Table 25.6 presents the costs of vitamin A fortification of oil, cereal flours (including wheat flour), sugar, and monosodium glutamate (MSG) and shows that vitamin A programmes have the potential to be cost-effective, with costs ranging from US$0.008/person/year for edible oils to US$ 0.121 for sugar [38]. Using comparable consumption and stability assumptions, Dary estimates that vitamin A fortification of wheat flour costs approximately 11 times more than oil fortification [37]. As mentioned above, another important cost consideration is the relative price increase of the fortified food vehicle compared with its unfortified version, because this price will determine the feasibility of production, trade, enforcement, and affordability among the lower-income groups who are often the main targets for food fortification. More comparative cost data are required to establish a reliable database across diverse food production and marketing systems that can adequately inform decisions on candidate food vehicles for vitamin A fortification.

The price of folic acid is likely to continue increasing, however, despite this increase, it remains one of the less expensive fortification interventions. Table 25.7 shows the calculated cost of folic acid for the four different levels of flour consumption.

The cost of adding vitamin B12 at 20 μg/kg is estimated at US$0.85/MT and will add 0.21% to the cost of wheat flour, assuming that flour costs US$ 0.40/kg, or one-tenth of the 2% increase in the final cost of fortified products that is generally considered acceptable to producers and the public [39].

The cost estimates for iron and zinc as fortificants shown in Table 25.8, apply to large-scale centralised fortification of a staple such as wheat flour, where the purchase price of the micronutrients is by far the greatest proportion (at least 80–90%) of the total fortification cost [25]. When fortification is carried out by many, smaller-scale enterprises, both the initial investment costs of e.g. equipment and the running costs, such as quality control procedures, are proportionally higher, and could therefore affect the viability and sustainability of the programme. Food fortification can be a very affordable way of correcting inadequate micronutrient intakes, but often the main challenge is finding a suitable industrially manufactured food vehicle that is consumed in sufficient amounts by the population at risk.

Table 25.5 Estimated cost of supplying enough micronutrient to meet 100% of the estimated average requirement (EAR) of an adult male, daily for 1 year using dry food (adapted from WHO/FAO [25])

	Adult EAR	% Nutrient content of fortificant	Cost of fortificant (US$)	% Overage—to compensate for losses[a]	Annual cost of fortificant (US$)[b]
Vitamin A (SD-250)	429 μg	7.5	42	50	0.136
Vitamin A palmitate one million IU in oil	429 μg	30	52	30	0.042
Water-soluble vitamin D	5 μg	0.25	33	20	0.035
Vitamin D—one million IU/g oil	5 μg	2.5	80	20	0.008
Vitamin E	8 mg	67	26	20	0.163
Vitamin C	37 mg	100	10	250[c]	0.257
Vitamin B1 (Thiamin)	1.0 mg	81	24	40	0.018
Vitamin B2 (riboflavin)	1.1 mg	100	38	30	0.024
Niacin	12 mg	99	9	10	0.053
Vitamin B6 (pyridoxal phosphate)	1.1 mg	82	28	20	0.020
Folic acid	188 μg[d]	100	90	50	0.011
Vitamin B12 (0.1%)	2.0 μg	0.1	38	30	0.043
[e]Iron					
NaFeEDTA	7.0 mg	13	15.45	5	0.383
Ferrous bisglycinate	7.0 mg	20	25	5	0.402
Ferrous fumarate	10.5 mg	33	5.12	5	0.075
$FeSO_4$, dried	10.5 mg	33	2.35	5	0.034
$FeSO_4$, encapsulated	10.5 mg	16	12.28	5	0.371
Electrolytic iron	21.1 mg	97	5.76	5	0.058
Zinc (oxide)	6.0 mg[f]	80	3.35	5	0.012
Calcium phosphate	833 mg	39	2.7	5	2.652
Potassium iodate	107 μg	59	20	25	0.002

NaFeEDTA sodium iron ethylenediaminetetraacetic acid; $FeSO_4$ ferrous sulphate

[a]Overage is an additional amount added to compensate for losses during production, storage, food production and distribution

[b]Includes an overage of +20% to cover variability in the fortification process

[c]Vitamin C is one of the least stable fortificants and a high overage is normally required. However, if the fortified food is not subject to heat or oxidation, the overage lowered

[d]As folic acid is 1.7 times more bioavailable than naturally occurring food folates, the EAR for folate has been divided by 1.7

[e]The EAR for iron depends on its bioavailability from the diet as well as the identity of the iron compound used as the fortificant. The values given here refer to white wheat flour (low extraction), and apply to diets with similar bioavailabilities. If the diet contains large amounts of iron absorption inhibitors, the EAR should be multiplied by a factor of around 2. Reduced iron is not included; its absorption would be at most about half that of electrolytic iron

[f]Assuming a moderate bioavailability of zinc

Table 25.6 Comparative cost of vitamin A fortification to supply 180 μg RAE (30% of RDI) with different food vehicle [37]

Food vehicle	Typical consumption (g/day)	Dietary goal at households (mg/kg)[a]	Dietary goal at shops[b] (mg/kg)	Overage at production[c] (%)	Cost/metric ton (US$)	% Purchasing price	Annual cost/person (US$)
Oil or margarine	15	12	15	20	1.87	0.37	0.008
Cereal flours	200	1.0	1.25	40	1.25	0.26	0.91
Sugar	50	3.5	4.5	100	6.65	1.39	0.121
MSG[d]	0.25	320	500	100	1,266	25.32	0.116

MSG monosodium glutamate; *RAE* retinol activity equivalent

[a]Dietary goal = μg RAE/consumption pattern (g/day)

[b]Assuming 25% additional amount to compensate for any losses

[c]Theoretical estimate based on reported stability information and length of product marketing life

[d]The cost of MSG estimated at US$5/kg

Table 25.7 Highest average level of folic acid added to flour and cost of fortificants for different ranges of usual daily intake of flour

	Low (<75)	Medium (75–149)	High (150–300)	Very high (>300)[a]
Highest average level of folic acid added to flour (mg/kg)	5.0	2.6	1.3	1.0
Cost (US$/MT flour)[b]	≤1.08	≤0.56	≤0.28	≤0.22

[a]Few countries have per capita consumption >300 g/day
[b]The worldwide price of folic acid in 2008 was US$195/kg for a product that is 90% folic acid

Table 25.8 Estimated costs of iron and zinc as fortificants [25]

Fortificant	Adult (EAR)[a] (mg)	Nutrient content of fortificant (%)	Cost of fortificant (US$/kg)	Overage[b] (%)	Annual cost of fortificant (US$)
NaFeEDTA	7.0	13	15.45	5	0.383
Ferrous bisglycinate	7.0	20	25	5	0.402
Ferrous fumarate	10.5	33	5.12	5	0.075
$FeSO_4$, dried	10.5	33	2.35	5	0.034
$FeSO_4$, encapsulated	10.5	16	12.28	5	0.371
Electrolytic iron	21.1[c]	97	5.76	5	0.058
Zinc	6[d]	80	3.35	5	0.012

NaFeEDTA sodium iron ethylenediaminetetraacetic acid; *$FeSO_4$* ferrous sulphate
[a]The cost of supplying enough micronutrient to meet 100% of the EAR of an adult male, daily or 1 year (via dry food)
[b]The overage is an additional amount that must be added to compensate for losses during production, storage, food production and distribution
[c]The EAR for iron depends on its bioavailability from the diet as well as the identity of the iron compound used as the fortificant. The values given here refer to white wheat flour (low extraction), and apply to diets with similar bioavailabilities. If the diet contains large amounts of iron absorption inhibitors, the EAR should be multiplied by a factor of around 2. Reduced iron is not included; its absorption would be at most about half that of electrolytic iron
[d]Assuming a moderate bioavailability of zinc

Bioavailability of the Micronutrients [34]

The term bioavailability generally refers to the extent to which a nutrient is capable of being absorbed (i.e. enters the blood stream) to be used by the body. The bioavailability of a nutrient in the diet is a function of:

- The form in which the nutrient is ingested i.e. the nutrient must be in a form that can either be directly transported through the intestinal mucosa or can easily be converted to a form, which can be transported through the mucosa.
- The extent of conversion of the nutrient into absorbable forms and the absorbed form of the nutrient must be able to be metabolised.
- The composition of the diet, i.e. other constituents in the diet can inhibit or enhance the transport of the micronutrient through the mucosa e.g. phytate (found in major cereals, and legumes) and polyphenols (found in sorghum) will diminish iron absorption, whereas vitamin C will enhance iron absorption [40].
- The physiological status and integrity of the gut can effect how much of the nutrient is absorbed and how efficiently, e.g. the presence of infection will depress the concentration of existing iron and vitamin A in the circulation [41, 42], gastrointestinal motility will affect transit time [43], the immaturity of intestinal function in infants may reduce absorption [44].
- The proportion of the nutrient, which is absorbed, may be affected by the concentration of the nutrient, i.e. whether it is in physiological or pharmacological doses or by taking certain drugs concurrently.

Therefore when considering a food fortification programme the bioavailability of the fortificant in relation to the type of diet consumed by the target population and the overall health of the population should be considered.

Legislation and Regulations for Food Fortification

The food industry has in some cases voluntarily fortified products. However the development of voluntarily fortified foods has been impaired in some countries because of consumer and government lack of awareness of the prevalence of micronutrient deficiencies and their impact on health [4]. To be effective, and to raise awareness of consumers and health policy makers, fortification programmes need to be supported by suitable legislation and/or regulations. It is essential to have in place the mechanisms through which the entire fortification programme can be controlled. Once policy makers are aware of the health problems of their population, and are motivated to instigate regulations and/or legislation for a fortification programme, then they are in a position to accelerate the fortification process and to protect the consumer from harmful practices, such as technical inadequacies in the fortification process [34].

Current Practices in Micronutrient Fortification

The following fortification technologies are already in use and widely applied:

(a) Iodisation of salt to combat IDD.
(b) Fortification of oil, fat, sugar, milk, dairy products and cereals with vitamin A.
(c) Fortification of flour, cereals, complementary foods and biscuits with multi-micronutrients.

Universal Salt Iodisation

The single fortification of salt with iodine occurs in both developed and developing countries and is the strategy recommended by WHO to correct iodine deficiency. Salt fulfills nearly all the characteristics of a suitable food vehicle and is one of the few commodities consumed by all members of a community regardless of social class. The two principal fortificants are potassium iodide (KI) and potassium iodate (KIO_3), neither of which affects the organoleptic properties of the salt. Therefore iodised salt is not distinguishable from non-iodised salt and is fully acceptable to the consumers. KI has been used as an additive in salt for about 80 years, and KIO_3 for about 50 years. Iodates are less soluble in water than the iodides, more resistant to oxidation and evaporation, and as they are more stable they do not require the addition of stabilisers. Although more expensive, KIO_3 is preferred to KI, especially in hot and humid climates. However, countries in Europe and North America still use KI. The current levels of iodisation vary from country to country and ranges from 20 to 165 ppm KIO_3 supplying 12–100 ppm iodine [34]. The level of fortification may be changed over time and is calculated using the following equation [45]:

Assuming a requirement of iodine of 200 μg/day and salt consumption is 10 g/day

Level of iodine required is 200/10 = 20 μg/g salt or 20 ppm

Compensation for transit and storage losses	20 ppm
Fixed level of iodisation required	40 ppm iodine
As potassium iodate is: 40 * 1.685[a] = 67 ppm KIO_3	

[a]Ratio of molecular weight of KIO_3/I i.e. 214/127 = 1.685

Iron

Bioavailability of a single iron source is difficult to predict because it can vary considerably due to the enhancing or inhibitory effects of other food components on absorption [46]. With this in mind iron fortification is considered to be a long-term approach to combating IDA.

Characteristics of Iron Compounds Used in Fortification of Foods

The iron compounds used for food fortification have to meet certain requisites related to their bioavailability, absorption mechanism and toxicity [47]. The choice of iron compound depends on its solubility in gastric juice and on the presence of activators or inhibitors [47]. The most common iron fortification compounds can be classified into four groups:

1. Freely water-soluble iron (ferrous sulphate, ferrous gluconate and ferrous lactate)—very bioavailable, however they tend to interact with the fortified food altering its sensory properties e.g. provoking fat rancidity.
2. Poorly water-soluble or soluble in dilute acids (ferrous fumarate, ferrous succinate)—good bioavailability but tend only to be used in solid dehydrated foods.
3. Water-insoluble or poorly soluble forms of iron in dilute acids (ferric orthophosphate, ferric pyrophosphate, elemental iron)—do not change the sensory properties or nutritional value of the food but have low bioavailability.
4. Recently a product containing ferrous sulphate micro-encapsulated with lecithin has been produced. This product has the same bioavailability as ferrous sulphate but the coat of phospholipids keeps the iron from coming in contact with the food vehicle preventing undesirable interactions seen with conventional ferrous sulphate.

Vitamin A

Experiences in developing countries with vitamin A fortification highlight the nutritional benefits that can be gained, but also some of the problems faced by fortification. Vitamin A and pro-vitamin A compounds are highly fat-soluble and when added to fats or oils distribute evenly. All vitamin A compounds are stable in fats and oils as they are protected from the air and hence oxidation is delayed, in addition the absorption of vitamin A is enhanced in the presence of dietary fats. High coverage of populations can be achieved as fats and oils are used directly or indirectly in most diets. In a large number of developed and only a few developing countries vitamin A (average amount 30,000 IU/kg) has been added to margarine for many years. However, the same technology is now being used for cooking oils. An initiative, by Helen Keller International in Benin, Burkina Faso, Côte d'Ivoire, Guinea-Bissau, Mali, Niger, Senegal and Togo aims to supply fortified cooking oil to at least 70% of the population, or 60 million people including 11 million children under age 5, by the end of 2010 [48]. In collaboration with Global Alliance for Improved Nutrition (GAIN), evaluation of the impact of the programmes on children 6–59 months and women of reproductive age in Mali and Côte d'Ivoire is currently underway.

In the early 1970s white refined sugar was identified as a potentially fortifiable food carrier for vitamin A in Central and South America. Tests in Chile [49] and Guatemala [8, 50] found vitamin A fortified sugar to be bioavailable, organoleptically acceptable and stable under ambient humid conditions (90% retention after 6–8 months) and after cooking (85–99% retention in a wide range of products). Continued testing during the 1990s showed 50–85% vitamin A potency after 9 months [51]. Sugar fortification was mandated in Guatemala in 1974, and the twice-yearly nutritional surveillance during the first 2 years provided strong evidence that the programme was achieving an impact on

vitamin A status. Increases in serum retinol were observed in wasted and non-wasted children, indicating the sugar was reaching the most disadvantaged [52]. In addition, breast milk retinol levels rose from a mean of 0.75 to 1.2 μmol/L, which was estimated to provide a dietary increment to the breastfed infant of 2.7 retinol equivalents (RE)/day (~60% increase to infants consuming 600 mL breast milk/day). Unfortunately, sugar fortification in Guatemala was suspended for almost 8 years due to civil conflict, lack of enforcement of the fortification law, a glut in the international sugar market (reduced profits) and a rise in the Swiss franc, which raised the price of the vitamin A [36]. Sugar manufacturers were required by law to absorb the cost of fortification, thus when the fortificant was too expensive, the programme stopped. This example illustrates that to sustain a fortification programme the consumers must ultimately bear the real cost of the fortification. Fortification also ceased in El Salvador, Panama and, to some extent, in Honduras for the same reasons as Guatemala. The sugar fortification programme was restarted in Guatemala in 1987–1988 as a universal programme to fortify all sugar regardless of final destination either for domestic or industrial use [53]. The strategy was selected to ensure there would be no 'cracks' in the system, but it generated opposition from industry because of a 2% price increase caused by the fortification with no clear benefit to the marketing of their products. To overcome the opposition, the sugar fortification law was revised to exempt sugar intended for industrial use. However, producers still have to shoulder the costs of fortifying domestic sugar at a cost of $0.121 US/per person/year [37].

It is essential that fortification programmes are effectively monitored, and QC in sugar mills is necessary to ensure that levels of the fortificant are reached and maintained. Not all of the Guatemalan sugar mills had QC procedures installed, but household surveys reported 96% of households used fortified sugar and 75% of the sugar had a vitamin A content greater than 5 mg/kg sugar [54]. However, when plasma retinol levels were measured as an indicator of vitamin A status, children aged 12–24 months were still showing biochemical VAD. The low sugar intake by infants aged 6–24 months meant the nutritional goal of 50% of the recommended dietary allowance (RDA) could not be achieved [53]. Complementary measures such as promotion of breastfeeding, development of complementary foods rich in vitamin A, and periodic (at least every 6 months) supplementation with vitamin A capsules were implemented for these infants. A survey by the International Eye Foundation in 1996 reported that the distribution of vitamin A capsules to infants brought the number of children reaching the RDA to almost 100% [55].

Nutrition in the Infant

Infants and Children Less Than 5 Years

For infants, a diet of exclusive breast milk is an effective way of preventing micronutrient deficiencies for the first 6 months of life and continuation of breastfeeding into the second year should be promoted. Furthermore, all lactating women should be encouraged to consume a healthy and varied diet so that adequate levels of micronutrients are secreted in their milk [25]. After the age of 6 months, it is important that complementary foods provided to breastfed infants are as diverse and as rich in micronutrients as possible [31], since infants reach a critical stage when there is increased demand for higher energy and iron for growth. The calories expected from breast milk during the second year of life comprise about 30–40% of the total dietary intake. Therefore the Pan American Health Organization (PAHO)/WHO has defined the energy needs from complementary foods for a breast fed child with an average intake of breast milk as 200 kcal/day for a 6–8.9 month child, 300 kcal/day for a 9–11.9-month-old child and 550 kcal/day for a 12–23.9-month-old child [56]. Non-breast fed infants and young children will require all their nutrients from complementary foods and will need between 600 and 900 kcal/day according to age, i.e. 600 kcal/day for infants 6–8 months, 700 kcal/day for infants 9–12 months and 900 kcal/day for 12–23.9-month-old children.

Fortificants in Infant Complementary Foods

Fortified complementary food is considered to be a cost-effective way to fulfill the nutritional micronutrient requirements of infants >6 months of age. Fortification of complementary foods can be done commercially or at home using, for example, MNP sachets containing dry MNP that can be sprinkled onto any semi-solid or solid food that is ready for consumption. In developed countries, and where it can be afforded in developing nations, manufactured infant cereals, which meet the solid food requirements, can be used as a complementary food.

Home fortification is recommended when the natural diet is poor in diversity e.g. the family might be too poor to buy more than staple foods, or because the normal foods prepared for the child are poor in quality, such as watery porridges which are low in micronutrient content, or the bioavailability of the micronutrients is poor due to inhibitors in the diet (e.g. phytates, tannin) [57]. Evidence from many countries suggests that the period of highest vulnerability is 6–23 months of age when food variety and quantity are limited. Children 24–59 months of age may also be at high risk of inadequate dietary intake of some nutrients. Home fortification increases micronutrient intake, which leads to an improvement of micronutrient status, and improved child health with potential to reduce morbidity and mortality, improve growth and cognition, appetite and other functional outcomes [57]. Currently, most countries use an MNP formulation containing 15 micronutrients, (vitamins A, C, D, E, B1, B2, B6, B12, niacin, folate, iron (lipid-encapsulated), zinc, copper, selenium and iodine) which is designed to provide one Recommended Nutrient Intake (RNI) of each micronutrient per sachet for children 6–59 months old.

Home fortification is best introduced as part of an infant and young child-feeding strategy by providing guidance and counselling on exclusive breastfeeding for the first 6 months of life, and continued breastfeeding thereafter together with complementary feeding combined with MNP. Providing MNP can be an incentive to come to information sessions about infant and young child feeding and contact with the health care sector or community-based services allows women to discuss health, breastfeeding and complementary feeding of young children. The ‘Avon Ladies’ system of selling sachets of Sprinkles has been successfully piloted in Kenya, where as part of the Safe Water and AIDS Project, an organised network of community-based, self-help groups, who were trained in health and business practices and received microcredit went from house-to-house selling a variety of products including Sprinkles [58]. As result of the sales, even when the caregiver only purchased Sprinkles ≤2 times/week, there were reductions in anaemia, iron deficiency and VAD in children aged 6–36 months after 12 months of use with no increase in hospitalisations or clinic visits due to malaria [58].

Micronutrient-dense fortified spreads for home fortification have been found to be very popular with children and include small-quantity LNS (<20 g/day, equivalent to ≤120 kcal/day). Studies in the Democratic Republic of Congo indicated that both MNP (Sprinkles) and LNS (Nutributter) were both products that were highly acceptable, with similar beneficial effects and very few negative effects reported [59]. In addition to improved nutrition and health, mothers cited benefits including increased interaction and more playfulness and 98% of mothers reported a willingness to buy Sprinkles daily for US$0.03 and 95% would buy Nutributter daily for US$0.05.

Iron and Complementary Foods

Various iron compounds can be used to fortify complementary foods, e.g. ferrous sulphate, ferrous fumarate and electrolytic iron [60] and selection of the iron fortificant is dependent on the food vehicle. The colour of iron compounds is often a critical factor when fortifying lightly coloured foods. The use of more soluble iron compounds such as ferrous sulphate often leads to the development of off-colours and off-flavours due to reactions with other components of the food material, but they have

the advantage of being highly bioavailable. The use of less effective iron sources may satisfy label claims and regulations but there is a question over their bioavailability. The most commonly used fortificants are elemental iron, ferric pyrophosphate, ferric orthophosphate, ferrous succinate and ferrous fumarate. All have lower bioavailability than ferrous sulphate. The best researched of the fortificants is elemental iron which is used for infant cereal fortification in the USA. Ferrous fumarate is often used in corn soy-milk and wheat-soy blend as the reddish-brown colour of fumarate is compatible with the yellowish-brown colour of the vehicles. Ferrous succinate appears to be just as suitable as fumarate without causing fat oxidation and discolouration [61]. Hence the main technological problems with iron fortification of infant foods concerns colour, bioavailability and off-flavour due to fat oxidation and to reduce the technological problems; encapsulation of ferrous sulphate has been underway for some time.

Another iron compound, sodium iron ethylenediaminetetraacetate (NaFeEDTA) has been recommended for food fortification of staples and home fortificants [60], but NaFeEDTA is more expensive compared to the other iron fortificants, however, the extra expense can be offset by its higher bioavailability, especially where diets are high in phytates.

Safety

Iron Fortification and NaFeEDTA

The Codex Alimentarius (2006) sets the minimal fortification level of iron in infant foods at 1 mg iron/100 kcal. Fortification levels vary from country to country: in the US the upper limit is 3 mg iron/100 kcal, the maximum level in the UK is 1 mg iron/100 kcal and in France it is 1.5–2 mg iron/100 kcal [34]. However, in Europe lower levels are common with more efficient use of iron from foods with lower fortification levels.

There have been concerns over the safety of overloading with iron or EDTA from NaFeEDTA compounds. Data summarised by the Joint FAO/WHO Expert Committee on Food Additive JECFA states that once in the gastrointestinal tract, the iron in NaFeEDTA dissociates from the chelate and is released into the common non-haem iron pool before absorption, and only a very small fraction of the EDTA complex (less than 1–2%) is absorbed intact and this is rapidly and completely excreted via the kidneys in the urine [31]. JECFA stated that the human body maintains iron levels through down-regulating systems, which control the amount of iron absorbed and protects it against the possibility of iron overload [62]. Also, in iron-replete subjects, non-haem iron absorption is reduced to a larger extent than the absorption of haem iron. This tight regulation of non-haem iron absorption is of importance, given that iron from NaFeEDTA will join the non-haem iron pool before absorption. These findings support the conclusion that dietary iron fortification with NaFeEDTA does not increase the risk for iron accumulation beyond normal physiological requirements in iron-replete individuals. The JECFA Committee concluded that NaFeEDTA is suitable for use as a source of iron for food fortification to fulfill the nutritional iron requirements, provided that the total intake of iron from all food sources including contaminants does not exceed the provisional tolerable daily intake of 0.8 mg/kg body weight [62]. Additionally, the total intake of EDTA should not exceed acceptable levels, also taking into account the intake of EDTA from the food additive use of other EDTA compounds.

The acceptable daily intake (ADI) for NaFeEDTA is based on body weight, and body weight increases rapidly for infants between 6 and 24 months of age. The recommendations for complementary foods by age are grouped as follows: 6–8 months, 9–11 months and 12–23 months. While the youngest children have a higher iron requirement, their weights are lower, and thus this puts them at greater risk of exceeding the ADI of 1.9 mg EDTA/kg body weight for 95% of 6–8-month-old infants. The daily iron dose from NaFeEDTA in fortified complementary foods should be set between 2.2 and

1.8 mg in countries where there is a prevalence of underweight among 6–8-month-old infants between 5% and 40%, respectively [63]. If 2 mg of iron were given to all 6–8-month-old infants, the percentage exceeding the ADI for EDTA would be <10% for populations with <30% of children who are underweight, which is the case for many countries. To ensure EDTA levels are below the ADI for infants 6–8 months of age, 2 mg of iron from NaFeEDTA could be used to fortify one daily serving of complementary food and an additional source of iron (e.g. ferrous sulphate) could be included to increase the iron dose to desired fortification level.

Possibly a more important reason to minimise iron fortification is the effect of iron on the absorption of copper and zinc as iron will compete with copper and zinc for absorption. However, a number of studies have shown no effect of iron fortification of infant cereals on zinc absorption [64–66].

Vitamin A

For long-term daily intakes, the Institute of Medicine's Food and Nutrition Board (IOM/FNB) have defined Tolerable Upper Intake Levels (ULs) for vitamin A, as follows [67]:

- 600 μg/day for children <3 years
- 900 μg/day for children 4–8 years
- 1,700 μg/day for children 9–13 years
- 2,800 μg/day for adolescents
- 3,000 μg/day for both women at risk of becoming pregnant and adult men

The UL for children, i.e. the highest level of daily vitamin A intake that is likely to pose no risk of adverse health effects, is a factor of 10 lower than the level of intake at which any toxic effect has been observed in this age group. The ULs as defined by the FNB are based on data obtained from healthy populations in developed countries. They may not apply, nor are intended to do so, to communities of malnourished individuals that receive vitamin A prophylactically, either periodically or through fortification, as a means of preventing VAD. A recent paper has indicated that the risk of excessive vitamin A consumption from fortified foods in women and young children is likely to be negligible [68] but that it is nevertheless a matter about which government bodies should be aware as many foods are increasingly being fortified with vitamin A.

Iodine

Salt iodisation is usually very safe. However, acute, excessive increase in iodine intake can increase the risk of iodine toxicity in sensitive people—iodine-induced hyperthyroidism (IIH). Outbreaks of IIH have been reported in the Democratic Republic of Congo and Zimbabwe in populations in which excessively iodised salt has been introduced after the population had been severely deficient for a long period of time [69]. Also, a recent publication from China using national monitoring data collected between 1995 and 2009, showed that since the implementation of USI, the median iodine content in edible salt increased from 16.2 mg/kg in 1995 to 42.3 mg/kg in 1999, then declined to 30.8 mg/kg in 2005 and was maintained at this level (31.3 mg/kg) in 2009 [70]. However, the median urinary iodine excretion level for children aged 8–10 years was classified as excessive (>300 μg/L urine) in surveys in 1997 and 1999 and more than adequate (200–299 μg/L) in 2002 and 2005, suggesting that although three adjustments to the standard of iodine content in edible salt were made, the current content of salt iodization was still probably too high. The recommendation in the paper was that the iodine content in edible salt could be lowered, and possibly adapted to local specific conditions such as water iodine

content and the average daily intake of salt among the population in order to achieve a balance between preventing deficiency and reducing the risk of excessive intake.

Conclusions

Optimal feeding of infants and young children is now one of the top priorities of the nutritional world and the 'first 1,000 days' is recognised as a 'window of opportunity'. Often complementary foods are traditionally prepared by families and are watery porridges with little micronutrient content. In the international community micronutrient fortification of complementary foods, either using industrially produced infant foods or fortified products for use at home is currently accepted as the option to ensure that such young children get a balanced diet during these important years of development.

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Chapter 26
Amino Acid Needs and Metabolism in Preterm and Term Infants

Willemijn E. Corpeleijn, Marijn J. Vermeulen, and Johannes B. van Goudoever

Key Points

- It is generally recognized that optimal nutrition to (preterm) neonates is of the highest importance.
- Especially in preterm infants, AA supply plays a crucial role in the clinical outcome. However, the exact parenteral and enteral AA requirements remain largely unknown.
- This is especially true for infants with a birth weight and gestational age on the limit of viability who are now surviving at an increased rate.
- We stress the need for more studies assessing the requirements of neonates with attention to the interactions of specific AA and other nutrients and under different clinical conditions.
- The use of stable isotopes has proven to be extremely useful in such studies, potentially in the combination with emerging technologies for AA research such as metabolomics, proteomics and transcriptomics.

Keywords Amino acids • Metabolism • Human milk • Preterm infants

Introduction

Organic substances that consist of both an amino group ($-NH_2$) and an acidic carboxyl group ($-COOH$) are named amino acids (AA). Over 300 amino acids are known to exist in nature but only 20 amino acids serve as the building blocks of protein in humans and animals. Proteins represent an important part of all cell membranes and intracellular matrix but also enzymes, blood transport molecules and hormones are proteins. All 20 amino acids must be present in the body in appropriate amounts to allow for protein synthesis and thus normal cell function and body growth. Disturbances in the metabolism of any amino acid, as seen in inborn errors of metabolism, will inevitably lead to disease, impairment or even death when left untreated. Of the 20 amino acids, 8 are called essential amino acids, as those cannot be synthesized by the human body and must therefore be provided in sufficient amounts by the diet. AA that can be synthesized by the body in sufficient amounts are called non-essential

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R.R. Watson et al. (eds.), *Nutrition in Infancy: Volume 1*, Nutrition and Health,
DOI 10.1007/978-1-62703-224-7_26,

Table 26.1 Essential, conditionally essential and non-essential amino acids

Essential	"Conditionally" essential	Non-essential amino acids
Isoleucine	Cysteine	Alanine
Leucine	Tyrosine	Aspartate
Valine	Arginine	Serine
Lysine	Glutamine	Asparagine
Methionine	Glycine	Glutamate
Phenylalanine	Proline	
Threonine		
Tryptophan		
Histidine		

AA. Some amino acids can be sufficiently synthesized by the body under normal conditions, but fall short under conditions where the utilization of a specific AA exceeds synthesis (e.g., sepsis) or when synthesis pathways are underdeveloped (e.g., after premature birth). These amino acids are called conditionally essential or semi-essential AA (see Table 26.1). In this chapter, various methods to study AA and protein metabolism are reviewed. This is followed by discussions on the general consequences of AA under- and overnutrition in preterm infants and differences in AA metabolism during parenteral and enteral nutrition. Lastly, parenteral and enteral AA administration is discussed. Some of the non-protein AA, such as taurine or citrulline, play important roles in cell signaling and metabolism, but this is outside the scope of this chapter.

Methods to Study Protein and AA Requirements

Providing optimal nutrition to preterm infants requires insight in the nutritional needs. Determination of the optimal protein and AA intakes in preterm infants is complicated by the fact that requirements widely vary between patient groups depending on gestational age and body composition (as seen in small for gestational age infants) and on the clinical state of the patient (e.g., higher needs during sepsis). Also the balance and interaction between amino acids and other nutrients such as carbohydrates and vitamins influence the protein needs. Furthermore, the requirement for individual AA is affected by the concentration of the other AAs, by sparing or competition in biological processes. Defining protein or AA requirements of (preterm) neonates is notoriously difficult and has been attempted using several techniques.

For healthy term infants, recommended daily intakes of protein and individual AA are mostly based on the content of human milk as this is considered the most optimal nutrition for this group of newborns. Requirements for this group of infants can be met in the first 6 months of life by breast milk alone. However, the amount of protein that is provided to a breastfed infant varies markedly as a function of the duration of lactation, providing >2 g/kg to the infant in the first weeks of life to around 1.5 g/kg at 4 months of age [1]. Infants that are born preterm have significantly higher protein requirements when compared to term infants and the optimal ratio in which individual AA should be present in the diet is not necessarily the same as is found in human milk.

A method often used in the past to estimate the protein requirement of preterm neonates is the factorial approach which considers the protein requirement to be equal to the sum of the obligatory nitrogen losses (in e.g., urine and feces) plus the amount required for growth. An estimate of the required amount of nitrogen for growth is based on the composition of tissue acquired during fetal growth, as analyzed in the carcasses of deceased fetuses. An important disadvantage of this technique is that these fetuses varied in body weight and may have been growth restricted or otherwise compromised and therefore poorly reflect the need of healthy fetuses. A correction should be made for the

incomplete utilization of dietary protein. Empirical approaches are based on measuring biochemical and physiological responses or anthropometric changes upon graded intakes of a specific nutrient. An empirical method that is often used is nitrogen balance, in which the difference between nitrogen intake (from the test diet) and excretion (in urine, feces, skin and miscellaneous losses) is calculated. When intake exceeds excretion, an infant is considered to be in an anabolic state. An advantage of this method is that it is non-invasive, but there are also several drawbacks. Due to problems with collecting all feces and urine from diapers and loss via vomiting, nitrogen excretion is easily underestimated, while intake is often overestimated. Furthermore, dermal losses are difficult to measure as these also vary with the environmental condition, e.g. incubator conditions.

The protein needs of premature neonates have also been determined by numerous clinical studies assessing diets consisting of modified human milk or specially designed preterm formulas, with levels of protein intake ranging from 2 to 8 g/kg/day. Subsequently, the effects on growth and a variety of biochemical parameters have been determined [2]. The results show that an enteral protein intake around 3.5 g per kg of body weight per day results in weight gain and nitrogen retention rates that resemble or slightly exceed intra-uterine rates [2] and it is assumed that this amount will approximate the requirement of the healthy preterm infant. Recommended intakes of, for example, the ESPGHAN committee on Nutrition are 4.0–4.5 g/kg/day for infants up to 1,000 g and 3.5–4.0 for infants between 1,000 and 1,800 g [3], taking into account that development of protein deficit is common in the first few weeks of NICU admission and needs (partial) compensation [4]. Furthermore, an intake slightly over the requirement has not shown to have detrimental effects but small deficits will already impair growth and development.

Although the debate often focuses on the protein requirement of (preterm) neonates, it is important to realize that organisms in fact not have a protein requirement but an AA requirement. So how should we determine the optimal AA intakes for preterm infants? In the 1970s, Snyderman et al. defined requirements of individual AA for (preterm) infants by feeding them a diet containing 18 synthetic L-amino acids. After an adaptation period to this diet, the test AA was eliminated and then reintroduced stepwise until normal growth was obtained. With this approach, they studied requirements of various AA [5–11] but it must be noted that the infants studied varied widely in gestational and postnatal ages and the number of infants was very low. Snyderman et al. have also compared these values with data on intakes of individual AA from a cow's milk formula diet of 2 g/kg/day what was assumed to be adequate [12]. However, more recent studies show that an adequate diet contains a substantially higher amount of protein, suggesting that their subjects were in fact undernourished. The factorial approach can also be used to study individual AA requirements, as has been done by Widdowson et al. [13]. They provided data on the amount of each AA that is accreted during normal intra-uterine development. With these data, requirements can be calculated by adding accretion rates to the maintenance protein needs. Also here a correction should be made for the incomplete retention of dietary AA. This method relies heavily on the assumption that AA for maintenance are used in the same ratio as the AA for tissue growth. Another major drawback of this method is that differences in physiology between intra-uterine and extra-uterine life are not taken into account. It must be concluded that after almost a century of scientific research to elucidate the optimal AA intake of preterm neonates, the requirements remain unclear. The importance of determining optimal intakes of individual amino acids in order to design preterm formula and breast milk fortifiers that meet all the requirements of the preterm infants without causing unfavorable effects due to protein overload must be emphasized.

In the absence of other data, the Life Sciences Research Office (LSRO) Expert Panel on Assessment of the Nutrient Requirement of (Preterm) Infant Formula defined the minimum AA content (in mg/100 kcal) as the amount of each AA present in 1.7 g/100 kcal of human milk proteins for term formula and 2.5 g/100 kcal for preterm formula. A similar approach is being followed by the ESPGHAN in their position statement on infant formula and the European Union commission directive on infant formula. This approach relies on the assumptions that the protein requirement of preterm infants approximates 2.5 g/100 kcal and that the ratio of the different AA found in human milk are the optimal

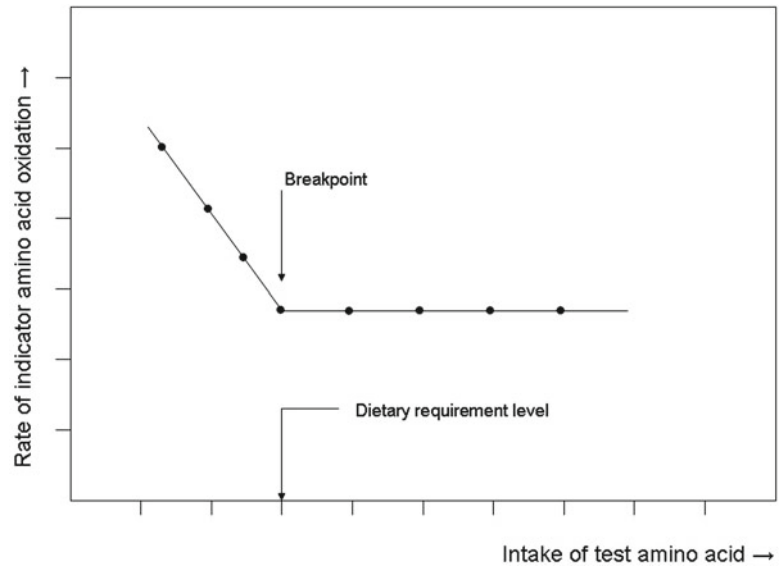

Fig. 26.1 AA Breakpoint

ratio for preterm infants [14]. Estimates of AA requirements vary considerably between the techniques that are described here as can been seen from Table 26.1. So are there other options to determine requirements of total protein and individual AA? Tracer studies with stable isotopes have proven to be very useful in nutritional research. Stable isotopes are molecules that have an extra neutron in the nucleus of one or more of their atoms. As the extra neutron does not affect the chemical characteristics, the labeled molecules are metabolized by the body in exactly the same way as unlabeled molecules. Mass-spectrometry techniques can differentiate between a normal isotope and a stable isotope as the latter is slightly heavier. So when stable isotopes of, for example, amino acids or glucose are administered intravenously or intragastrically, their metabolism can be studied by taking samples from blood, urine or exhaled breath. Differently labeled stable isotopes of all amino acids are commercially available and this creates the opportunity to investigate AA metabolism extensively. However, when studying (preterm) infants, the volume per sample and the number of blood samples that can be taken for research purposes is limited due to the small circulating volume.

A stable isotope technique that has been used successfully and does not require blood sampling is the Indicator Amino Acid Oxidation Method (IAAO). This technique is based on the fact that if one indispensible AA is not being supplied sufficiently, protein synthesis comes to a hold. Since AA cannot be stored by the body, all other amino acids in excess will be oxidized to CO_2. When diets with a varying amount of the test AA are administered to infants, the oxidation of the other AA will be higher when the test AA is insufficiently available and lower when it is sufficiently available. Oxidation rate can be measured when concomitantly with the test diets an isotopically labeled AA (the indicator amino acid) is administered and labeled CO_2 in breath or blood is determined. The lowest measured oxidation of the indicator AA indentifies when AA are being utilized to the greatest extent. See Fig. 26.1. This point, named the breakpoint, reflects the minimum requirement of the test AA. Recently, this method was used by Huang et al. to study lysine requirement of term infants [15]. The results of the study show that the breakpoint lies at a lysine intake of 130 mg/kg/day (95% confidence interval 76.3–183.7 mg/kg/day). This is somewhat higher than the requirement found by Holt and Snyderman (90–105 mg/kg/day) but substantially lower than lysine content of current term formulas (172–256 mg/kg/day). Studies determining the requirements of the other AA in term and preterm infants are ongoing.

General Consequences of Over and Under AA Administration

During early life, much of the nutrients that are being acquired by an individual are being employed to accomplish brain and body growth. A period of over or under nutrition during this critical phase of development may have lifelong effects on physiology. Impaired postnatal growth has been associated with a poorer neurodevelopmental outcome and an increased risk of stroke in adulthood. Rapid weight gain in infancy on the other hand has been associated with obesity in later life. Providing optimal nutritional support to all newborns and ensuring appropriate growth patterns is therefore of the highest importance. This is specifically true for infants that are born preterm, as these infants are born during a phase of rapid brain growth. According to Heird et al., the protein and energy reserves of a 1,000 g infant are only sufficient to survive for approximately 5 days during total starvation [16]. When no exogenous protein or AA are administered to these infants, protein will be excreted and development comes to a hold. While its healthy intra-uterine counterpart receives via the umbilical cord a continuous and large supply of amino acids and other substrates mandatory for optimal development, the preterm infant is dependent on exogenous supply. The aim of providing nutritional support to preterm neonates is not only to achieve growth rates comparable to intra-uterine growth but also to let them have a functional outcome that is comparable to healthy term born infant [3, 17]. Quantity and quality of the nutrients supplied in the first weeks postpartum are among the chief determinants of long-term functional outcome, with a crucial role for the protein and AA content. Even a short period of AA under nutrition can have substantial detrimental effects on brain development. Stephens et al. showed an association of administered amino acids in the first week of life and mental development at 18 months corrected age. Every additional gram of amino acids as intake in the first week of life corresponded to an 8.2-point increase on the Mental Developmental Index [18]. Nutritional support for the preterm infants has been shown to be problematic for various reasons such as the high complication rate of intravenous nutrient administration and low tolerance to enteral substrates due to immaturity of the gastrointestinal tract.

As individuals AA have very distinct functions [19], a (relative) deficiency of a particular AA will result in a different clinical feature when compared to a deficiency of another AA. Deficiencies do not always lead to faltering growth but may also result in decreased concentrations of anti-oxidants, hormones, neurotransmitters, etc. For example, glutathion the most abundant intracellular anti-oxidant is a tripeptide, consisting from glutamate, glycine and cysteine. Cysteine is considered to be the rate limiting component of glutathione synthesis. In the past, it was often suggested that the enzyme cystathionase, crucial in the final step of the transulfaration pathway in which cyste(i)ne is formed from methionine, is lacking in preterm infants and thereby making cyste(i)ne an essential AA for this group of patients. Although evidence is accumulating that preterm infants are able to synthesize cyste(i)ne [20, 21], demands may still exceed synthetic capacity. Low glutathione levels may predispose the preterm infants to free radical diseases such as retinopathy of prematurity (ROP) and bronchopulmonary dysplasia (BPD), especially in infants that are mechanically ventilated with high oxygen fractions. However, most AA solutions do not contain cyste(i)ne due to difficulties with solvability and stability. Administration of high-dose cysteine (81 mg/kg/day) to parenterally fed preterm neonates has shown to be safe but failed to show an increase in glutathione synthesis rate compared to a lower dose (45 mg/kg/day) [22]. The study was not powered to detect a change in incidence of, for example, ROP or BPD. Therefore, it still has to be demonstrated if supplemental cyste(i)ne administration has clinical benefits in the parenterally fed preterm infant. However, at the time it seems appropriate to continue provide cysteine in parenteral nutrition. Cysteine might also decrease the need for methionine, which is suggested to be hepatotoxic in high concentrations.

Excess intake of protein or AA may lead to toxic AA concentration due to immaturity of degradation pathways and a reduced kidney function for nitrogen excretion. Studies from the 1960s and 1970s do report adverse outcomes such as lethargy, poor feeding [23], lower IQ scores [24] and a trend toward

higher incidence of mortality [25] in infants fed high amounts of protein (> 6 g/kg/day). Intake in these studies was almost double the contemporary recommended daily intake.

Enteral Versus Parenteral Intake

The AA requirement depends on the route of administration, due to metabolism in the GI tract by host cells and microbiota. The intestinal epithelium consists mainly of absorptive enterocytes and for 25% of other types of specialized cells with important functions in innate immunity and digestion. For example, goblet cells synthesize and secrete large gel forming glycoproteins, called mucins, that form a physical barrier against luminal pathogens. Paneth cells are specialized secretory cells that secrete antimicrobial peptides. The functioning of these cells requires energy and substrates for secreted products. This is reflected by the fact that the portal drained viscera (PDV), although only accounting for 6% of total body weight, can be responsible for up to 35% of total energy expenditure. When nutrients are administered enterally, the intestine is the first organ that has access to the supplied AA and its needs will be met first. Therefore, the intestinal utilization rate of AA influences the availability of AA to the rest of the body and thereby whole body growth. From studies performed in animals and human neonates, we know that the intestine sequesters both essential and non-essential amino acids from the diet. The possible metabolic fates of the sequestered AA are protein synthesis (e.g., for incorporation into mucosal cellular proteins), intermediate metabolism (including conversion into other amino acids via transamination) and irreversible oxidation to CO_2 and ammonia. Amino acids that are incorporated into new glycoproteins could become systemically available after recycling. The percentage of the dietary intake that is sequestered by the gut differs substantially between the different amino acids. In preterm neonates, the non-essential AA glutamine, glutamate and aspartate are oxidized extensively by the PDV and almost none of these AA reach the systemic circulation [26–28]. Van der Schoor et al. assessed uptake of the essential AA threonine by the gut during partial and full enteral feeding [29]. They found that during partial enteral feeding, the PDV sequester approximately 80% of enteral threonine intake, whereas during full enteral feeding, approximately 70% of threonine is sequestered. Interestingly enough, only a very small amount of total threonine flux (6%) was used as energy source. As threonine is not incorporated into constitutive cellular proteins to a great extent, it is likely that it is used for the synthesis of secretory proteins. In a healthy intestine, the mucosa is protected by a complex network of glycoproteins such as mucins. Mucin molecules have a backbone that is very rich in threonine. This shows the importance of feeding preterm infants an enteral diet that contains sufficient threonine but also highlights the fact that threonine concentrations in parenteral AA solutions most likely are in excess of requirement. In contrast, for another essential amino acid, lysine, the first pass utilization rate is relatively low. During partial and full enteral feeding, preterm infants utilize only 32% and 18% of the administered lysine, respectively [30]. From the preceding, it can be concluded that the intestine is an important modulator of whole body AA fluxes and bypassing the intestine during TPN will result in a lower AA requirement but also in an altered composition of the required AA mixture when compared to enterally fed infants.

Another important difference between parenteral and enteral AA administration is the circumvention of intestinal bacteria during parenteral nutrition. In adults, 25% of the urea that is excreted in the colon is utilized by bacteria for the formation of free AA which come subsequently available to the host. Studies in healthy term infants suggest that around 3% of milk urea is incorporated in serum proteins. Bacterial colonization is aberrant and delayed following preterm birth and the frequently used antibiotics have dramatic effects on the composition of the intestinal microbiota. The role of the intestinal microbiota in the whole-body AA metabolism in this group of patients is still subject of research.

Intravenous AA Administration

The unfounded fear for toxicity of AA solutions has been deeply rooted in clinical practice and makes clinicians prudent to start AA supplementation directly after preterm birth in an adequate dosage. It has become clear that the metabolic disarrangements that were seen in the past in infants receiving relatively low amounts of intravenous AA were not so much caused by the AA themselves but rather by the manufacturing process of these solutions [31]. From the studies by van den Akker et al., we have learned that the fetus of 30 weeks has a higher albumin synthesis rate compared to the term fetus, indicating that the fetal liver is capable of the synthesis of large amounts of albumin [32]. And although results cannot completely be extrapolated to the age matched preterm infant, it is likely that at least part of the common hypoalbuminemia after preterm birth is a result of inadequate AA supply. Modern AA solutions can be given safely directly after birth up to around 3.5 g/kg/day and there is no scientific basis to start with a lower dosage and increase stepwise. Parameters used to monitor tolerance include urea concentration and sometimes ammonia. Reference values for preterm neonates are unknown but urea reference values in the fetus range from 7.5 to 14.3 mmol/L (corresponding blood urea nitrogen: 21–40 mg/dL). However, cut-off values for discontinuing or decreasing parenteral amino acids are much lower.

Composition of intravenous AA mixtures currently available for the pediatric population varies tremendously between the different manufacturers, as shown in Table 26.2. This reflects the lack of consensus on the requirements. Although all essential amino acids are present in all solutions listed, some may contain insufficient amounts of the conditionally essential AA. In order to make the deficient AA available and to let protein synthesis continue, the body will increase proteolysis. Consequently, also other AA will become available in excess and since these cannot be stored, they are inevitably disposed through the process of oxidation, which results in elevated urea levels. Table 26.2 shows that

Table 26.2 Amino acid concentrations of commercially available parental AA solutions (g/100 g AA)

Amino Acid	Primene 10% Baxter	Travasol 10% Baxter	FreAmineIII 10% B. Braun	TrophAmine 10% B. Braun	Aminoven 10% Fresenius Kabi	Vaminolact 6.5% Fresenius Kabi	Aminosyn-PF 10% Fresenius Kabi	Novamine 10% Hospira
Essential								
Isoleucine	6.7	6.0	6.9	8.2	5.0	5.5	7.6	5.0
Leucine	9.9	7.3	9.1	14.0	7.4	10.8	11.9	6.9
Valine	7.6	5.8	6.6	7.8	6.2	5.5	6.6	6.7
Lysine	10.9	5.8	7.3	8.2	9.3	8.6	6.8	7.9
Methionine	2.4	4.0	5.3	3.4	4.3	2.0	1.8	5.0
Phenylalanine	4.2	5.6	5.6	4.8	5.1	4.2	4.3	6.9
Threonine	3.7	4.2	4.0	4.2	4.4	5.5	5.1	5.0
Tryptophan	2.0	1.8	1.5	2.0	2.0	2.2	1.8	1.7
Histidine	3.8	4.8	2.8	4.8	3.0	3.2	3.1	6.0
Conditionally essential								
Cysteine	1.9	0.0	0.0	0.1	0.0	1.5	0.0	0.0
Tyrosine	0.9	0.4	0.0	2.3	0.4	0.8	0.6	0.3
Arginine	8.4	11.2	9.5	12.2	12.0	6.3	12.3	9.8
Glutamine	9.9	0.0	0.0	5.0	0.0	10.9	8.2	5.0
Glycine	4.0	10.3	14.0	3.6	11.0	3.2	3.9	6.9
Proline	3.0	6.8	11.2	6.8	11.2	8.6	8.1	6.0
Non-essential								
Alanine	7.9	20.7	7.1	5.4	14.0	9.7	7.0	14.5
Aspartate	6.0	0.0	0.0	3.2	0.0	6.3	5.3	0.0
Serine	4.0	5.0	5.9	3.8	6.5	5.8	5.0	3.9

arginine concentration in TPN varies widely between the different AA solutions and might be below requirements in some solutions. Arginine is considered to be a conditionally essential AA for TPN fed (preterm) neonates, with an important role in a variety of neonatal diseases. For example, low arginine levels will hamper nitric oxide formation, potentially leading pulmonary hypertension. In addition, arginine is an essential substrate in the urea cycle, responsible for the detoxification of neurotoxic ammonia. Enhanced protein degradation and the subsequent oxidation of the surplus of other released AA might be even more unfavorable in the absence of sufficient arginine, causing a vicious circle leading to severe hyperammonaemia. This effect has been shown in TPN fed piglets fed an arginine free solution who developed hyperammonaemia rapidly after the initiation of this diet. When this diet was administered intragastrically, no metabolic arrangements are as enterocytes are the main producers of arginine [33]. This stresses the need of supplying sufficient amounts of arginine to infants that are exclusively TPN fed as it might promote tolerance to TPN.

Not only the amount but also the ratios in which certain AA are administered should be considered, as many AA share (and compete for) degradation pathways or transporters across the blood brain barrier. For example, the large neutral amino acids (LNAA), that is, valine, methionine, isoleucine, leucine, tyrosine, histidine and tryptophan, share a common transporter across the blood brain barrier and therefore their availability for brain growth and function depends on the concentration and ratio in which they are present in the plasma. The synthesis of important neurotransmitters such as serotonine is dependent on the presence of the non-essential AA tyrosine or its precursor the essential AA phenylalanine. Tyrosine is poorly soluble and most TPN solutions contain little or no tyrosine. Although the preterm infant is capable of hydroxylating phenylalanine to tyrosine, demands may still exceed capacity. It has been suggested that phenylalanine is metabolized differently when administered parenterally [34]. A low availability of tyrosine might cause a reduced production of catecholamines in the brain which in turn might hamper development of the rapidly growing brain. However, Lopez et al. showed that a short period of TPN in preterm rabbits caused a low tyrosine brain concentration without evident effects on brain catecholamines in their study [35]. They do mention that the effect and impact of a suboptimal tyrosine intake can be better studied by evaluation of the catecholaminergic regions of the brain or over a longer period of TPN. Although such studies have not been performed in human neonates for obvious reason, it is known that sleep patterns in human neonates are influenced by AA content of the enteral diet [36]. It is likely that a period of low serum concentrations of conditionally essential AA has a substantial negative influence on brain development.

To ensure for a balanced protein diet, one should also care for sufficient supply of energy in the form of carbohydrates or fat must during TPN to avoid the use of AA carbon skeletons for energy generation.

Composition of Enteral Nutrition

When composing an enteral diet, both the digestibility of the proteins and the AA composition should be taken into account as they may alter the protein requirement as stated in the previous paragraph. Fresh milk of the own mother is considered to be the optimal nutrition for neonates, also for preterm neonates. If milk of the own mother and donor milk are both not available, preterm formula may be used as an alternative. The protein fraction of infant formula is derived from cow milk. Milk proteins consist of two major classes: the whey proteins and the casein proteins. Especially the casein fraction of cow's milk shows relatively little homology to human casein. The dominant casein protein in bovine milk, α-casein (50–55% of total casein), is totally absent in human milk. Also the ratio in which the whey and casein proteins are present in the milk differs between species; human milk has a whey-to-casein ratio of 80:20 (colostrums) to 60:40 (mature milk), whereas bovine milk has a ratio of 20:80. As a result, the AA profiles that become available after digestion of cow milk and human

milk protein differ substantially. Low birth weight infants fed casein predominant protein, whey dominant protein or human milk protein all show similar growth rates. Nevertheless, the whey-to-casein ratio in most formulas has been adapted to resemble that of human milk. One of the benefits could be that infants fed a whey dominant formula have a somewhat higher cyste(i)ne intake compared to infants fed casein dominant formula. A study of Raiha et al. [37] also suggests that metabolic acidosis is less common in infants receiving a whey predominant formula but this could not be confirmed by others [38].

It must be noted that pasteurized human donor milk as well as fresh preterm human milk will not meet the high protein requirements of a premature infant. Extra protein, but also vitamins, trace elements and minerals, need to be added in the form of a nutritional supplements named fortifiers to achieve growth rates resembling those in utero.

Conclusions

It is generally recognized that optimal nutrition to (preterm) neonates is of the highest importance. Especially in preterm infants, AA supply plays a crucial role in the clinical outcome. However, the exact parenteral and enteral AA requirements remain largely unknown. This is especially true for infants with a birth weight and gestational age on the limit of viability who are now surviving at an increased rate. We stress the need for more studies assessing the requirements of neonates with attention to the interactions of specific AA and other nutrients and under different clinical conditions. The use of stable isotopes has proven to be extremely useful in such studies, potentially in the combination with emerging technologies for AA research such as metabolomics, proteomics and transcriptomics [39].

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Chapter 27
Perinatal Taurine Exposure on Infants

Sanya Roysommuti and J. Michael Wyss

Key Points

- Taurine is the physiologic beta-amino acid found in all human cells and is the common composition in maternal and infant nutrition formulas.
- Taurine plays many physiological roles from conception throughout life.
- Perinatal taurine exposure influences growth and development, and then programs adult function and diseases.
- Perinatal taurine deficit or excess program cardiovascular function and diseases in mature offspring.
- This chapter mainly reviews the effect of perinatal taurine exposure on organs related to arterial pressure control and abnormalities in infants and adults.

Keywords Taurine • Perinatal life • Cardiovascular system • Brain • Kidney • Nutrition • Infants • Arterial pressure • Autonomic nervous system • Pregnancy

Epidemiological and animal research studies indicate that perinatal environment influences adult health and diseases [1–3]. In some cases, these influences affect the organism early in life, while in other cases, epigenetic or phenotypic changes occur that are not manifest until later life. Maternal nutrition appears to contribute significantly to both the early and late effects by which adaptation of the fetus or neonate to environmental stimuli may permanently alter the physiological function of tissues, organs, and/or systems. Often these changes are not obvious in the young animals, but only become apparent at later stages of life, when the animal is challenged by normal physiological (e.g., stress) and/or pathological stimuli that thereby can alter adult functions. Thus, maternal nutrition is important not only for the organism's development during pregnancy and lactation but also for functions in adult life. Among the micronutrients that appear to be important for perinatal development,

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R.R. Watson et al. (eds.), *Nutrition in Infancy: Volume 1*, Nutrition and Health,
DOI 10.1007/978-1-62703-224-7_27,

taurine contributes significantly not only to neonatal growth and development but also to adult normal physiology and susceptibility to disease. This chapter considers the evidence that indicates that perinatal taurine exposure both affects perinatal development and adult physiology.

An Overview of Taurine

Taurine (2-aminoethansulfonic acid) is a nonprotein, β-amino sulfur amino-acid that is found in many tissues, particularly brain, retina, myocardium, liver, and kidney (Fig. 27.1). Taurine was named in 1827 for the ox in which it was first isolated from bile. Taurine occurs naturally in food, especially in seafood and red meat, but it is absent in most plants, with small amounts found only in a few plant forms. Taurine plays an important role in several essential biological processes including osmoregulation, cell membrane stabilization, neuromodulation, cholesterol degradation, antioxidation, growth, and differentiation [4, 5]. During pregnancy, taurine accumulates in maternal tissues and is released during the perinatal period to the fetus via the placenta and to the newborn via the maternal milk. In general, taurine content in the body is highest during early postnatal life and declines with advancing age. Due to its many significant roles throughout life, taurine is used as an additive for food products and energy drinks and is a common additive in children's food and animal feed [6].

Within the body, taurine is synthesized from methionine and cysteine primarily in the liver [5]. It is produced by oxidation of cysteine to cysteinesulfinate (by the enzyme cysteine dioxygenase), followed by the decarboxylation of cysteinesulfinate to hypotaurine (catalyzed by cysteine sulfinic acid decarboxylase). Hypotaurine is then spontaneously or enzymatically oxidized to yield taurine. Mammals also metabolize cysteine sulfinate to taurine; however, their capacity to do this is highly variable and species specific. Taurine is an essential dietary requirement for feline health, since cats cannot synthesize the compound due to their deficiency in cysteine sulfinic acid decarboxylase. In mammals, taurine is either excreted as a free amino acid or in the form of bile salts such as taurocholate. Taurine is an amino acid that differs from the more familiar substances in this class, because it is a sulfonic rather than a carboxylic amino acid and has a β-rather than an alpha-amino acid. Taurine ($C_2H_7NO_3S$) is a colorless, relatively tasteless substance with a molecular weight of 125.

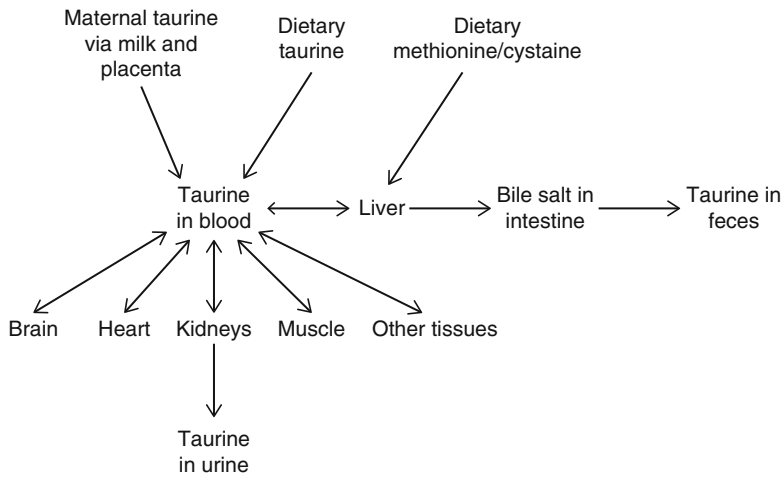

Fig. 27.1 Taurine distribution in human body

There are several important factors that regulate taurine production. Pyridoxal-5′-phosphate is required as coenzyme for cystathionine synthase, cystathionase, and cysteine sulfinic acid decarboxylase. Further, a dietary deficiency of vitamin B_6 decreases taurine biosynthesis [5]. Hormonal influences on cysteine sulfinic acid decarboxylase have been described. Compared to females, males have higher liver cysteine sulfinic acid decarboxylase activity, and estradiol injections decrease this activity, suggesting this gender difference is related to estrogen availability. Interestingly, in non-human primates, dietary taurine depletion retards growth of females more than that of males.

Throughout life, taurine is involved in a number of physiological processes. Low levels of taurine have been associated with many disorders including growth retardation and cardiomyopathy. The taurine transporter knockout (TauTKO) mouse exhibits a deficiency in myocardial and skeletal muscle taurine content. They develop many abnormalities, including reduction in ventricular wall thickness, cardiac atrophy with smaller cardiomyocytes, decreased cardiac output, and increased expression of heart failure marker genes [7]. Further, altered expression of the renal taurine transporter results in reduction of intracellular taurine content, which can lead to abnormal cell volume regulation, cell death, and defective renal development [8]. These data indicate that taurine is very important for structural and functional maintenance of many systems.

Normally during development and early-life, animals have high levels of taurine, but after weaning the levels decrease [4]. Supplementation or replacement of taurine has been studied in many conditions in perinatal and adult animals. Some reports indicate that taurine is safe and effective for the management of various types of cardiovascular disease [9]. Taurine contributes to the regulation of intracellular calcium concentration; therefore, it protects heart muscles from calcium imbalance and as a modulator of potassium flux, taurine could prevent arrhythmias. In addition, its antioxidant activity could improve the clinical manifestations of heart failure [10].

Perinatal Programming of Adult Function and Diseases

The perinatal developmental origins (programming) of adult diseases that relate to taurine have been intensely studied (Fig. 27.2). During development, the mother can transfer environmental information to her embryo or fetus through placenta and to her infant through lactation [2]. Since different organs develop at different rates, timing is important to determine specificity of this programming effect. Both the duration and nature of the programming stimuli during pregnancy and lactation are also important.

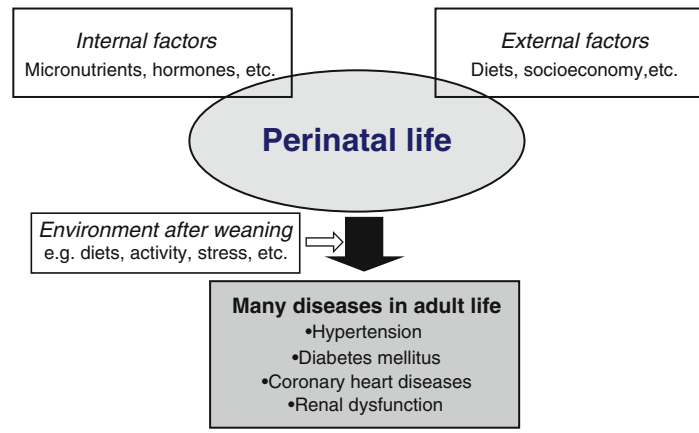

Fig. 27.2 The possible factors during perinatal and young life determining adult diseases

Perinatal programming can occur at any time from conception to weaning (pregnancy and lactation), and perinatal life includes most of critical periods that such programming occurs, e.g., embryogenesis, placental development, organogenesis, prepartum maturation of the fetus, and sucking period or lactation [11]. Thus, nearly all structural, physiological, and metabolic development can be affected by altered taurine exposure, depending on timing of a challenge. The programming is integral to developmental plasticity and/or adaptation leading to survival of the fetus. It can occur at any level within the physiological system, and structural and functional changes in genes, cells, tissues, and organs may be involved. It also may become a predisposing factor for adult diseases.

Maternal conditions such as maternal nutrition, stress, hypoxia, glucocorticoid administration, or placental insufficiency are able to alter development. Cardiovascular, metabolic, nervous, respiratory, reproductive, endocrine, and skeletal systems have been reported to be affected and some mechanisms have been established [1, 11].

Nutritional environment in utero and early-life has been wildly studied. Maternal undernutrition produces low birth weight and has long-term effects on the offspring. Adult abnormalities from undernutrition include physiological changes and other diseases, especially coronary heart disease, hypertension, diabetes, impaired glucose tolerance, and renal dysfunction. Some of these changes can be permanent and can transfer to next generation of the species (primarily via epigenetic mechanisms). In addition, maternal overnutrition causes developmental adaptation and has long-term effects in adult life.

Taurine Distribution During Perinatal Life

In all animals, embryonic development involves four stages, i.e., cleavage, patterning, differentiation, and growth. Increases in cell numbers and changes in cell environment are the usual path to form a final organism. Cells respond to varying environmental stimuli, extracellular fluid demands, homeostatic mechanisms, and cell volume regulation, all of which are vital to normal growth and phenotypic development. As a main organic osmolyte within cells, taurine appears to be required by all cells to protect them from osmotic distortion. In human fetus and in early postnatal life, body taurine content markedly increases, particularly in the brain [4]. The human fetus accumulates about 50–60 μmole/24 h during the last 4 weeks of pregnancy [12]. Taurine appears to preferentially accumulate to certain areas of the body. In rats, an intraperitoneal injection of taurine into lactating dams after birth is accumulated in the brain to a greater extent than in the liver of the pups. Its maximal accumulation in rodent brain is reached by 5 days after birth, and it remains constant for at least 10 days [4].

During fetal and postnatal development, amino acid synthesis is very limited and is not sufficient for the demands of perinatal life. Thus, fetuses and newborns are dependent on maternal nutritional supply of taurine through placenta or milk. Although pregnant women can synthesize taurine from internal enzymatic pathways, this is limited by increased requirements of the mother's body during pregnancy and lactation [4]. Thus, supplemental dietary taurine is necessary during the perinatal period. Its deficiency can retard growth and can lead to low birth weights in newborns, a condition especially seen in offspring of vegan mothers.

Maternal urinary taurine excretion falls dramatically following week 9 of pregnancy in omnivore and vegan/vegetarian women and continues to fall during pregnancy and lactation. In vegan/vegetarian compared to meat eating mothers, such decrement is even greater during lactation [13]. Although the concentration of taurine in breast milk is lower in vegan subjects, the mean value falls within the range found in omnivore subjects. This suggests that taurine is stored in the maternal tissues in early pregnancy for later transfer to the fetus.

Taurine and other free amino acids are present in milk of humans and other species. It is the most abundant free amino acid in the milk of the gerbil, mouse, cat, dog, and rhesus monkey and is the

second most abundant amino acid in rats, sheep, Java monkeys, baboons, chimpanzees, and humans. In contrast, it is not a major constituent in the milk of the guinea pig, rabbit, cow, and horse [14]. A variable characteristic of taurine and other amino acids in the milk of each species indicates their significance for protein synthesis and other function during early postnatal development.

To date, it is well known that taurine is necessary for fetuses and infants; however, many of the physiological effects of taurine are still only partially understood. While, adverse effects of taurine excess have not been definitively demonstrated in humans and animal models, our previous experiments indicate that perinatal taurine supplementation alters renal function and arterial pressure in adult rats [14–20]. Nevertheless, these long-term effects do not appear to lead to severe abnormalities. In contrast, perinatal taurine depletion causes many disorders in both young and adult animals [4].

The role of taurine during development is linked to the specific organs/systems that are being developed. If a physiological trait that is taurine-dependent is not exposed to adequate taurine during a critical developmental window, optimal taurine exposure during other times may not rescue the trait. For instance, cow's milk formula (with and without supplemental taurine; 480 μmol/L) was fed for 16 weeks to 20 low-birth-weight infants considered to be taurine-deficient [21]. In the 2nd and 16th weeks of life, growth, sonography of heart and brain, ECG, EEG, neurological development, and plasma taurine concentration were not influenced by taurine supplementation. Only urinary taurine excretion was increased. This suggests that postnatal taurine supplementation may not improve the development of heart and brain function in low-birth-weight infants. Our experiments in rats also indicate that perinatal taurine depletion alters renal and neural control of arterial pressure at adult life, even if the young adults are placed on chronic taurine supplementation following weaning [15–20].

Perinatal Taurine on Growth and Development

Taurine appears to be especially important for fetal and neonatal development. Taurine-deficient female cats frequently resorb or abort their fetuses and have stillborn or live low-birth-weight kittens at term [4]. Taurine supplementation of a low protein diet in female mice consistently improves the survival rate of pups. Similar taurine supplementation effects have not been seen in mice fed a normal protein diet, since all of the pups survived. Weanling rats fed a low protein diet significantly reduce plasma and retinal taurine concentrations. Pregnant cats fed a normal taurine diet until 2 weeks prior to birth and then a taurine-free diet for the remainder of pregnancy and throughout lactation have a dramatic drop in 20 % of normal milk taurine concentration and growth rate and cerebellar development of the offspring is abnormally low. Interestingly, daily oral taurine supplementation of the offspring eliminated these abnormalities in the pups.

Although taurine content is very high in the brain, its role in development is not restricted to the nervous system (see below). Taurine is also present in high concentrations in mammalian heart, and, at least, in the mouse, cardiac taurine shows a dramatic increase in the early postnatal period [4]. Cardiac taurine levels are primarily maintained by a carrier-mediated, sodium-dependent transport system, and the concentration of taurine in both developing and mature heart appears to be under osmoregulatory control. Hypernatremia increases and hyponatremia decreases cardiac taurine concentration [10]. Taurine-mediated protection against cardiac abnormalities and damage has been reported in numerous studies. The kidney has been shown to play a major role in regulating the total body taurine, since the removal of taurine from the body occurs chiefly by urinary excretion [8]. This ability of the kidney to conserve taurine is the property of the renal brush border membrane. Isolated brush border membranes prepared from rodents fed a taurine-restricted diet have a greater rate of taurine transport than those prepared from rodents fed a high taurine diet.

Taurine and the Nervous System

Since taurine is essential for fetal and infant development, taurine is added to cow's milk and soy protein-based milk used for infants, especially premature infant, formulas [22]. Taurine is the free amino acid present in the highest concentration in newborn and neonatal brain, usually at a three to four times greater concentration than in mature brain [4]. Taurine deficiency in the mother leads to impaired development of central nervous system particularly the autonomic nervous system and to learning and memory impairment in adult life. However, there is little data on the acute adverse effect of taurine supplementation in infants.

In addition to cellular osmoregulation, taurine contributes to several other functions in the brain [23]. Taurine inhibits glutamate-induced calcium entry, cell apoptosis, and voltage-sensitive calcium channel phosphorylation (decreased active calcium channel availability). Taurine decreases overall gamma-aminobutyric acid (GABA) neurotransmission, but it can also partially activate $GABA_A$ receptors. Taurine also increases glutamate decarboxylase expression (a key enzyme converting glutamate to GABA) but decreases GABA receptors in nerve and glial cells. Brain somatostatin levels also increase in taurine-supplemented animals. Taurine supplementation induces hyperactive behaviors and improves memory and learning in animals especially mice. Inhibition of GABA and increased somatostatin levels are suggested to underlie these effects [24]. Taurine also alters CA1 hippocampal neurons [25]. However, taurine acts on the systems in perinatal and mature rodents, and taurine supplementation increases both GABA and glutamate activity and improves hypoactive behaviors and learning and memory in aged animals [26]. These parameters usually decline with advancing age in relation to decreases in brain taurine content.

Taurine also acts to stabilize excitable membranes of many neurons and suppresses synaptic release of neurotransmitters, e.g., acetylcholine and norepinephrine [23]. Studies also suggest that taurine plays an important role in neuronal calcium signaling and modulation of glycine-A and γ-aminobutyric acid-A receptors in many areas of pain pathway [27, 28]. Taurine has analgesic action in various pain models.

Hypothalamic taurine content is highest during perinatal life and influences several hypothalamic functions including autonomic nervous system regulation, feeding and appetite, glucose-insulin regulation, and pituitary hormonal function. Taurine also alters protein expression and phosphorylation, mRNA expression of cell membrane transporters and modulation of genes belonging to the MAPK and protein kinase C signaling pathways by taurine exposure were also reported [29]. Taken together, perinatal taurine excess or deficiency can alter growth and development of nervous system, and these changes can result in adult neural function disorders (Fig. 27.3).

Previous experiment from our laboratory demonstrate that perinatal taurine depletion causes dysregulation of the autonomic nervous system and can exacerbate the hypertensive response to a high sugar diet in adult offspring [20]. In female rats, this effect appears to be mediated by interactions with overactivity of the renin-angiotensin system, and this interaction is not attenuated by the estrogen [16, 30]. Further, perinatal taurine supplementation is effective in protecting synaptic plasticity deficits in hippocampus in adult rats that are exposed to lead during fetal and neonatal age [31]. Taurine administration during lactation reduces the effects of postnatal stress-induced inhibition of analgesic responses in young male mice, and it reduces hippocampal plasticity, anxiety, and depressive behavior in adults [32].

Excess supplementation of taurine during prenatal and early postnatal life can lead to impairment in visual discrimination learning in later life while taurine supplementation after weaning improves visual discrimination learning [33]. Therefore, excessive taurine might be toxic. Timing of taurine supplementation is important in these effects. Although there is no definitive data in humans, our animal experiments in Sprague–Dawley rats indicate that perinatal taurine supplementation has long-term effects on neural control of the heart and the kidney [15–20, 34]. Baroreceptor reflex control of

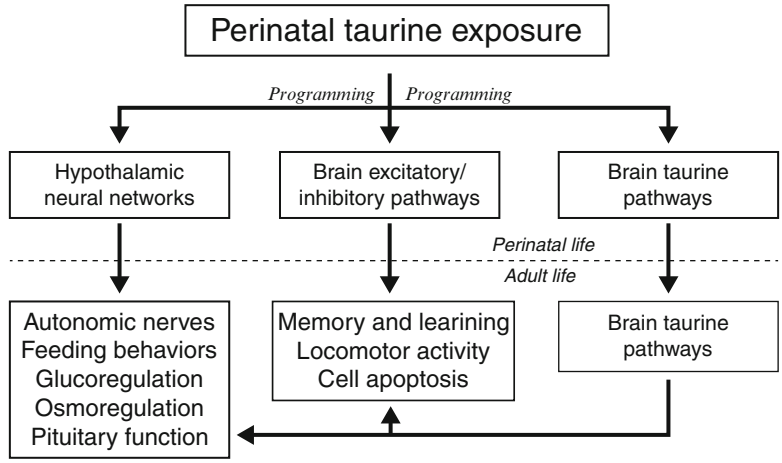

Fig. 27.3 A diagram depicts the possible programming of some neural pathways by perinatal taurine exposure. It is noteworthy that in brain, taurine directly influences other neural mechanisms. Once improperly programmed in perinatal life, taurine may function abnormally in the adult nervous system

heart rate and renal sympathetic nerve activity is partially impaired in adult female rats that are perinatally supplemented with taurine and subsequently treated with glucose in drinking water after weaning. In contrast, these changes are not observed in male rats following same treatment. The abnormality in the female may depend in part on the presence of estrogen, since estrogen receptor blockade with tamoxifen partially restores normal neural control of the heart and the kidneys in perinatal taurine supplemented rats [30]. Interactions with the renin-angiotensin system may not underline this phenomenon, since treatment with angiotensin converting enzyme inhibitor does not inhibit these responses.

Taurine and Renal Function

Sorbitol, myo-inositol, betaine, alpha-glycerophosphorylcholine, and taurine have been reported to be major osmolytes in renal medulla [8]. This means that taurine plays an important role in renal dilution and concentration of urine. The kidney regulates taurine balance by modulating proximal tubule reabsorption in response to fluctuation in dietary intake of this nutrient. Taurine is found in collecting duct cells throughout cortex and medulla, in proximal straight tubular cells, and in cells of the descending thin limbs of Henle's loop [35]. In normal rats, taurine is found primarily in medullary tubules, with minimal staining of proximal tubules and glomeruli. Increased taurine staining is observed in all renal structures, especially medullary tubules, in rats with streptozotocin diabetes and puromycin aminonucleoside nephropathy. Some studies indicate that taurine depletion by a taurine transporter blocker (including β-alanine or guanidioethane sulfonate; GES) decreases taurine level in renal cells [8]. Taurine depletion reduces the initial rates of fluid and sodium excretion after an intravenous saline load. β-alanine-induced inhibition of tubular reabsorption of taurine may result in subsequent excretion of taurine with attendant natriuresis early in the course of beta-alanine treatment [36].

Active transport of taurine occurs via a sodium-dependent transporter (TauT), and taurine uptake by renal epithelia requires chloride or bromide, in addition to sodium [8]. The model that describes this transporter is 2 Na^+: 1 taurine: 1 Cl^-. Sodium and chloride move into the cell by means of an external to internal downhill Na^+ gradient (a chemical gradient), with sodium being pumped out of the

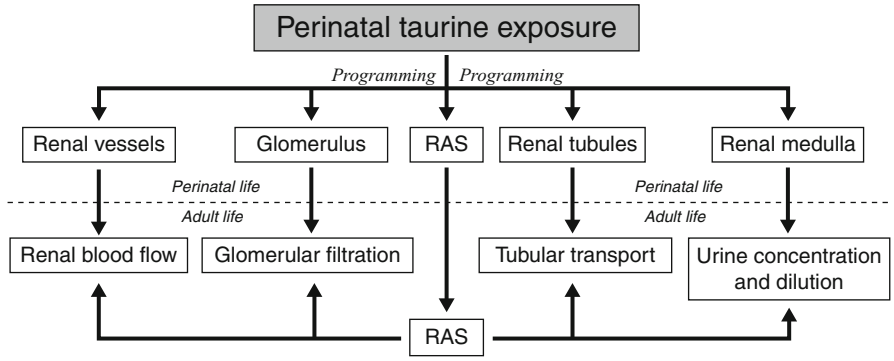

Fig. 27.4 Possible sites of programming of adult renal function and disorders induced by perinatal taurine deficit or excess (RAS, renin-angiotensin system)

cell by Na^+/K^+ATPase. In a proximal tubule cell line, taurine uptake is maximal on the apical surface while in the distal tubule cell line, taurine uptake occurs at basolateral surface [37]. Taurine efflux from renal cells is dependent on the intracellular taurine concentration and requires the presence of both Na^+ and Cl^- in the system.

Previous experiments in our laboratory indicate that perinatal taurine deficiency impairs renal function in adult rats and that prenatal (compared to postnatal) taurine deficiency is more deleterious [15]. The autonomic nervous system is also impaired in the adult male offspring following this treatment. Surprisingly, this treatment also causes sympathetic nerve hyperactivity when treated animals are challenged with a high sugar diet postweaning. Baroreflex control of heart rate and renal nerve activity is also blunted following this treatment. These dysfunctions can be greatly reduced by oral captopril treatment in adult female offspring, suggesting that renin-angiotensin system overactivity contributes to these dysfunctions. High sugar intake alone has been reported to impair renal function via renin-angiotensin system overactivity in adult, male Sprague–Dawley rats [38]. In contrast, perinatal taurine supplementation appears to improve renal function in adult female rats, with no attendant alteration of autonomic nervous system activity or baroreflex sensitivity.

Although number of nephrons is established before birth, their growth and differentiation continue throughout lactation. There are at least five sites of perinatal programming of adult renal function and abnormality induced by perinatal taurine deficit or excess (Fig. 27.4): renal vasculature, glomerulus, tubular transports, renal medulla, and renal renin-angiotensin system. First, changes in renal vasculature underlie renal blood flow regulation. Second, glomerular dysfunction decreases renal filtration and renal scavenging of reactive oxygen species. Third, tubular transport alteration underlies sodium and water excretion, as well as, taurine conserving ability of the kidney. Fourth, renal medulla programming determines renal concentrating and diluting ability and osmoregulation. Fifth, alteration of the renin release mechanism and/or intrarenal renin-angiotensin system may contribute to renin-angiotensin system dysregulation in adult animals or humans that were perinatally deficit or excess of taurine.

Taurine on Arterial Pressure

Epidemiological studies have reported a negative relationship between the incidence of cardiovascular diseases and consumption of diets high in taurine, particularly fish. Japanese, Koreans, and South Americans who regularly consume large amounts of fish have a low incidence of hypertension and

coronary vascular diseases and have longer longevity compared to other western people who consume low taurine diets [9]. This taurine relationship is supported by animal studies. In adult animals, treatment with diets high in taurine decreases the rate of organ damage with advancing age, especially brain, kidneys, and heart damage [5]. Hypertension in animal models can also be prevented or reduced by dietary taurine supplementation. Prenatal taurine deficiency induces low birth weights, and these animals have a high risk of adult diseases, including coronary vascular disease and hypertension, diabetes and renal dysfunction [4]. In addition, these changes can be transferred to the next generation, likely by epigenetic mechanisms [4].

Perinatal taurine exposure has long-term effects on arterial pressure and renal function in adult life. Taurine supplementation decreases hypertension in many animal models. Perinatal taurine supplementation prevents hypertension in spontaneously hypertensive rats (SHR), likely, in part, by an antioxidant effect [39]. In addition, the renin-angiotensin-aldosterone axis is inhibited [10], and elevated cytokine and endothelin levels [40] are reduced by taurine. Taurine administration also ameliorates hypertension directly via the suppression of NE release from the peripheral sympathetic nerves and improves baroreflex sensitivity in SHR [41].

Perinatal taurine supplementation slightly increases arterial pressure, but not heart rate, in adult rats, and this change is not exacerbated by a high sugar diet [20]. Baroreflex sensitivity and autonomic nervous system responses are unaffected in these animals. In adult female rats, perinatal taurine supplementation does not alter arterial pressure with taurine, even following treatment with a high sugar diet [16]. In addition, inhibition of the renin-angiotensin system by captopril decreases, while inhibition of estrogen receptors by tamoxifen does not affect, arterial pressure similarly to those observed in normal taurine female rats [30]. This suggests that the different arterial pressure responses to high sugar intake between male and female rats that were perinatally supplemented by taurine may not be due to the renin-angiotensin system or estrogen dysregulation.

Although perinatal taurine depletion does not alter arterial pressure in adult male and female rats, high sugar intake significantly increases the arterial pressure only in male animals. Baroreflex control of heart rate and renal nerve activity is blunted and the sympathetic nerve activity is heightened in these male and female animals when they are treated with glucose in tap water since weaning [16, 20]. These disorders are returned to normal control when the female animals are treated with an angiotensin converting enzyme inhibitor captopril, but not following treatment with the estrogen receptor blocker tamoxifen [16, 30]. This suggests that the baroreceptor dysfunction in adult female rats that were perinatally depleted of taurine is linked to the renin-angiotensin system but not the estrogen system. Whether this effect also occurs in adult male rats has to be addressed.

During perinatal life, optimal taurine exposure is necessary for the organism to develop normotensive arterial pressure in adult life (Fig. 27.5). Perinatal taurine exposure may alter the autonomic nervous system control of arterial pressure in adult female rats on a high sugar diet, due to a complex interaction of the renin-angiotensin system, glucose-insulin regulation, and estrogen action. While the renin-angiotensin system plays a primary or dominant role in the effects of perinatal taurine depletion, an estrogen adaptation may, at least in part, contribute to the effects of excess perinatal taurine. Glucose-insulin regulation changes significantly following the perinatal taurine depletion in rats, and this may interact with the renin-angiotensin system to adversely affect the cardiovascular system especially at the aged. In addition, previous experiments indicate that perinatal taurine deficit induces renal dysfunction in adult life with or without high sugar intake [15, 17, 18]. Moreover, the renin-angiotensin system, glucose-insulin regulation, estrogen function, and sympathetic nerve activity all affect renal function. Thus, it is possible that all of these four factors mediate the taurine effects on the kidney leading to salt and water retention and producing sustained hypertension in both male and female animals.

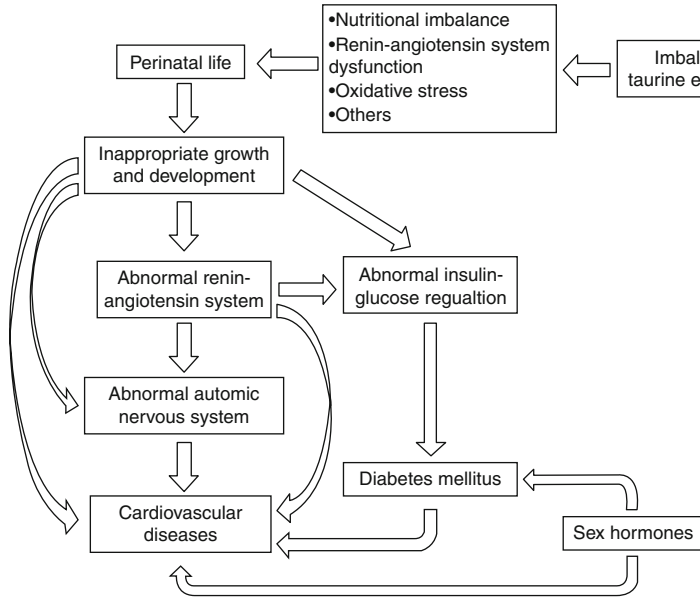

Fig. 27.5 Possible mechanisms by which perinatal taurine exposure programs adult cardiovascular diseases

Taurine on Glucose-Insulin Regulation

Pancreatic islets contain a high concentration of taurine partly because they can synthesize taurine themselves. Taurine supplementation can prevent pancreatic damage induced by gestational protein malnutrition [42, 43]. In addition, the taurine supplementation during gestation delays the onset of diabetes mellitus in non-obese diabetic mice [44]. Taurine increases pancreatic hormonal function in fragile X mice, i.e., insulin, glucagon, and somatostatin secretion are all improved. This may result from taurine-increased cell number and size of pancreatic islets that increase much more in wild-type than fragile X mice [45]. Hyperinsulinemia and glucose tolerance are also observed in these animals.

Taurine possess hypoglycemic action that can improve diabetes mellitus and prevents sugar-induced hypertension. The sugar-induced hypertension involves not only sympathetic nervous system and the renin-angiotensin system overactivity, but also insulin regulatory system dysfunction [46]. Our previous studies report that high sugar intake does not induce hyperglycemia and glucose intolerance in either control or perinatal taurine depleted female or male rats [18, 20] with all animals displaying euglycemia. However, perinatal taurine depletion increases plasma insulin concentration, but this is not increased further by high sugar intake [16]. In contrast, captopril treatment greatly increases plasma insulin concentration in taurine-depleted rats. The high sugar intake exacerbated this increment. In addition, fasting blood glucose is not affected by perinatal taurine exposure, suggesting that perinatal taurine depletion induces insulin resistance in female rats. However, this effect seems to be minimal since hyperglycemia and glucose intolerance were not observed in these animals. It is well known that inhibition of the renin-angiotensin system increases insulin sensitivity and insulin secretion in humans and animals [47, 48]. A marked rise in insulin concentrations in all captopril-treated (compared to control) rats indicates an abnormal insulin/angiotensin II relationship in these animals that is exacerbated by the high sugar intake [16]. An abnormal insulin feedback inhibition may also contribute to this effect.

Glucose-insulin regulation is a complex phenomenon that depends on many factors including pancreatic hormones, taurine and other plasma micronutrients, sex hormones, renin-angiotensin system,

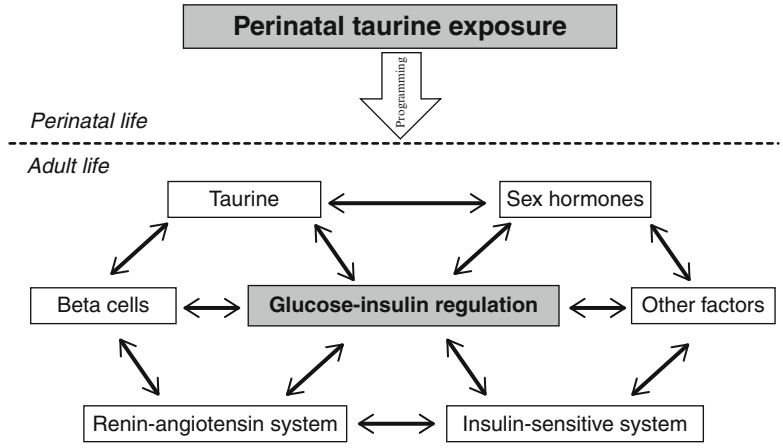

Fig. 27.6 A diagram indicating perinatal taurine exposure programming of glucose-insulin regulation in adult life

tissue metabolism and responses to insulin, and neural function (Fig. 27.6). Thus, perinatal taurine exposure may program their optimal interplay of these factors on the glucose-insulin regulation in mature life. As mentioned earlier, the perinatal taurine exposure with optimal timing and doses is very important to this phenomenon.

Taurine and the Renin-Angiotensin System

As demonstrated above, the renin-angiotensin system is important in the effects of taurine on physiological systems. It also regulates neural, renal, and cardiovascular functions, playing a pivotal role in the homeostasis of arterial pressure, body fluids, and electrolyte balance. Enhanced activation of the renin-angiotensin system contributes to hypertension in several models. In addition to the well-known peripheral renin-angiotensin system actions, recent work demonstrates that the renin-angiotensin system also exists in the brain and has significant effects via this pathway (often totally separated from the renin-angiotensin system's peripheral effects [49]). All the components of the renin-angiotensin system have been identified in the brain. Anatomic and functional studies have provided evidence that enhanced renin-angiotensin system activity in brain may play a role in the pathogenesis of hypertension in SHR. Some of the strongest evidence for a potential role of the brain renin-angiotensin system in hypertension comes from studies that indicate both short-term and long-term intracerebroventricular administration of either angiotensin II receptor antagonists or angiotensin converting enzyme inhibitors lower arterial pressure in the SHR, at doses that are peripherally ineffective [50]. Further, treatment with angiotensin converting enzyme inhibitors can protect against hypertension if it is given from conception throughout life in the SHR [51]. However, this treatment does not prevent salt-induced hypertension in the male offspring [52]. Renal excretory function is also improved in these animals. Although early treatment with oral angiotensin converting enzyme inhibitor captopril does not damage the kidneys of the SHR, the treatment impairs renal function and induces renal damage in normotensive rats [53]. This indicates that programming of the renin-angiotensin system occurs early in life, and this affects adult regulation of the autonomic nervous system.

Taurine and angiotensin II have some similar and some opposite effects, e.g., they both are growth promoting factors. However, the two do not affect the same organs to equal extent. Angiotensin II induced cardiac hypertrophy both in in vivo and in vitro studies. Thus, angiotensin converting enzyme

inhibitors and AT_1 receptors antagonists reduce cardiac hypertrophy in heart failure patients [54]. Taurine can inhibit the cardiac hypertrophy induced by angiotensin II treatment in rats [55]. Whether perinatal taurine treatment leads to this antagonizing action is untested. In addition, taurine supplementation [56] or angiotensin-converting enzyme inhibition [57] can prevent or abolish hypertension induced by high carbohydrate intake. Thus, both may act via a common mechanism.

Previous studies show that lack of the renin-angiotensin system in early life induces renal damage and dysfunction in adult rats [53], and perinatal taurine depletion also alters renal function in adult rats [15]. However, their interactions during perinatal period that program neural, renal, and cardiovascular functions are still unclear. Nevertheless, perinatal taurine depletion increases sympathetic nervous activity and blunts baroreceptor function induced by a high sugar diet that is administered from weaning. This action is mediated by renin-angiotensin system overactivity [16]. Although high sugar intake slightly blunts baroreflex control of renal nerve activity in perinatal taurine supplemented rats, this effect is not eliminated by captropril treatment or estrogen receptor blockade. These findings suggest that perinatal taurine excess and deficit have different actions on the programming of the adult renin-angiotensin system.

In adult animals, taurine supplementation improves insulin resistance and hypertension in sugar-induced hypertension by inhibition of angiotensin II, by antioxidant and other actions [58]. It also reduces the cardiac hypertrophic effect of angiotensin II in animals [10]. In contrast, taurine deficiency in mature animals accelerates many adverse actions of angiotensin II on the heart, blood vessels, and kidney [59]. The interaction between taurine and the renin-angiotensin system on the heart is also observed in perinatal taurine supplemented rats, in which baroreflex control of heart rate, but not renal nerve activity, is not altered by perinatal taurine supplementation; rather it is depressed by acute captopril treatment; an effect that is not observed in control rats. This indicates that the normal baroreflex control of the heart in perinatal taurine supplemented animals is partially maintained by the renin-angiotensin system. With a high sugar diet, the perinatal taurine supplemented rats display a blunted baroreflex control of the heart, the effect that cannot be restored by captopril treatment. In contrast, the blunted baroreflex function in perinatal taurine depleted rats treated with the high sugar diet can be abolished by the captopril treatment [16]. This further suggests that perinatal taurine excess and deficit differentially induce renin-angiotensin system dysfunction in adult life.

In the kidney, taurine increases water and sodium excretion while angiotensin II acts in an opposite direction. In the medulla, angiotensin II injection increases taurine secretion [60]. Moreover, taurine stimulates [61], while angiotensin II inhibits insulin secretion from pancreatic islets. Together, these findings indicate that taurine and the renin-angiotensin system share many physiological pathways in humans.

The renin-angiotensin system is crucial for growth and development during perinatal life. Its deficiency produces organ damage and abnormalities in adults, especially related to the kidney [53] and the nervous system [62]. Similarly, appropriate taurine exposure during a perinatal period leads to normal adult organ function [4]. Perinatal taurine depletion may increase the renin-angiotensin system activity at early life and this change may lead to permanent effects that cannot be reversed by later taurine availability, i.e., the programming of renin-angiotensin system function in mature life is likely dictated by the perinatal exposure.

Taurine and Sex Hormones

Like other steroid hormones, the synthesis of estrogens begins with cholesterol. The most dominant estrogen in humans is 17β-estradiol (E2), but lower levels of other estrogens (estrone and estriol) are also present. Incidence of cardiovascular and other related diseases are higher in postmenopausal than

in premenopausal women and age-matched men. Hypertension in ovariectomized animals can be prevented by diets high in phytoestrogens or by estrogen replacement [63, 64]. The low incidence of hypertension in vegetarians appears to be related to their high dietary phytoestrogens intake. Oral contraceptives increase arterial pressure in women, and this can be abolished by inhibition of the renin-angiotensin system [65]. Estrogen may act directly or indirectly via inhibition of the renin-angiotensin system and the sympathetic nervous system [66]. These effects include down-regulation of angiotensin-converting enzyme and AT_1 receptor and up-regulation of AT_2 receptor [67]. The AT_1 receptor is the primary AT receptor that induces vasoconstriction and hypertension, while AT_2 receptors oppose most AT_1 actions and regulates growth and development in early life [68].

Increased sympathetic nerve activity in menopausal women has also been reported to underlie a high risk of cardiovascular disease. Female SHR that are usually salt-resistant become hypertension on a high salt diet after ovariectomy. Their sympathetic nerve overactivity is a consequence of a low catecholamine level in the anterior hypothalamus and can be restored to normotensive state by estrogen replacement [64] or a high phytoestrogen diet [63]. Together, the above review suggests that both the renin-angiotensin system and the sympathetic nerve activity underlie the hypotensive action of estrogen. In addition, heighten sympathetic nerve activity stimulates the renin-angiotensin system and vice versa.

Gender differences in perinatal programmed hypertension have been reported in animal models and epidemiological studies. Rats with placental insufficiency as nutritional imbalance produce hypertension in both male and female offspring at a prepubertal age. However, the male offspring remain hypertension even after puberty while those females become normotensive [69, 70]. Gonadectomy abolishes hypertension in the male but induces hypertension in the female offspring [71]. Hormone replacement reinstalls hypertension in castrated male but abolishes hypertension in ovariectomized female offspring. This indicates a significant role of sex hormones to program adult cardiovascular function and diseases at earlier life.

As mentioned earlier, taurine plays a crucial role in the perinatal period to promote growth and development that program the outcome of cardiovascular function and abnormality at later life. Its effect on the arterial pressure control is sex-dependent and depends on a subsequent stimuli especially high sugar or salt intake [19]. Recent experiments in our laboratory indicate that high sugar intake alters the autonomic nervous system control of arterial pressure via the renin-angiotensin system and this effect cannot be attenuated by estrogen in adult female rats [30]. However, there is still no direct experiment to support the possible interaction between endogenous estrogen action and taurine during growth and development that programs adult function and disease.

Summary

Taurine plays many physiological roles in animals and humans. Perinatal taurine deficit or excess affects adult function and disease through a complex interaction among cardiovascular, hormonal, neural, renal, and other systems (Fig. 27.7). Taurine thus alters the programming during fetal and early postnatal life to affect both organ function in the neonate and the adult. While perinatal taurine imbalance has long-term effect on adult life, perinatal taurine deficiency has been reported to underlie or contribute to many adult disorders, particularly cardiovascular diseases and diabetes mellitus. At least in animal models, these abnormalities can be transferred to the next generation, suggesting that epigenetic adaptation is influenced by perinatal taurine depletion. Taurine supplementation is common during pregnancy and lactation. In addition, several nutrition formulas for health and energy drinks contain large amounts of free taurine. However, it should be noted that excess taurine consumption can adversely affect animals, and although not rigorously studied yet, it may also adversely affect humans.

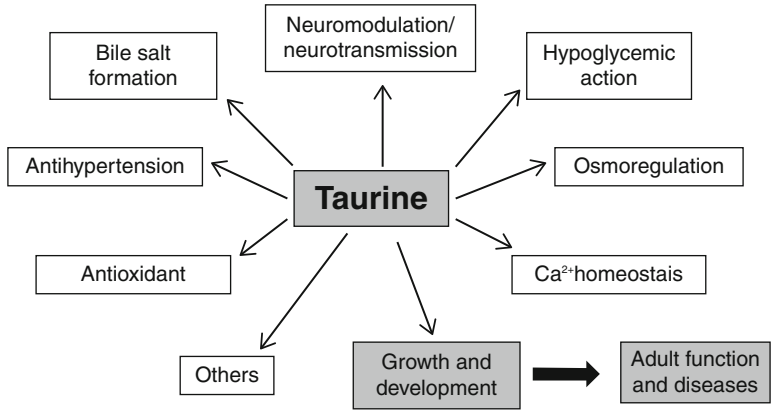

Fig. 27.7 Summary of taurine function in human body

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Chapter 28
Micronutrient Deficiencies and Treatment of Infant Skin Problems

Sambasiviah Chidambara Murthy

Key Points

1. Infants are at risk to develop micronutrient deficiencies, due to various causes.
2. Mucocutaneous manifestations help in early recognition and treatment of nutritional deficiencies.

Keywords Micronutrient deficiency • Infancy • Hypovitaminosis • Mucocutaneous manifestations • Nutritional dermatoses • Deficiency dermatoses

The term micronutrient refers to substances that are needed in small quantities by the body for healthy living. These include vitamins and trace elements like iron, copper, zinc, etc [1]. Micronutrients promote optimal physical growth and neuromotor development. They are required for the integrity and optimal functioning of the immune system [2]. Infants are prone to develop micronutrient deficiencies, due to various causes.

Mucocutaneous manifestations are one of the earliest, most frequent, and easily recognizable features of nutritional deficiency disorders. Early recognition and correction helps in preventing further damage. Although certain deficiencies have typical manifestations, in practice, an individual is likely to have more than one micronutrient deficiency. This chapter focusses on micronutrient deficiencies with predominant mucocutaneous findings.

Fat-Soluble Vitamins

Vitamin A

Vitamin A (retinol) is involved in retinal photoreceptor function, epithelial proliferation, keratinization, and development. The two clinically important forms of vitamin A are retinal, involved in rhodopsin generation and retinoic acid, which modulates cell differentiation. Vitamin A (as retinyl esters) is found in animal products such as cow's milk, liver, egg, fish oil, etc. In plants, vitamin A is present as β(Beta)–carotene consisting of two covalently linked retinal molecules. Plant sources are green

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R.R. Watson et al. (eds.), *Nutrition in Infancy: Volume 1*, Nutrition and Health,
DOI 10.1007/978-1-62703-224-7_28,

leafy vegetables, papaya, mango, carrots, tomatoes, and apricots [3, 4]. Clinical deficiency is rare in infancy [5, 6].

Clinical Features: The earliest manifestations in vitamin A deficiency are ocular changes. Cutaneous involvement in mild deficiency is characterized by xerosis and scaling. Severe deficiency results in deep skin fissuring known as dermomalacia. Xerostomia, hyposmia, and hypogeusia can occur [3, 4]. The cutaneous hallmark is "phrynoderma" characterized by keratotic follicular papules over the anterolateral thighs, posterolateral upper arms, extensor extremities, shoulders, abdomen, back, buttocks, and posterior neck [3, 4]. Although, earlier described as a manifestation of hypovitaminosis A, phrynoderma has now been liked with deficiencies of vitamins E, B, A, essential fatty acids, and general malnutrition [6]. Noncutaneous findings include nyctalopia, xerophthalmia, Bitot's spots, keratomalacia, impaired bone growth, and cranial nerve involvement.

Diagnosis [4, 7]: Serum vitamin A levels <(less than)20 μg (micrograms)/dl (normal 20–50 μg (micrograms)/dl) is diagnostic.

Treatment [4]: The recommended daily allowance (RDA) of vitamin A is 1,000–5,000 IU. Treatment is 100,000–300,000 IU of oral vitamin A daily until symptoms resolve.

Hypervitaminosis A

Infants should not receive vitamin A more than 20,000 IU/day or preformed vitamin A >(greater than) 100,000 IU/day for more than 6 months as toxicity can occur [4, 8]. It can occur with excessive intake of vitamin supplements, frequent consumption of chicken liver, liver disease, or cystic fibrosis. Clinical manifestations of chronic, hypervitaminosis A include xerosis, cheilitis, epistaxis, alopecia, weakness, fatigue, bone, and joint pain, hepatosplenomegaly, insomnia, drowsiness, anorexia, irritability, vomiting, bulging fontanelles (in infants), pseudotumor cerebri, and psychiatric symptoms [3].

Vitamin D (Calcitriol)

Vitamin D is essential for regulation of calcium and phosphorous metabolism. Vitamin D is obtained by dietary intake or exposure to sunlight. Vitamin D rich sources include fortified milk, fish oil, fish, and orange juice. The most common disorder of vitamin D metabolism is vitamin D-deficient rickets, due to decreased dietary intake. Two types of vitamin-D-dependent rickets are described. Exclusively breast-fed infants (especially with dark skin tone) and preterm infants are at risk [3, 4].

Clinical features: Vitamin D deficiency may have acute or chronic manifestations. Infants and adolescents may manifest with hypocalcaemia as seizures or tetany. Chronic deficiency predominantly involves skeletal system resulting in fraying and widening of the metaphysis, rachitic rosary, thinned bone cortex, frontal bossing, bowing of legs, and fractures. Delayed tooth eruption, caries, and poor growth may result [3, 4].

Cutaneous involvement [9, 10] is seen in vitamin-D-resistant rickets type II A, characterized by alopecia, papules, and cutaneous cysts over jaw line, neck, chest, and upper arms. In this autosomal recessive disorder, hair is present at birth; loss begins by fifth week and is completely lost by 12 months. Eyelashes are spared. Hair loss may precede bone changes. Bone changes resolve and metabolic defect can normalize with age, but the alopecia is permanent.

Diagnosis [3]: Hypophosphatemia, hypocalcemia, elevated alkaline phospatase, parathyroid hormone, decreased 25-hydroxyvitamin D, and radiology of bones confirm the diagnosis.

Treatment [3]: RDA ranges from 200 to 600 IU. Deficient infants from unsupplemented breastfeeding should receive 1,000–5,000 IU of ergocalciferol (vitamin D2) daily until radiological healing. Breastfed infants need 400 IU of vitamin D daily as prophylaxis.

Vitamin-K

Vitamin-K is necessary for synthesis of several coagulation factors in the liver: factors II,VII,IX, X, proteins C & S. Dietary form, phylloquinone (vitamin K_1) is found in green leafy vegetables, liver, brussel sprouts, lentils, plant oil, and soya beans, providing 50 % of daily requirement. Remaining 50 % requirement is provided by gastrointestinal bacteria as menaquinone (vitamin K_2). Deficiency can be seen in healthy term infants, premature infants, newborns of mothers taking coumadin, high doses of salicylates, cephalosporins, phenytoin, isoniazid, cholestyramine, and rifampicin [3, 7].

Clinical features [3]: Neonatal vitamin K deficiency bleeding (VKDB) is classified as early, classical, or late types. Early VKDB occurs during first 24 h of life and is seen in newborns of mothers taking medication as above. Classical VKDB occurs between 2 and 7 days in infants with inadequate intake or breastfed infants. Late VKDB occurs after 8 days (3–8 weeks), in infants without vitamin K prophylaxis or with underlying fat malabsorption diseases.

It presents as cutaneous (purpura/echymoses), gastrointestinal, nasal, subgaleal, and intracranial hemorrhages.

Diagnosis: Prolonged prothrombin time (> (greater than) 2 s over control), activated partial thromboplastin time are seen. Serum vitamin K levels may be low [3, 7].

Treatment: RDA is 2–120 μg (micrograms). Neonates routinely receive a single prophylactic intramuscular dose of 0.5–1 mg of vitamin K at birth. Acute bleeding episodes may be treated with fresh frozen plasma or prothrombin complex concentrates. Vitamin K deficiency may be treated with intramuscular phytonadione, 2 mg in children [3].

Water Soluble Vitamins

Vitamin B_1 (Thiamine)

It acts as a coenzyme in many cellular metabolic processes [11]. Dietary sources are whole grains, enriched bread products, dried peas, beans, potatoes, and fish. Deficiency in infants occurs during unsupplemented parenteral nutrition, breastfed infants of thiamine-deficient mothers, congestive heart failure, and severe malnutrition [4].

Clinical Features: Myocarditis, central neurologic alterations (Gayet-Wernicke) and peripheral nervous manifestations along with nonspecific symptoms like fatigue, apathy, and irritability may occur. Cutaneous features [11] include skin breakdown, edema, waxy skin, consequences of peripheral neuropathy, Strachan's syndrome (orogenital dermatitis, sensory neuritis, and amblyopia), seborrheic dermatitis, and angular and diffuse cheilitis.

Diagnosis [4]: By measuring erythrocyte thiamine transketolase activity or blood thiamine concentration.

Treatment [4, 8]: RDA for infants is 0.5 mg. Deficiency is treated with intravenous/intramuscular thiamine of 50–100 mg/day for 7–14 days followed by oral administration until resolution.

Vitamin B2 (Riboflavin) [3, 7, 11]

Riboflavin is involved in many metabolic and oxidation–reduction reactions. It is present in milk, meat, fish, eggs, green leafy vegetables, whole grains, and enriched bread. Deficiency is seen in breastfed infants of riboflavin-deficient mothers, infants weaned to non-milk products, protein energy malnutrition, and preterm infants if banked milk is exposed to light and phototherapy for neonatal hyperbilurubinemia.

Clinical Features: Deficiency results in oro-oculo-genital syndrome. Angular stomatitis begins as small papules at the corner of the mouth, develops maceration and fissuring that bleeds at angles, on lateral extension. Cheilosis with erythema, xerosis, and vertical fissuring of lips, glossitis with magenta or blackish tongue, and seborrheic dermatitis-like eruption can occur. Erythema, lichenification, and crusting of scrotum/vulva extending to inner thighs may be seen more often in infants. Ocular manifestations include photophobia, conjunctivitis, and corneal visualization.

Diagnosis: Erythrocyte glutathione reductase activity coefficient >(greater than) 1.2 is diagnostic.

Treatment: RDA is 0.3–1.6 mg. Treatment is 1–2 mg/day in infants and children.

Vitamin B3 (Niacin)

Niacin is an important cofactor for many metabolic reactions. It is found in meat, eggs, fish, dry beans, nuts, and fortified grains [3]. Deficiency causes pellagra, which is rare in infancy [12]. Skin changes similar to pellagra may be seen in Hartnup disease and other rare hereditary enzymatic alterations [11].

Clinical Features [3, 12]: The classical triad of pellagra is dermatitis, diarrhea, and dementia. Typically, symmetrical, erythematous photosensitive rash occurs, which may eventually result in bullae. Dorsal hands, face, neck (Casal's necklace), and feet may be involved. It eventually results in hyperpigmented, keratotic plaques. Hypertrophic tongue with erosions/ulcers, cheilitis, angular stomatits, and glossitis may occur. Nausea, vomiting, diarrhea, and neurologic manifestations may occur.

Diagnosis: A combined excretion of *N*-methylnicotinamide and pyridone <(less than) 1.5 mg/day is suggestive [12].

Treatment [12]: RDA 5–6 mg for infants. For treatment 10–50 mg orally every 6 h.

Vitamin B6 (Pyridoxine)

Pyridoxine acts as a coenzyme in the metabolism of many aminoacids. Deficiency is rare in infants [13] and is seen in those on formula fed B6-deficient diet.

Clinical Features: Convulsions, anemia, and mucocutaneous lesions are seen. Mucocutaneous findings include seborrheic eruptions on face, scalp, neck, shoulders, buttocks, and perineum. Glossitis, cheilitis, angular stomatitis, and pellagra-like dermatitis may be seen [3, 13].

Diagnosis: Serum pyridoxine-6-phosphate levels <(less than) 20 ng(nanograms)/mL, increased activity of erythrocyte aminotransferases after addition of pyridoxine and tryptopan–loading test [3, 7].

Treatment: RDA is 0.1–2 mg. Treatment consists of intramuscular injection of 100 mg of pyridoxine followed by 2–10 mg intramuscular daily or 10–100 mg orally [13].

Vitamin B9 (Folic Acid) and B12 (Cobalamin)

Folic acid is found in liver, grains, green leafy vegetables, and dried beans. Vitamin B12 is found in liver, egg, beef, and organ meats. Folic acid deficiency [3] may occur due to ingestion of excessively boiled cow's milk or on exclusive goat milk diet or antifolate medications. Vitamin B12 deficiency is caused by inborn errors of transport/absorption, and breastfed infants of vegetarian mothers [3].

Clinical features: Both deficiencies result in megaloblastic anemia and hypersegmented neutrophils. Mucocutaneous manifestations are angular cheilitis, Hunter glossitis, poliosis, and hyperpigmentation [3]. Hyperpigmentation may be generalized but more pronounced over interphalangeal joints, terminal phalanges, dorsa of the wrists, palmar creases, flexures, thighs, shins, trunk, buccal mucosa, and nails [14]. Associated neurologic involvement is seen in vitamin B12 deficiency.

Diagnosis: By serum level estimations.

Treatment [3]: RDA, folic acid, 65–600 μg (micrograms); vitamin B12, 0.4–2.8 μg (micrograms). Treatment is with oral folic acid 1–5 mg/day; vitamin B 12 oral or parenteral 1 mg weekly for 1 month.

Vitamin C (Ascorbic Acid)

Vitamin C is a cofactor for several enzymes. It is an essential cofactor for proline hydroxylase in collagen synthesis. Rich sources include citrus fruits, strawberries, tomatoes, green leafy vegetables, and potatoes [3]. Infants fed on boiled or evaporated milk and dietary restrictions from psychiatric or developmental disorders are predisposed to develop scurvy [15].

Clinical Features: Infantile scurvy occurs between 6 and 24 months of age and rarely occurs in neonates. The disease manifests only after 1–3 months of insufficient vitamin C intake. Early signs are nonspecific and include irritability, fever, fatigue, malaise, and loss of appetite. Generalized tenderness mainly involves legs resulting in pseudoparalysis [16]. Bowing of long bones, depressed sternum, and swollen costochondral junctions may be seen [3].

Cutaneous findings like follicular hyperkeratosis, perifollicular hemorrhage, cork screw hair, and swan neck hair rarely occur in children. Diffuse non-scarring alopecia of scalp may be the earliest indicator of infantile scurvy. The gums become spongy, swollen, and bluish purple secondary to hemorrhage, only if teeth have erupted [16]. Sjogren-like syndrome may occur. Ecchymosis can occur at the site of trauma, pressure, or irritation [11]. Subungual, subconjunctival, and subcutaneous hemorrhages may occur [7]. Anemia due to blood loss, folate, and iron deficiency may occur [3].

Diagnosis: Serum levels <(less than)0.1 mg and leukocyte assay <(less than)7 mg/dL are diagnostic. Radiological signs like Wimberger sign, white line of Frankl, and scurvy line are characteristic [3, 7].

Treatment: RDA is 40–120 mg. Infants and children should be treated with 150–300 mg/day for a month or upto resolution. Fatigue, pain, and spontaneous bleeding resolves within 24 h, joint swelling in days, gum changes in 2–3 days, ecchymoses in 10–12 days, anemia in 2–4 weeks, and normal hair growth in 4 weeks [3, 17].

Biotin (Vitamin H)

Biotin is an essential cofactor for four carboxylase enzymes involved in aminoacid and carbohydrate metabolism. Dietary sources include eggs, liver, nuts, cowmilk, and soyabeans. Deficiency is seen in

multiple carboxylase deficiencies, long term use of anticonvulsants like valproic acid, carbamezapine and phenytoin, long-term parenteral nutrition/elemental infant formula without biotin supplement, and in infant with short gut syndrome receiving broad-spectrum antibiotics [3, 7].

Clinical features: Multiple carboxylase deficiencies, an autosomal recessive disorder present as early neonatal (holocarboxylase synthetase deficiency) or late juvenile (biotinidase deficiency) forms. Neonatal form presents in first few days or rarely delayed upto 15 months. Manifestations are feeding/breathing difficulties, hypotonia, seizures, developmental delay, or ketoacidotic coma. Skin involvement is rare and presents as a seborrheic rash over scalp, eyebrows, eyelashes spreading on to perioral, perinasal, and other flexural areas. Alopecia totalis/universalis may occur [18]. Rarely, it may present as collodion baby and icthyosis [19].

Juvenile form starts after 3 months with myoclonic spasms, hypotonia, ataxia, developmental delay, metabolic acidosis, organic aciduria, sensorineural hearing loss, optic atrophy, keratoconjunctivitis, and blepharitis. Periorificial dermatitis with alopecia may be seen. Superadded candidal infection may occur [18].

Acquired deficiency [3] occurs after 3–6 months of deficient diet and presents as erythematous, scaly crusted dermatitis around eyes, nose, mouth, and other periorificial areas. Alopecia, glossitis, and conjunctivitis with neurologic findings may be seen. Differential diagnosis [18, 20] includes acrodermatitis enteropathica, essential fatty acids deficiency, aminoacidurias, seborrheic dermatitis, and immunodeficiency syndromes.

Diagnosis: Low serum biotin levels, abnormal urine organic acids, decreased biotinidase activity in serum, and leukocytes or cultured fibroblasts are diagnostic. Prenatal diagnosis is possible [3].

Treatment: RDA 5–35 μg (micrograms). Acquired biotin deficiency is treated with 150 μg (micrograms)/day, holocarboxylase synthetase deficiency with 10–40 mg/day, and biotinidase deficiency with 5–10 mg/day [3, 7].

Zinc

Zinc is an essential trace element required for many biochemical pathways. It is found in most animal products, legumes, whole grains, and dairy products. Zinc deficiency may be genetic or acquired [3]. Infants on formula diet with low zinc, premature infants, and low levels of zinc in breast milk are at risk. Hypozincemia in infancy is of three types. Type I (classical acrodermatitis enteropathica) is autosomal recessively inherited with an inherent defect in zinc absorption from gut, type II is due to defective zinc secretion in breast milk and type III in preterm infants on prolonged parenteral alimentation without zinc supplementation [21].

Clinical Features: Acrodermatitis enteropathica presents after weaning or between 4 and 10 weeks of life in formula fed infants. It is characterized by the triad of dermatitis, diarrhea, and alopecia. Type II develops in an exclusively breastfed infant without weaning.

Psoriasiform or annular, erythematous, scaly, crusted plaques, vesiculobullous, pustular, and erosive lesions may be found over face, hands, feet, and anogenital regions. Stomatitis, apathy, irritability, growth retardation, failure to thrive, hair loss, paronychia, delayed wound healing, and ocular involvement may occur [21]. Differential diagnosis [21] includes biotin deficiency, essential fatty acids deficiency, amino acidopathies, organic acidemias, and methylmalonic aciduria.

Diagnosis [22]: Serum zinc levels <(less than)70 μg (micrograms)/dl, levels of zinc-dependent enzymes (e.g., alkaline phosphate).

Treatment [3, 21]: RDA 2–13 mg. In acrodermatitis enteropathica, lifelong zinc supplementation at 2–3 mg/kg/day of elemental zinc and in nutritional deficiency states 0.5–1 mg/kg/day of elemental zinc is given.

Iron

Iron is found in red meat, egg yolk, dried beans, nuts, dried fruits green leafy vegetables, etc. Infants with blood loss, those on an iron fortified formula after transition to cow's formula are at risk [4, 23].

Clinical Features [4]: Nail changes are fragile, longitudinally ridged, lamellated or brittle nails, and koilonychia. Hair changes are lusterless, brittle, dry, split hair shafts, hairloss, and heterochromia with alternate brown, white, and silver bands are described. Aphthous stomatitis, angular stomatitis, and atrophic tongue papillae may be seen.

Diagnosis [4]: Serum iron levels, ferritin, total iron binding capacity, and transferrin saturation levels.

Treatment [23]: RDA 10–15 mg/day. For treatment, oral ferrous sulphate 1.5 mg/kg/dose, three times daily is given in infants and children.

Copper

Copper is an essential component of several metalloenzymes. It is found in fish, oysters, whole grains, liver, chocolates, and eggs [4]. Copper deficiency can be acquired or inherited. Acquired deficiency is seen with malnutrition, long-term unsupplemented parenteral nutrition, exclusive cow's milk diet, cystic fibrosis, and short bowel syndrome. Inherited deficiency is seen in Menkes disease [4].

Clinical Features: In acquired deficiency, hypopigmentation of hair and skin with bone abnormalities are seen. Microcytic anemia and neutropenia are seen [4]. Menkes disease [24] is inherited X-linked recessively. It is characterized by neuronal deterioration and arterial abnormalities. In the neonatal period, some patients display hypothermia, hyperbilurubinemia, and mild hair abnormalities. After 2–3 months, developmental delay, hypothermia, hair abnormalities, hypotonia, and convulsions are seen.

The hair abnormalities [24] are characteristic. There may be no visible hair, but there is always a palpable stubble on the scalp. The hair is depigmented and lusterless. Microscopically, pili torti, monilethrix, and trichorrhexis nodosa are seen. Characteristic facies is seen with pale skin, fat pudgy cheeks that droop and a rather expressionless, dull looking appearance. The skin and joints are lax. The skin is hypopigmented and does not tan on sun exposure. Bone changes, hernia, and urinary tract abnormalities may be seen.

Diagnosis [24]: Low serum copper and ceruloplasmin are seen. Copper levels in cultured fibroblasts and lymphoblasts are high. The activity of enzymes cytochrome c oxidase and dopamine β(beta) hydroxylase is reduced. Radiological changes may be seen. Prenatal diagnosis is possible.

Treatment [24]: Intravenous/subcutaneous copper-histidine injection 200–1,000 μg (micrograms)/day, once per day or 2–3 times per week is recommended.

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Chapter 29
Magnesium and Infant Health

Gema Ariceta

Key Points

- Magnesium (Mg) is the second most abundant intracellular cation of the body and plays an essential function in the synthesis of nucleotides and proteins and in electrolytic transportation.
- The kidney is the major regulator of total body Mg homeostasis, and maintains plasma Mg levels within the normal range.
- Hypomagnesemia may result from insufficient intake, or from excessive intestinal, renal, or skin wasting of Mg.
- Tubular handling and causes of hypomagnesemia of renal origin are described.
- Hypermagnesemia usually follows the administration of large doses of Mg in patients with diminished renal function, or in total parental nutrition errors.

Keywords Magnesium • Hypomagnesemia • Hypermagnesemia • Tubulopathy

Introduction

Biologic Function of Magnesium

Magnesium (Mg) is a divalent cation widely distributed in nature [1], characterized by an atomic number of 12 and an atomic mass of 24.3 Da (12.3 mg are equivalent to 0.5 mmol or 1 mEq) [2]. In humans, it represents the second more abundant intracellular cation after Potassium (K) [3]. Mg functions as a cofactor in many cellular processes and is involved in >300 enzymatic reactions [4]. It plays a central role in the energy metabolism, nucleotide and DNA transcription, and protein synthesis too [5]. Further, Mg regulates sodium (Na), K, and calcium (Ca) channels, influences K intracellular content by its action on the Na,K-ATPase [6], modulates parathyroid hormone (PTH) secretion, release, and activity [7, 8], and participates in bone formation, and neuromuscular stability as well [9]. The main biologic function of Mg is expressed at the nervous and cardiovascular systems where it participates in multiple processes (axonal conductivity, synaptic activity, motor plate function, cardiac rhythm, and vascular peripheral resistance) [4].

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R.R. Watson et al. (eds.), *Nutrition in Infancy: Volume 1*, Nutrition and Health,
DOI 10.1007/978-1-62703-224-7_29, © Springer Science+Business Media New York 2013

Table 29.1 Recommended magnesium intakes (from refs. [12–17]). 1. Daily requirements of Magnesium intake

Age	RDA (recommended dietary allowance) in the USA [14]	RDA (recommended dietary allowance) in UK [15]
Very preterm newborn	20 mg/kg	
Preterm newborn	10 mg/kg	
Term newborn-4 months infant	30 mg	
Infants (4–12 months)	40 mg	
	55–80 mg	55–80 mg
Children	(1–3 years) 80 mg	(1–3 years) 85 mg
	(4–8 years) 30 mg	(4–6 years) 120 mg
	(8–13 years) 240 mg	(7–10 years) 200 mg
		(11–14 years) 280 mg
Adolescents		
Boys (14–18 years)	410 mg	300 mg
Girls (14–18 years)	360 mg	270 mg
Men	400 mg	300 mg
Women	310 mg	270 mg

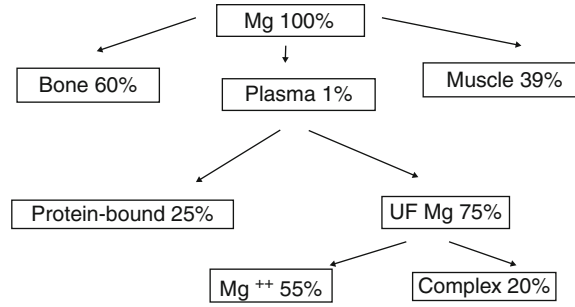

Fig. 29.1 Body magnesium distribution UF (ultrafiltrable)

Mg is also crucial for normal fetus development and maintenance of gestation [10]. In animals chronic maternal Mg deficiency causes uterine hyperexcitability, higher rate of miscarriages, malformations, and impaired fetal growth [11]. Increased postnatal morbidity (hematological disorders and impaired thermoregulation), and mortality is also described. Many women, especially those from disadvantaged backgrounds have intakes of Mg below the recommendations (Table 29.1). Despite some observational studies reported less fetal growth retardation, and preeclampsia following maternal Mg supplementation, large poorly designed studies failed to demonstrate it [18]. However pharmacological tocolytic magnesium therapy is widely used [19]. Mg deficiency is claimed to be a potential factor in the development of neonatal apneas, bronchopulmonary dysplasia, and sudden infant death syndrome [20].

Body Distribution of Mg

Total body content of Mg in a 70 Kg adult subject is ≈21–28 g (875–1,200 mmol or 1,750–2,400 mEq [9], whereas in a newborn of 3.5 kg is ≈5 g (30 mmol or 60 mEq) [21]. More than 99% of body Mg is located intracellularly, in bone and skeletal muscle [22], and <1% is extracellular. Plasma Mg circulates in three separate fractions: ionized (55–60%), complexed with citrate, phosphate, oxalate, or sulphate (20–25%), and albumin-bound (20–30%) [1, 23]. Ionized and complexed Mg fractions compose the ultrafilterable form (UFMg) which represents the biological active fraction of Mg (Fig. 29.1).

Table 29.2 Normal plasma levels of magnesium in children (from refs. [25, 30, 31])

Age	Mg (mg/dL)[a]	UF Mg (mg/dL)[b]
Neonates <30 weeks	2.20±0.50	1.19±0.27
≥30 weeks	1.76±0.22	1.06±0.02
Infants (1–12 months)	1.86±0.20	1.24±0.17
Children (1–15 years)	1.70±0.15	1.18±0.10
Adults	2 (1.7–2.4)[c]	

[a]Mg normal levels in plasma: infants 0.76±0.08 mmol/L, children 0.70±0.06 mmol/L ($p<0.001$)
[b]UFMg normal levels in plasma: infants 0.51±0.07 mmol/L, children 0.49±0.04 mmol/L ($p<0.001$)
[c]Mean (range)

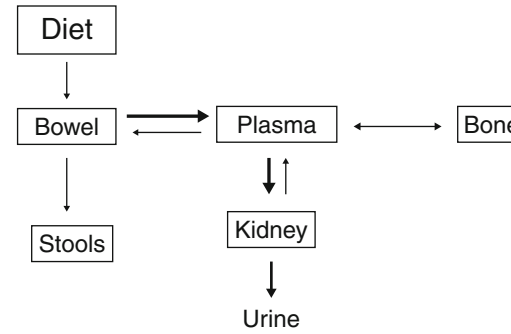

Fig. 29.2 Magnesium body balance

Plasma level of Mg is closely regulated. In adults normal values are 0.85 mmol/L (range 0.7–1.05) [3], 1.55 mEq/L (1.4–1.9 mEq/L) [24], and 2 mg/dL (1.7–2.4) [25]. In children, plasma Mg is elevated in preterms [26], and gestational age and birth weight are inversely related to magnesemia ($p<0.001$) [26–28]. Plasma level of Mg is increased during the first year of life ($p<0.001$) [26, 29] (Table 29.2). Breast- or formula-fed infants have similar plasma Mg level [32].

Perinatal Mg Metabolism

Mg concentration in amniotic fluid is 1.7 mg/dL or 0.7 mmol/L. During pregnancy Mg freely crosses the placenta and accumulates in the fetus, mainly during the first trimester [21]. Placental transfer continues throughout the whole gestation with a daily accumulation of Mg of about 6 mg [33]. Transfer of Mg across the placenta depends upon an active transport mechanism, necessary to maintain higher serum fetal than maternal concentrations [34].

Mg concentration in cord blood is varies from 1.89±0.36 to 2.09±0.2 mg/dL [21]; 0.81±0.04 mmol/L [35]. Fetal levels reflect maternal Mg status [33].

Body Balance of Mg

Three organs determine the level of plasma Mg (Fig. 29.2): the intestine, by which Mg is taken up from the food; the bone, which stores and releases Mg, and the kidney which determines the urinary excretion of Mg, and thus controls the body balance of Mg.

Intake of Mg

Standard daily diet in western countries is enough to fulfill normal daily requirements (Table 29.1). Mg is found in a wide variety of foods, and at particularly high levels in unrefined whole grain cereals, green leafy vegetables, nuts, seeds, peas, soy beans, chocolate, and seafood [4]. Mg content in human milk is ≈20–40 mg/dL [36] lower than in adapted formula ≈40–50 mg/dL [32]. Human milk supplementation of Mg for low-birth-weight infant is unneeded [37].

Intestinal Absorption of Mg

About 40% of ingested Mg is absorbed along the gut, mainly in proximal parts of the small intestine [1, 2]. Newborns, especially preterm infants, have a higher Mg absorption capacity [32]. The main site of Mg absorption is the small bowel where approximately one third of dietary Mg is reabsorbed. In adults, the intestine secretes ≈40 mg of Mg daily, and ≈20 mg is absorbed in colon. Gastrointestinal Mg absorption in the small bowel involves two mechanisms: a non-saturable paracellular passive transport, and a saturable transcellular active pathway [38]. Absorption in the small bowel occurs via paracellular simple diffusion at high intraluminal Mg concentrations, and at low concentrations, by active transcellular uptake via the recently identified Mg channel TRPM6 (transient receptor potential channel metastatin 6), which is expressed along the brush border membrane of the small intestine [39]. Inherited mutations of this TRPM6 channel cause the syndrome of congenital chronic hypomagnesemia, first described in the sixties [40, 41].

With normal dietary content, Mg is most efficiently absorbed in the distal part of the small bowel in a passive manner. When Mg intake is low, the Mg absorption is increased through active transport systems in the large intestine [42]. Regulation of intestinal absorption of Mg is not well known, but it is influenced by the food content of Mg and Ca, K, proteins, and carbohydrates. Thus, Mg absorption may be reduced by the formation of intraluminal complexes containing fitates [3]. Several hormones (PTH, 1,25 $(OH)_2$vitamin D_3, aldosterone, growth hormone, calcitonin) also influence Mg absorption [43].

Renal Homeostasis of Mg

The kidney is the major regulator of total body Mg homeostasis, and plays an important role in maintaining plasma Mg levels within the normal range. In the setting of hypomagnesemia, the kidney decreases Mg excretion to as little as 0.5% of the filtered load. Conversely, in the setting of hypermagnesemia, up to 80% of the filtered load can be excreted [44]. Renal Mg handling is a process of filtration and reabsorption; 10–15% of filtered Mg is reabsorbed at the proximal tubule (PT), whereas ≈70% of total filtered Mg is reabsorbed at the thick ascending limb of the loop of Henle (TAL). In these segments transepithelial Mg reabsorption occurs in a passive paracellular fashion [45]. At the TAL Mg reabsorption is closely linked with Ca, and the driven force is the electrical gradient that results from K exit across the apical membrane through ROMK channels. Claudin 16/19 complex, two tight junction proteins, are involved in controlling Mg and Ca permeability at the paracellular pathway, through selective Na permeability [46]. The Calcium sensing receptor (CasR) reduces the positive luminal voltage due its action on Na,Cl, and K cotransporter (NKCC2), and thus influences Mg reabsorption. The distal convoluted tubule (DCT) reabsorbs the remaining 10–15% and determines the final amount of Mg present in the urine, ≈3–5% of filtered Mg in normal conditions. At DCT Mg reabsorption is an active mechanism through a specific epithelial Mg channel named

Table 29.3 Normal urinary magnesium excretion values in children (modified from [26, 30, 31]

Age	UMg/Cr[a] (mg/mg)	VMg (mg/k/d)	FE Mg%[b]
Neonates <34 weeks	0.010 (0–0.15)[c]		1.21 (0–11.3)[c]
≥34 weeks	0.017 (0.02–0.14)[c]		1.66 (0.2–8.2)[c]
Infants (1–12 months)	0.13 ± 0.08	1.5 ± 0.9	3.77 ± 2.09
Children (1–15 years)	0.08 ± 0.08	1.6 ± 0.8	3.93 ± 1.72

[a]Normal UMg/Cr: infants 0.023(0.009–0.07) mmol/mmol, children 0.015 (0.006–0.04) mmol/mmol ($p < 0.001$)
[b]Normal EFMg: infants 3.2 (1–7.8)%, children 3.4 (1.6–8.1)%
[c]Median and range

TRPM6, that colocalizes with the Na-Cl cotransport (NCC), and the Kv1.1 along the apical membrane. The epidermal growth factor (EGFR), the Cl channel CLC-kb, channel Kir4.1, the Na-K-ATPase, and its FXYD2 γ subunit are all localized at the basolateral membrane and influences Mg reabsorption as well. Further, FXYD2 γ gene expression is controlled by the hepatocyte nuclear factor (HNF1β), that this way, also participates in Mg reabsorption. Mutations of genes participating in Mg tubular transport lead to tubular hypomagnesemia [47]. Excellent reviews of Mg renal handling had been published [45–49].

Mg renal handling is regulated by the concentration of luminal Mg, acid–base balance and plasmatic levels of Ca, K, and inorganic phosphate. PTH is the main hormone that increases tubular reabsorption of Mg at the TAL. Hypermagnesemia, hypercalcemia and acidosis increase urinary Mg wasting. The role of aldosterone is misunderstood but Mg reabsorption follows Na reabsorption: it increases under conditions of volume depletion and it decreases under conditions of volume expansion [43, 44].

Urine Mg daily excretion is ≈120–140 mg in adults [9]. In children, normal Mg in urine is 1.6–2.8 mg/kg body weight [30, 50, 51]. UMg/Creatinine ratio and Fractional excretion of Mg (FEMg%) in children [31] are described in Table 29.3.

Hypomagnesemia

Hypomagnesemia is defined by Mg plasma levels: ≤1.4 mg/dL in children older than 3 months, and ≤ 1.6 mg/dL in younger than 3 months of age, respectively [26, 31]. Hypomagnesemia may result from insufficient intake, or from excessive intestinal, renal, or skin wasting of Mg. As Mg is present in a wide variety of foods, significant dietary deficiencies in children are very rare [52]. Maternal milk Mg is very well absorbed, and there are no reports of limitations of breast milk providing adequate Mg nutrition for the exclusively breast-fed infant [36]. Diuretics constitute the most frequent cause of hypomagnesemia, but Mg deficiency is also often seen in hospitalized or dependent individuals with poor nutrition, and/or intestinal wasting [22]. Table 29.4 describes hypomagnesemia differential diagnosis; most relevant in children are:

Transient Neonatal Hypomagnesemia

This situation is common in infants born to diabetic mothers [21, 53], in low-birth-weight newborns [28], or coexisting with hyperphosphatemia [33].

Infants born of insulin-dependent diabetic mothers, and even those of class A (controlled only with diet), have a high rate of neonatal hypomagnesemia, related to decreased maternal level of blood Mg [54]. In general, the risk of infant hypomagnesemia is related to maternal diabetes severity and maternal

Table 29.4 Etiology of hypomagnesemia (modified from [22])

Carencial
Alcoholism
Protein-calorie malnutrition
Prolonged fluid or total parenteral nutrition
Maternal deficient Mg intake during pregnancy or lactation
Bulimia and anorexia nervosa
Refeeding syndrome
Digestive
Prolonged gastric suction
Malabsorption (celiac disease, pancreatic insufficiency, Crohn's disease, ulcerative colitis)
Short-bowel syndrome
"By-pass" surgery
Laxatives abuse
Colon cancer
Congenital chronic hypomagnesemia
Renal
Inherited "Mg-losing" tubulopathies (isolated renal hypomagnesemia, FHHNC, Bartter syndrome, Gitelman syndrome)
Post-tubular necrosis
Post-obstructive uropathy
Distal renal tubular acidosis
Chronic kidney disease
Endocrine
Hyperaldosteronism
Hyperparathyroidism
Hyperthyroidism
Diabetes
Drugs
Diuretics
Aminoglycosides
Amphotericin B
Cisplatinum
Anticalcineurinics (cyclosporin A, tacrolimus)
Pentamidine
Foscarnet
Proton pump inhibitors
Electrolyte disorders
Hypercalcemia
Hypervolemia
Phosphate depletion
Miscellaneous
Transient neonatal hypomagnesemia
Porphyria with inappropriate antidiuretic hormone secretion
Repeated blood transfusion
Hungry-bone syndrome
Burns

deficiency [53]. Uncontrolled maternal diabetes leads to diminished fetal Ca and Mg placental accretion [10]. Maternal PTH-vitamin D axis dysfunction, hyperglucemia-induced Mg intracellular shift, and increased Mg excretion by osmotic diuresis justify Mg deficiency in diabetic mothers and their offsprings as well [33].

Mild transient neonatal hypomagnesemia corrects spontaneously with feeding but occasionally it may require the therapeutic administration of Mg [12].

Hypomagnesemia of Gastrointestinal Origin

Mg dietary deficiency is rare, but it can occur after prolonged fasting, protein-calorie malnutrition or feeding disorders (Table 29.4). Malabsorption, short bowel syndrome, or laxatives abuse among others produce hypomagnesemia of intestinal origin. Estimation of intracellular Mg content and body Mg balance can rely on intravenous Mg loading test [55], or more contemporary isotopic techniques [13], but their use is limited to research.

Congenital Chronic Hypomagnesemia

This syndrome, also called familial hypomagnesemia with secondary hypocalcemia (OMIM #602014) is a rare autosomal recessive disorder caused by homologous or compound heterozygous mutations in the TRPM6 gene on chromosome 9q21 [56]. The TRPM6 protein, a member of the long transient receptor potential channel (TRPM) family, is expressed in intestinal epithelia and kidney cells and represents the intestinal saturable Mg carrier [57]. Clinically, it typically manifests between 2 and 8 weeks of life with generalized convulsions or signs of increased neuromuscular excitability, such as muscle spasms or tetany (Table 29.5) [58]. Occasionally it manifests later in life [59]. Hypocalcemia and severe hypomagnesemia are characteristic. Hypocalcemia results from PTH failure and resistance that lead to severe magnesium deficiency. Convulsions are refractory to calcium salts administration.

Table 29.5 Hypomagnesemia: clinical and biochemical findings (modified from [9])

	Symptom	Mechanism
Biochemical secretion	Hypocalcemia	Impaired PTH
		PTH resistance
		Vit D resistance
	Hypokalemia	Renal K wasting
Neuromuscular	Muscular irritability	Hypocalcemia
	Hyperreflexia	Hypomagnesemia
	Tetany	
	Muscle weakness	
	Nystagmus, dizziness, ataxia	
	Depression, psychosis	
Cardiovascular	Arrhythmias	Hypocalcemia
	Δ sensitivity to digitalis	Hypomagnesemia
	Hypertension	
Digestive	Dysphagia	Muscular irritability
Endocrine	Bone resistance to PTH	
	Hyperreninism	
	Hyperaldosteronism	
	Reduced lipolysis	
Hematological	Anemia	Reduced erythrocyte half live

Treatment includes immediate administration of magnesium, usually intravenously, followed by life-long high-dose oral magnesium. Oral Mg must be maintained long-life to prevent symptoms. Prognosis is favorable if diagnosis is made early enough, but untreated, the disease may be fatal or produce neurologic damage [56].

Hypomagnesemia of Renal Origin

A renal origin must be suspected when Mg is present in the urine despite the coexistence of significant hypomagnesemia. This situation may have an intrinsic renal origin or be secondary to metabolic and endocrine causes or administration of drugs and toxins [30]. Less often, mutations of genes modulating Mg tubular handling cause inherited hypomagnesemia (Table 29.6).

Table 29.6 Inherited renal hypomagnesemia (modified from [45, 49])

Disease	Gene	Protein	Chromosome	Inheritance	Symptoms
Familial hypomagnesemia hipercalciuria nephrocalcinosis (FHHNC)	CLDN 16 (OMIM # 248250)	Claudin 16	3q27–29	AR	Hypomagnesemia Hypercalciuria
	CLDN 19 (OMIM #248190)	Claudin19	1p34.2	AR	Nephrocalcinosis CKD Ocular involvement
Dominant hypomagnesemia with hypocalciuria	FXYD2 (OMIM # 154020)	γ subunit Na/K ATPase	11q23	AD	Hypomagnesemia Hypocalciuria
Isolated recessive hypomagnesemia	EGF(OMIM #611718)	EGF	4q25	AR	Hypomagnesemia
Hypomagnesemia with hypocalcemia	TRPM6 (OMIM #602014)	TRPM6	9q22	AR	Hypomagnesemia Hypocalcemia
Autosomal dominant hypocalcemia	CasR (OMIM # 601198)	CasR	3q21	AD	Hypocalcemia Hypomagnesemia Hypoparathyroidism
Isolated dominant hypomagnesemia	KCNA1 (OMIM # 160120)	Kv1.1	12p13	AD	Hypomagnesemia Cerebral atrophy
EAST/SeSAME syndrome	KCNJ10 (OMIM # 612780)	Kir4.1	1q23	AR	"Gitelman-like" tubulopathy, hypocalcemia Ataxia, epilepsy, deafness
Mody 5 diabetes	HNF1β (OMIM # 137920)	HNF1β	17q12	ND	Renal cystic displasia, Mody diabetes Hypomagnesemia
Gitelman's syndrome	SLC12A3 (OMIM # 263800)	NCCT	16q13	AR	Renal Na, K, and Mg wasting Hypocalciuria
Bartter's syndrome	SLC12A1	NKCC2	15q21	AR	Renal Na, K, Ca, and Mg wasting, deafness, CKD
	KCNJ1	ROMK	11q24	AR	
	CLCNKA/B (OMIM # 601678, 241200, 602522, 607364)	CLCNKA/B	1p36	AR	
		Barttin	1p31	AR	

AR autosomal recessive, *AD* autosomal dominant, *ND* non-determined, *CKD* chronic kidney disease

Clinical Findings

Symptoms generally appear when plasma Mg concentration drops <1.2 mg/dL, and can be related to hypokalemia or hypocalcemia, commonly associated. Table 29.5 summarizes the clinical signs and symptoms of hypomagnesemia and underlying mechanisms. It should be recognized that states of severe Mg deficiency may remain completely asymptomatic [22].

Diagnosis

Mg deficiency is often underdiagnosed. Mg determination is not routine in many centers, and symptoms may be erroneously attributed to the frequently associated hypokalemia or hypocalcemia [2]. Plasma Mg quantification has limited value to reflect the intracellular Mg, and therefore many subclinical deficiencies may remain unapparent [22].

In clinical practice, a state of Mg deficiency is always diagnosed by the presence of hypomagnesemia. The simultaneous determination of urinary Mg will permit to suspect its pathogenesis. If urinary Mg excretion is low or nil, a carencial or digestive origin is probably the cause. If Mg is present in the urine in appreciable quantities, the hypomagnesemia is probably of renal origin [30].

Therapy

Replenishment of intracellular Mg stores remains largely empirical. The amount of Mg to be administered is usually based on an estimated deficit of 1–2 mEq/kg body weight. In many circumstances oral administration of 10–20 mg/kg/day of an Mg salt (hydroxide, lactate, chloride, citrate, glycerophosphate, etc.) may be sufficient. It must be taken into account that only about 50% of administered Mg is being absorbed and that large doses have a noxious catartic effect. In cases of symptomatic severe hypomagnesemia it may be necessary to give parenteral Mg as Mg sulfate. About half of the calculated deficit must be given during the first 24 h and the remaining amount along the following 2–4 days. In patients with chronic deficiency of digestive origin, parenteral Mg supplements should be given repeatedly to avoid symptomatic hypomagnesemia [30].

Hypermagnesemia

Definition

The term hypermagnesemia is defined as plasma Mg concentration >2.5 mg/dL in infants younger than 1 year of age, and >2.0 mg/dL in those older than 1 year (Table 29.2) [26, 31].

Etiology

Hypermagnesemia usually follows the administration of large doses of Mg in patients with diminished renal function (Table 29.7), or in total parental nutrition errors [60]. In neonates is described following Mg sulfate administration for neonatal pulmonary hypertension treatment. Hypermagnesemia may be also observed transiently following perinatal asphyxia as the consequence of transcellular Mg exit [61].

Table 29.7 Etiology of hypermagnesemia

Renal failure
Acute (oliguric)
Chronic
Acidosis
Acute metabolic acidosis
Ketoacidosis
Endocrine
Addison disease
Hypothyroidism
Pheochromocytoma
Exogenous Mg administration
Laxatives
Antiacids
Enemas
Solutions for irrigation of urinary bladder
Parenteral Mg (myocardial ischemia, arrhythmia, eclampsia, placental insufficiency, primary pulmonary hypertension, asthma)

Table 29.8 Hypermagnesemia: clinical and biochemical findings (adapted from [9])

	Symptom	Mechanism
Biochemical	Hypocalcemia	Low PTH secretion renal Ca loss
Neuromuscular	Neuromuscular depression	Impaired nerve transmission
	Muscular weakness	
	Hyporeflexia	Altered postsynaptic response
	Headache	
	Dizziness	
	Depression	
	Lethargy	
Cardiovascular	Facial redness	Hypermagnesemia
	Arrhythmias	Hypocalcemia
Digestive	Nausea	
	Vomiting	

Clinical Findings

Moderate elevation of plasma Mg concentration is only accompanied by few signs such as nausea and vomiting but marked hypermagnesemia is followed by severe neurological and cardiovascular impairment (Table 29.8). Newborns present with apnea, refractory bradicardia, and hypotension, mimicking a septic shock [60].

Therapy

In situations of moderate hypermagnesemia it may be sufficient to stop the administration of the offending Mg salt and to increase diuresis by administering a loop diuretic such as furosemide. However, in cases of severe hypermagnesemia the patient is in risk of immediate death and therapy must include intravenous administration of calcium gluconate and urgent initiation of dialysis if there is evidence of impaired renal function [22].

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Chapter 30
Vitamin K Deficiency and its Prevention and Treatment in Infants

Eugen-Matthias Strehle

Key Points

- Neonates lack vitamin K which can lead to vitamin K deficiency bleeding (VKDB).
- There is scientific evidence that enteral and parenteral administration of vitamin K can prevent and treat this potentially life-threatening condition.
- Vitamin K prophylaxis should be made available to every newborn baby worldwide.

Keywords Hemorrhagic disease of the newborn • Vitamin K • Vitamin K deficiency bleeding • Vitamin K prophylaxis • Proteins induced by vitamin K absence or antagonism • PIVKA

Vitamin K

Nomenclature

Vitamin K (VK) is the name for a group of fat-soluble organic substances that consist of a 2-methyl-1,4-naphthoquinone ring structure with differing carbon side chains at the 3-position. There are approximately 30 natural and synthetic forms of vitamin K [1, 2]. VK_1 (phylloquinone, phytylmenadione) is present in green fruit and vegetables such as asparagus, avocado, broccoli, kale, kiwi, lettuce, spinach, and sprouts. Menaquinones (VK_2) are produced by gram-positive bacteria in the gastrointestinal tract and can be found in significant concentrations in the human liver (Fig. 30.1). VK_3 (menadione) is a water-soluble synthetic vitamin analog that used to be administered to neonates as prophylaxis in the 1950s under the brand name "Synkavit." When given in high doses, the preparation can cause hemolytic anemia and kernicterus, and therefore it was taken off the market [3]. Menadiol (VK_4) is another water-soluble, synthetic form of vitamin K which is available as food supplement. Vitamin K_5 has fungistatic effects and acts as preservative in pharmaceuticals, food, and drinks [4].

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R.R. Watson et al. (eds.), *Nutrition in Infancy: Volume 1*, Nutrition and Health,
DOI 10.1007/978-1-62703-224-7_30,

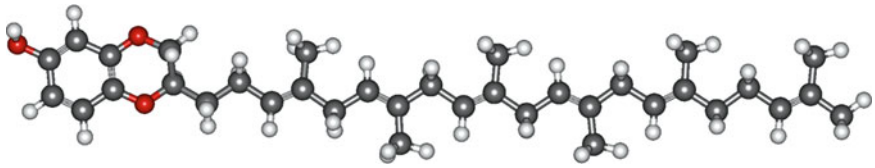

Fig. 30.1 Molecular structure of vitamin K2 (menaquinone; *white*: hydrogen atoms; *grey*: carbon atoms; *red*: oxygen atoms; image in public domain)

Fig. 30.2 Medicago sativa (alfalfa, lucerne; courtesy of Gerhard Rheinnecker, Hassloch/Germany)

History

In 1894 the Boston obstetrician and pediatrician Charles Wendell Townsend described 50 neonates who presented with spontaneous bleeding from various sites during the first 2 weeks of life. Thirty one of the infants died and 19 made a spontaneous recovery, some of them with neurological sequelae. Townsend distinguished between this hemorrhagic disease of the newborn (HDN) which he assumed to have an infectious cause, and true hemophilia [5, 6]. In the early 1930s Dam, Schønheyder and others published several papers in which they reported a bleeding tendency in chickens fed on a sterol-free diet. They demonstrated that this condition was caused by a lack of a fat-soluble substance which they named vitamin K; firstly, because this letter of the alphabet had not yet been used for other vitamins, and secondly, because the Scandinavian word for clotting is "koagulation" [7]. Dam and Doisy [8] received the Nobel Prize in Physiology or Medicine 1943 in 1944 for their discovery of vitamin K and its chemical nature [9]. Warner et al. showed that low blood prothrombin concentrations in patients with obstructive jaundice could be restored by feeding them human bile mixed with alfalfa which is rich in vitamin K ([10], Fig. 30.2).

Physiology

Human hemostasis is a complex process that requires the activation of platelets (primary hemostasis) and coagulation factors (secondary hemostasis); it also involves cofactors such as vitamin K and phospholipids, and regulators such as protein C and antithrombin. Clotting factors are predominantly

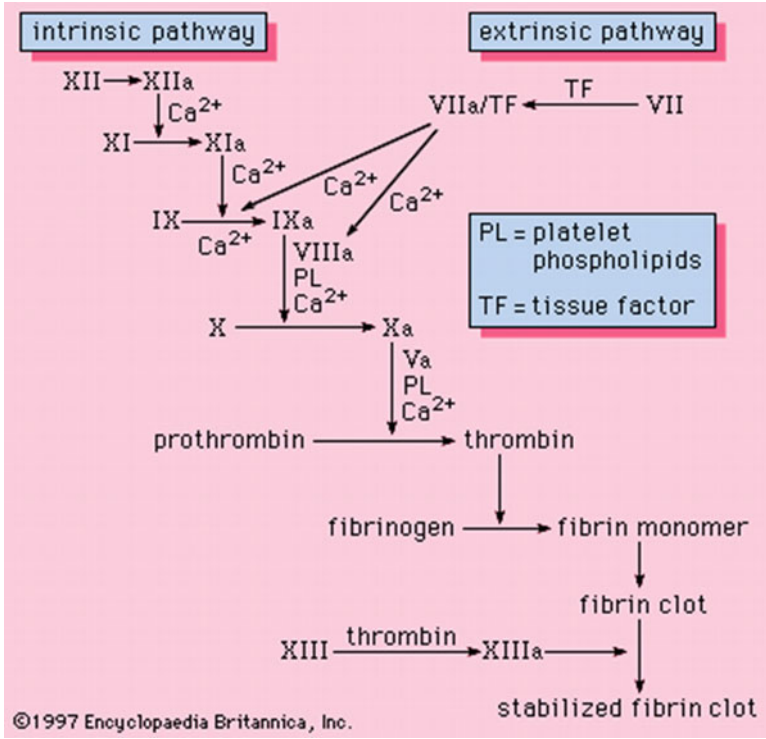

Fig. 30.3 Clotting cascade (reprinted with permission from *Encyclopaedia Britannica*, © 1997 by Encyclopaedia Britannica, Inc.)

serine endopeptidases which circulate as inactive precursor enzymes (zymogens) in the blood. They carry Roman numbers for identification (I, II, III, IV, V, VII, VIII, IX, X, XI, XII, XIII, and XIV). In essence, following tissue damage a platelet plug is formed to stop bleeding from small- and medium-sized blood vessels; simultaneously, prothrombin is converted to thrombin, and fibrinogen to fibrin. The resulting fibrin clot stabilizes the platelet plug (Fig. 30.3).

In pre-term and full-term neonates the levels of the vitamin K dependent coagulation factors II, VII, IX, and X are reduced by 50% compared to adults [11]. Their concentrations reach adult values by ca. 6 months of age. Reduced vitamin K, in combination with oxygen and carbon dioxide, is an essential cofactor that enables activation of these Gla-proteins [12]. During the so-called posttranslational γ-carboxylation the glutamic acid (Glu) residues present in factors II, VII, IX, and X are modified to γ-carboxyglutamate by the enzyme γ-glutamyl carboxylase (GGCX). The enzyme vitamin K epoxide reductase (VKOR), which can be inhibited by the anticoagulant drug warfarin, recycles the oxidized vitamin K (vitamin K 2,3-epoxide) back to its reduced form (Fig. 30.4). The active clotting factors can bind calcium and phospholipids. Other Gla-proteins found in humans are proteins C, S, and Z, matrix Gla protein (MGP), and osteocalcin [13].

Pathophysiology

Coagulation factors are produced in the liver, and certain diseases of the liver and gall bladder can lead to acquired coagulopathies. Examples are fulminant hepatitis, liver cirrhosis, and bile duct obstruction.

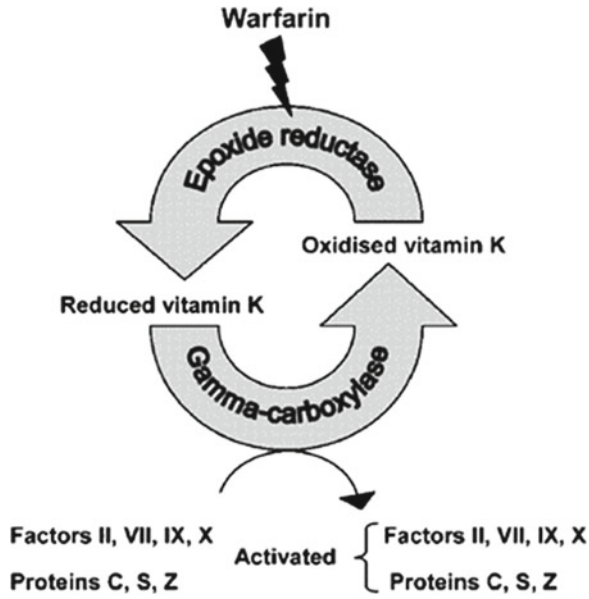

Fig. 30.4 Vitamin K cycle (courtesy of JE Sadler, Division of Hematology, Department of Medicine, Washington University, St. Louis, MO; reprinted by permission from Macmillan Publishers Ltd.)

In hemophilia (types A, B, or C), individual clotting factors (VIII, IX, or XI) are deficient due to inherited or de novo gene mutations. This results in spontaneous hemorrhages in subcutaneous fat tissue, muscles, joints, or internal organs ([14], Fig. 30.5). In vitamin K deficiency, the hydroquinone-dependent conversion of glutamic acid to γ-carboxyglutamic acid can no longer take place, leaving the coagulation factors undercarboxylated and therefore inactive. These "proteins induced by vitamin K absence or antagonism" (PIVKA) circulate in the blood where they act as biomarkers for a patient's vitamin K status. Acute bleeding of different severity can occur ([15], Fig. 30.6).

Genetics

The gene for γ-glutamyl carboxylase, GGCX, was identified in 1991 [16, 17]. It resides on chromosome 2p12 and spans 12.5 kilo bases. GGCX encodes a multi-pass membrane protein located in the endoplasmic reticulum. It consists of 758 amino acids and has a molecular weight of 87.6 k Da. The second enzyme necessary for recycling vitamin K is VKOR which is also an endoplasmic protein and which has three transmembrane domains. With a length of 163 amino acids and a weight of 18.2 k Da it is considerably smaller than GGCX. The gene for VKOR has been named vitamin K epoxide reductase complex, subunit 1 (VKORC1), as potentially other enzymes are involved in the vitamin K cycle. VKORC1 is 4.1 kilo bases long and located on chromosome 16p11.2 [18]. Wadelius et al. demonstrated that the variable response of patients to the anticoagulant effect of warfarin is due to single-nucleotide polymorphisms of VKORC1 [19].

Vitamin K dependent clotting factor deficiency (VKCFD) is a rare, autosomal-recessive disease characterized by a combined absence of factors II, VII, IX, and X. It is caused by mutations of either GGCX (= VKCFD1) or VKORC1 (= VKCFD2) and leads to easy bruising and mucosal bleeding of varying degrees. The condition was first described by McMillan and Roberts in 1966 and is part of a larger group called familial multiple coagulation factor deficiencies (FMCFD, [20]).

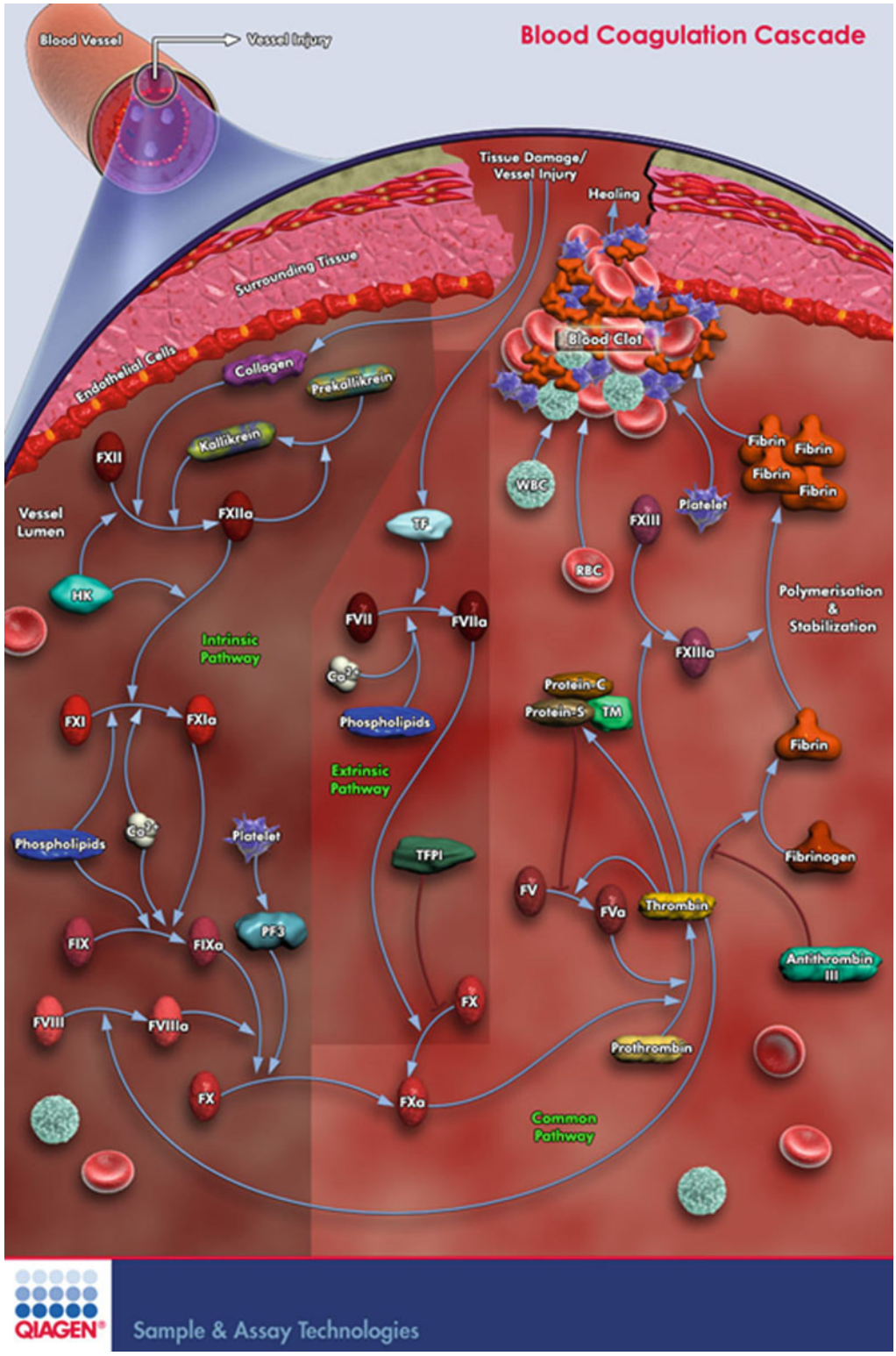

Fig. 30.5 Three-dimensional image of the human coagulation cascade depicting activation of intrinsic, extrinsic, and common pathways following blood vessel injury (© QIAGEN, all rights reserved)

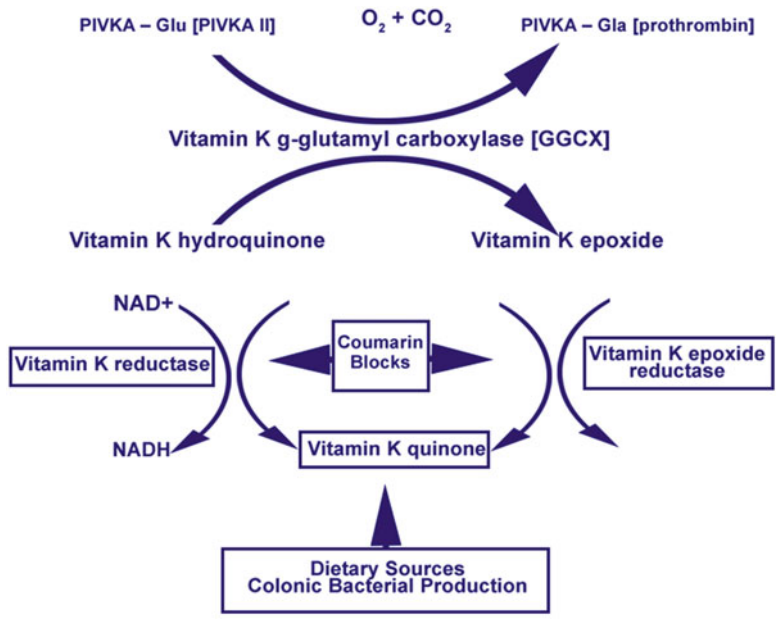

Fig. 30.6 Cyclical metabolism of vitamin K including conversion of the protein induced by vitamin K absence or antagonist II (PIVKA II) to prothrombin (reprinted with permission from eMedicine.com, 2010. Article: Hemorrhagic disease of newborn. Authors: Nimavat DJ, Sherman MP)

Vitamin K Deficiency

Nomenclature

The term "hemorrhagic disease of the newborn" was coined by Townsend in the 1890s and served its purpose for approximately one century. In 1999, the International Society on Thrombosis and Haemostasis (ISTH) suggested that the name be changed to vitamin K deficiency bleeding (VKDB) to better describe the underlying pathology [21]. Another reason was the fact that bleeding in affected infants can occur beyond the newborn (neonatal) period; and to distinguish it from "hemolytic disease of the newborn" which has the same abbreviation "HDN." However, the new term also has a disadvantage as it does not differentiate between VKDB in infants, older children and adults. Perhaps the letter "I" for "infantile" could be added to the acronym "VKDB."

Clinical Presentation

Infantile VKDB is caused by a lack of the vitamin K dependent clotting factors II, VII, IX, and X. Vitamin K is detectable in low concentrations in fetuses but placental transfer is limited. This and the absence of vitamin K producing gut flora are the reasons for the relative vitamin K deficiency in newborns [22]. Infantile VKDB can be divided into early, classical, and late forms depending on the age of onset. *Early VKDB* is defined as bleeding at less than 24 h of age. In the majority of cases it is

caused by maternal drugs that interfere with the infant's vitamin K metabolism in the liver, for instance enzyme inducing antiepileptic drugs (AEDs), anticoagulants, and antituberculous drugs [23]. Common sites of bleeding are extra- and intracranial, pulmonary and gastrointestinal. It has been suggested that mothers with epilepsy should take oral vitamin K daily for 4 weeks prior to delivery but supporting evidence for this recommendation is weak [24]. Similarly, vitamin K given to mothers in premature labor does not reduce the risk of their premature infants developing periventricular hemorrhage [25]. *Classical VKDB* occurs between day 1 and day 7 of life. Infants show spontaneous bleeding from nose, skin, umbilicus and rectum, or following venepuncture and circumcision. This type is associated with sole breastfeeding, low milk intake, and unrelated neonatal illness [11, 15]. The recommended daily amount of vitamin K for babies from 0 to 6 months is 10 μg. Breast milk contains only 0.21 μg per 100 ml, whereas formula milk contains between 2.7 and 6.7 μg per 100 ml [26]. *Late VKDB* presents after the first week and up to 6 months of age in exclusively breastfed infants and those with abnormalities of the hepatobiliary tract, for example biliary atresia, alpha-1-antitrypsin deficiency, cystic fibrosis, or galactosemia [21, 27]. Bile salts are necessary for the normal absorption of vitamin K. Signs and symptoms of affected infants include poor feeding, vomiting, seizures, intracranial hemorrhage (ICH), bruising, and melena [28]. ICH is common (30–60%), may be preceded by "warning bleeds" from other sites and often results in neurological sequelae or death.

Diagnosis

From 10 weeks' gestation onwards fetal plasma concentrations of the coagulation proteins II, VII, IX, and X increase steadily and reach about 50% of normal at the time of birth. Vitamin K levels in cord blood samples are minimal even when taken after maternal vitamin K injection at the time of delivery [29]. An isolated prolonged prothrombin time (PT) in the presence of a normal fibrinogen value and platelet count points towards vitamin K deficiency [30]. The international normalized ratio (INR) measures the PT of a patient divided by the PT of a control. An INR of more than 3.5 is considered significantly prolonged. In severe cases of VKDB the activated partial thromboplastin time (APTT) may also be raised. A more sensitive test for subclinical vitamin K deficiency is the determination of undercarboxylated prothrombin (PIVKA II). A study on newborn infants demonstrated elevated PIVKA II cord blood levels in 48%. The levels in these breastfed infants returned to normal over a period of 2 weeks after a single intramuscular injection of vitamin K [31].

Treatment

As in any sick child airway, breathing and circulation must be secured first. The specific treatment of early, classical, and late VKDB is essentially the same but it varies according to the severity of bleeding. Slow intravenous or subcutaneous administration of vitamin K at a dose of 1–2 mg will reverse the coagulopathy clinically and hematologically within a couple of hours in most cases [30]. The intramuscular route should be avoided because of the risk of causing a haematoma. No toxic effects of vitamin K have been reported in humans but anaphylaxis is a possibility. In infants with severe hemorrhages it may be necessary to give additionally an infusion of fresh frozen plasma (10–15 mL/kg) or of a concentrate containing factors II, VII, IX, and X. If ICH is present, neurosurgical intervention may be required [27].

Vitamin K Prophylaxis

Epidemiology

The incidence of idiopathic VKDB varies significantly depending on the onset of the disease, the mode of feeding and whether infants have received intramuscular, oral, or no vitamin K prophylaxis. It is highest in breastfed babies who are not supplemented with vitamin K. The incidence of early VKDB without vitamin K prophylaxis ranges from 6 to 12% [21, 32]. Early studies in developed countries and more recent ones from Africa suggested an occurrence of classical VKDB in 0.8–1.7% among infants not receiving prophylaxis. Two current epidemiological studies from Malaysia and Thailand reported an incidence (per 100,000) of 25 and 71.5, respectively for classical VKDB in unsupplemented infants. The corresponding figures for late VKDB in these countries were 13 and 35 [27]. Pooled data from Europe and Asia estimated the incidence of late VKDB as 4.4–7.2 in predominantly supplemented infants [33]. In 2007 the results of three consecutive incidence surveys from the British Isles were published [34–36]. The incidence of VKDB was 0.96 in 1990, 1.45 in 1994, and 0.14 in 2002 (per 100,000). Comparing the different modes of vitamin K administration with each other revealed estimated incidences of 1/845,000 for the intramuscular route, of 1/232,000 for a long oral course, of 1/34,000 for a short oral course, and of 1/8,500 for no vitamin K prophylaxis. Overall, morbidity and mortality were decreasing during the study period.

Route of Administration

Among health professionals there is currently a consensus that vitamin K prophylaxis should be given to all neonates at birth but this practice is not followed universally across the world due to a lack of resources in some regions. Breastfed babies are disadvantaged compared to formula fed infants as breast milk contains significantly less vitamin K than formula milk. When fat-soluble vitamin K_1 (phytomenadione) became available in the 1960s, it was administered intramuscularly at a dose of 1 mg at birth in many developed countries, and this practice has continued in North America until today [3]. In 1990, Golding, Paterson and Kinlen published a cohort study of 16,193 young adults born 20 years earlier, with the aim to detect risk factors associated with cancer. Thirty three of them had developed liquid or solid tumors during the first decade of life. Neonatal vitamin K injection was identified as a significant risk factor [37]. As possible reasons for this association high vitamin K levels achieved soon after an injection (more than 1,000 times of normal) and effects of other ingredients, for instance castor oil, polysorbate 80, or benzyl alcohol, were discussed. However, subsequent studies provided no conclusive evidence corroborating this finding [38, 39]. Oral vitamin K, given in single or repeated doses, is a less distressing alternative to intramuscular injection but there is no standard regimen, and compliance can be a problem [40, 41]. Furthermore, dedicated oral preparations are not widely available, and one paper has reported significant side effects [42]. A recent survey of British maternity units revealed that 60% of infants received intramuscular and 24% oral vitamin K. Sixteen percent of parents were given a choice between the two routes [34]. In a similar Irish survey the proportion of intramuscular injection was 78% [43].

Dosage

A systematic review of randomized trials investigated the efficacy of prophylactic vitamin K in preventing classical and late VKDB. Most trials used biochemical rather than clinical outcomes.

Table 30.1 Preparations of vitamin K currently used in the United Kingdom [46]

Generic name	Brand name	Company	Concentration	Route	Dose
Menadiol sodium phosphate	Menadiol phosphate	Non-proprietary	10 mg tablet	Oral	Children: 5–10 mg
Phytomenadione	Konakion MM	Roche	10 mg/mL, 1 mL ampule	Intravenous	1 mg
Phytomenadione	Konakion MM paediatric	Roche	10 mg/mL, 0.2 mL ampule	Intramuscular, intravenous, oral	0.5–1 mg
Phytomenadione	Neokay capsule	Neoceuticals	1 mg capsule	Oral	1 mg
Phytomenadione	Neokay drops	Neoceuticals	50 μg per 0.25 mL	Oral	50 μg

The conclusion was that 1 mg of intramuscular vitamin K given after birth prevents classical VKDB. Both intramuscular and oral vitamin K (1 mg) have a positive effect on the clotting parameters in the first week of life. There was no strong evidence to suggest that single doses of intramuscular or oral vitamin K or multiple of oral vitamin K prevent late VKDB [44]. Several oral dosage regimens have been tried which range from 1 to 90 doses and which vary for bottle fed and breastfed infants [27, 40]. The company Merck produces Aqua-MEPHYTON (phytonadione, vitamin K_1) which is licensed for the intravenous, intramuscular, and subcutaneous route. Aqua-MEPHYTON is available in 1 and 10 mg vials and contains polyoxyethylated fatty acids, dextrose, and benzyl alcohol [45]. Given intramuscularly, it is the preferred vitamin K prophylaxis for infants in North America. Konakion MM and Konakion MM Paediatric are manufactured by Roche. Konakion MM is a mixed micellar solution of phytomenadione, glycocholic acid, sodium hydroxide, lecithin, and hydrochloric acid. It is licensed for oral and parenteral administration [46]. Some of the Vitamin K preparations that are currently in use in Europe are listed in Table 30.1. Neokay Oral Drops is a food supplement that does not require a prescription. Each 0.25 mL dose which is suctioned into a dropper contains 50 μg vitamin K_1. If given once daily, one bottle lasts for 3 months. Neokay 1 mg capsule is a prescription-only-medicine which was granted a license by the Medicines Healthcare products Regulatory Agency (MHRA) in 2010. The shell of the capsule is made from gelatine, glycerol, iron oxide, and water. Each capsule contains 1 mg of vitamin K_1 mixed with coconut oil [47].

Conclusion

The overriding message of this review is that all neonates require vitamin K supplementation to prevent vitamin K deficiency bleeding. Intramuscular injection of vitamin K is the most effective route. Unfortunately this objective can currently only be achieved in developed nations. In developing countries prevention and treatment of infectious diseases have a higher priority, and vitamin K prophylaxis is not considered cost effective [33]. Giving small amounts of cow's milk to breastfed babies in the first week of life may be an alternative, cheaper solution where it is feasible [48].

More basic research is needed to improve our understanding of the vitamin K cycle and vitamin K dependent proteins other than coagulation factors. Due to the low incidence of infantile VKDB high-quality human trials are difficult to set up and complete. Instead, developed countries should have national databases where cases of VKDB are recorded and analyzed such as the British Paediatric Surveillance Unit (BPSU).

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Chapter 31
The Role of Vitamin A in Health of Infants and Vitamin A Status Assessment Methods

Masako Fujita and Mariana Rendon

Key Points

- Vitamin A plays an important role in a multitude of biological functions including normal vision, growth and development, and immune defense.
- Prevention of vitamin A deficiency would improve the health of infants particularly through improvements in their resistance against and recovery from infectious diseases.
- Weaning children in developing countries are vulnerable to severe vitamin A deficiency and susceptible to infectious mortality due to the transition from maternal milk, a good source of vitamin A, to relatively vitamin A poor, non-milk foods.
- The weaning transition, as a risk factor for vitamin A deficiency, may be ameliorated by improving maternal vitamin A and hence milk vitamin A which would allow infants to build sufficient body reserves of vitamin A prior to the transition. Improving vitamin A content in weaning foods is also important.
- Serum concentrations of vitamin A may not always reflect body reserves of vitamin A. Some biochemical vitamin A status indicators estimate serum circulating vitamin A concentrations while others can address the levels of body stores.
- Vitamin A status assessment for infants and young children must be done with an awareness of strengths and limitations of various assessment methods.

Keywords Vitamin A • Retinol • Carotenoids • Vitamin A deficiency • Serum retinol • Liver retinol • Vitamin A status assessment methods

Introduction

Vitamin A is a fat-soluble essential vitamin. It is indispensable for human health especially for the health of infants. This chapter reviews (1) important metabolic functions of vitamin A, (2) the role of vitamin A in the health of infants, and (3) vitamin A assessment methods.

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R.R. Watson et al. (eds.), *Nutrition in Infancy: Volume 1*, Nutrition and Health,
DOI 10.1007/978-1-62703-224-7_31,

Definitions and Overview of Vitamin A and Vitamin A Status/Deficiency

Vitamin A is the generic term for retinoids which possess the biological activity of the vitamin, including: *retinol*, preformed vitamin A exclusively from animal sources (except for artificially fortified foods), retinol's metabolites such as *retinoic acids* (RAs) [1, 2], and *provitamin A carotenoids*, precursors of retinol found in both plant and animal sources [2, 3].

Free retinol is chemically unstable [1], so dietary sources of preformed vitamin A commonly occur in esterified form, retinyl esters [1]. Major biologically active retinoids include retinol, retinaldehyde, all-trans-RA, and 9-cis-RA [1]. In almost all tissues, vitamin A functions are carried out by the acid form, such as all-trans-RA [4].

In nature, only plants and microorganisms can synthesize carotenoids [4]. α-Carotene, β-carotene, and γ-carotene are examples of provitamin A carotenoids. β-carotene has the highest vitamin A activity on a molar basis [5] and is widely distributed in plant products [3] while α-carotene and γ-carotene have about half of the biological activity of β-carotene [4, 6].

Examples of food sources of β-carotene are dark green leafy vegetables, carrots, ripe yellow-orange vegetables, tubers and fruits, and red palm oil [4, 7–9]. Examples of food sources of preformed vitamin A include liver, milk, cheese, eggs, certain fish, and liver oils [9].

As a vitamin A source, retinol is superior to provitamin A carotenoids. While the carotenoids can obtain the biological activity of vitamin A after ingestion, mostly in the intestines, compared to preformed retinol, carotenoids have lower *bioavailability* and *bioconversion* [10, 11]. The term bioavailability refers to the fraction of ingested carotenoids absorbed for use or storage, while bioconversion refers to the fraction of bioavailable carotenoid converted to retinoids [12]. Low bioavailability of carotenoids is because they are less absorbable in the human intestine, and only a fraction of absorbed carotenoids can be converted to vitamin A in our body [10, 11]. To help assess the levels of vitamin A activity in provitamin A carotenoids, the unit of *retinol equivalents* (RE) is commonly used [3, 4]. One microgram (μg) RE is defined as 1 μg all-trans retinol [1]. The biological activity for all-trans β-carotene is only about 1/6 of all-trans retinol [4], assuming that β-carotene is fully bioconvertible to retinol. In reality, many factors affect bioavailability and bioconversion of carotenoids. Bioavailability of provitamin A carotenoids can be impaired by excessive cooking, and/or absence of enhancers of absorption (e.g. fat) or presence of inhibitors of absorption (e.g. alcohol) in the meal. Therefore, plant-based diets with adequate provitamin A carotinoids may not support one's vitamin A requirements if cooking methods or food combinations impair their bioavailability. It should be added that provitamin A carotenoids have anti-oxidative effects which provide additional health benefits over and above their vitamin A function [3].

Ingested (or converted) vitamin A that is not used immediately can be stored in the body as reserves, mostly in the liver. When necessary, liver reserves are mobilized to the target tissue via serum, bound to retinol-binding protein (RBP; the transporter protein specific to retinol). Vitamin A serves important roles in a wide range of biological functions such as normal vision and eye health, growth and development, and immune defenses [1, 3, 4].

Vitamin A status refers to the level of one's body reserve. *Vitamin A deficiency* refers to the condition in which body reserves of vitamin A becomes depleted due to insufficient dietary intake or increased utilization and loss of reserves, or both. For practical reasons, vitamin A status is often assessed in terms of serum concentrations of retinol or RBP which may not always represent the body reserves. Early signs of vitamin A deficiency include growth failure, anorexia, and impaired immune system [6]. When more advanced, night blindness and various types and degrees of ocular lesions will occur, including conjunctival xerosis (abnormally dry conjunctiva), corneal xerosis (abnormally dry cornea), Bitot's spots (triangular, gray spots on the conjunctiva), and keratomalacia (irreversible lesions on cornea associated with blindness) [6], all of which are collectively referred to as xerophthalmia [3].

Table 31.1 Vitamin A deficiency severity and functional consequences

	Subclinical (serum retinol <0.7 μmol/L)	Clinical (serum retinol <0.35 μmol/L)
Ocular signs	Abnormal epithelia	Impaired function and structure
Growth and development	Possible deceleration in weight and height gain	Stunting and wasting
Immune function	Compromised; elevated infectious susceptibility	Compromised; increased susceptibility to and mortality from infection

Xerophthalmia is associated with increased mortality, as exemplified by a 2.7–8.6 times higher relative risk of mortality among children as compared to those equally generally malnourished but without ocular signs [4, 13, 14]. However, even at the subclinical level without xerophthalmia, vitamin A deficiency is associated with an elevated risk of infectious disease and death [4, 15, 16]. Though less fatal than severe deficiency with xerophthalmia, subclinical deficiency is more prevalent and thus more likely to make a larger contribution to the childhood mortality from infection [4]. Table 31.1 summarizes vitamin A deficiency and functional consequences.

The foremost risk group of vitamin A deficiency is young children [4, 17]. Obviously, diets customarily low in vitamin A and a seasonal decline of vitamin A intake are major risk factors for anybody. Other important risk factors include infections (systemic, diarrheal, intestinal parasitic, respiratory, measles, HIV), malabsorption (usually related to infection, intestinal parasites or iron deficiency), protein-energy malnutrition, and zinc and iron deficiencies, all of which further increase the vulnerability of children [4]. Bottle feeding, weaning, and maternal vitamin A deficiency are also well-recognized risk factors for preschool aged children [4]. Low socioeconomic status and low education levels have also been reported as risk factors [4] that probably subsume at least one of the above risk factors. Occurrence of corneal xerophthalmia with serious lesions among hospitalized preschool children appears to peak at the ages of 2–3 years [14, 18]. This appears to relate to their high requirements for growth, low liver stores, and low dietary intake of vitamin A during infancy and just after weaning [4].

The Role of Vitamin A in Infant's Health

Nuclear receptors for vitamin A exist in almost every type of cell, indicating the importance of retinoids for a wide range of biological functions. For the health of infants, important ones include: (1) vision, (2) growth and development, and (3) immune response [4, 19].

Vision

The role of retinol in the human visual cycle has been reviewed by Gerster [7], Gropper et al. [20], and Saari [21]. In short, all-trans retinol in plasma is taken up into the pigment epithelium of the retina and then isomerized to 11-cis-retinol which is either esterified for storage or oxidized to 11-cis-retinol and transported to the photoreceptor cells for visual function. In the rods and cones of the retina, 11-cis-retinol plays a central role in cascade events that involve ultraviolet wavelength-dependent photoisomerization and a change in the conformation of the visual pigment, which in turn leads to hyperpolorization of the photoreceptor cell. This results in a reduction of the release of excitatory neurotransmitters which is interpreted by the visual cortex of the brain as "seeing" [7, 21]. All-trans retinol is then reconverted to 11-cis-retinol which once again restarts the visual cycle. Vitamin A deficiency compromises the visual cycle, leading to dark adaptation impairment and eventually night blindness [7, 21].

Growth and Development

Aside from its role in vision, RAs serve both a general role in growth and a specific morphogenic role in development and tissue differentiation. Growth and development involve cell differentiation and the increase in number and size of cells. Genes provide the template for the rate of cell division, but the outcome is determined by the interactions between genetics, growth factors, environment, and diet, particularly the supply and utilization of specific nutrients including vitamin A [22]. Milk of a healthy mother provides all necessary nutrients, enzymes, hormones, and growth factors to support normal growth of the term infant during the first 4–6 months of life [22].

All-trans RA and its acid isoforms affect a wide spectrum of biological systems, including lymphoid, embryonic, nerve and muscle [23], adipose tissue [24–27], and alveolar cells [28]. Such specific roles of RAs involve genomic actions of RA [1, 19], mediated by the cell's nuclear receptors. Retinoic acid and retinoid X receptors, belonging to the family of steroid-thyroid hormone receptors, are ligand-activated transcription factors [22]. RAs bind these receptors which in turn interact with DNA response elements and thereby activates, inhibits, or influences rates of DNA transcription [19] and hence growth and development.

Laboratory and observational studies have shown an association between vitamin A deficiency and poor growth patterns in children [4, 29–31]. Animal studies report a deceleration in weight gain and eventual weight loss in response to vitamin A depletion [32]. Xerophthalmia, a clinical symptom of vitamin A deficiency, is related to linear growth, stunting and wasting [32–35]. Recovery from xerophthalmia has been associated with weight gain and catch-up linear growth to a lesser extent [32]. A study in Sudan [36] reports an association between dietary intake of pro-vitamin A carotenoids and growth as well as the incidence of recovery of stunting among very young children and chronically malnourished children. The biological mechanism that might explain the relationship between pro-vitamin A carotenoids and infant growth is the upregulation of growth hormone by all-trans-RA, the active metabolite of vitamin A [37].

Immune Function

Vitamin A is responsible for the maintenance of both innate immunity—including the skin, mucosal barriers, phagocytes, and cytotoxic cells—and pathogen-specific adaptive immunity, particularly antibody-mediated responses based on t-helper (Th) cells and B-cells [38, 39]. The skin and mucosal epithelial barriers provide an important first line of defense against infection [39], and the maintenance of these barriers is dependent on vitamin A. Vitamin A deficiency results in disturbances in the skin integrity and a loss of mucus-producing goblet cells and hence the protective mucus blanket in the respiratory or digestive tract which ordinarily traps and sweeps away pathogens out of the body [38, 39]. Low vitamin A stores in the lung also compromise the gene expression of surfactant proteins, alveoli formation, and the development of the respiratory epithelium, elevating the risk for respiratory diseases such as bronchopulmonary dysplasia and frequent infections in early childhood [28].

Vitamin A plays roles in normal functioning of other components of innate immunity such as phagocytes and cytotoxic cells [39]. For example, normal development of neutrophils and other granulocytes in the myeloid stem cells in the bone marrow is regulated by retinoic acid receptor-medicated nuclear modulation [39].

In adaptive immunity, vitamin A also plays key roles in cross-regulating cell-mediated and humoral immune responses [40], for example, by modulating the balance between two types of memory Th cells. Generally, high dietary intake of vitamin A facilitates humoral immunity to fight extracellular pathogens (via Th2 cytokines such as interleukin-4 or IL-4) while diminishing cell-mediated immune responses that deal with intracellular pathogens (via reduction in Th1 cytokines such as IL-12 and interferon-γ) [39]. Thus vitamin A deficiency impairs Th2-mediated antibody responses such as serum

immunoglobulin (Ig) G1 and E responses and salivary and intestinal Ig A responses, depending on the antigens [39].

However, the vitamin A modulation of the immunity is not the completely dichotomous alterations in Th1/Th2 balance [39], and is likely mediated or conditioned by other factors such as other nutrients [40–44] or hormonal status and stage of life of the individual [44]. For example, a study with human infants found that high-dose vitamin A supplements enhance the delayed-type hypersensitivity response, indicating that the Th1 response was impaired in deficiency [45]. Additionally, some experiments demonstrate that deficiency can decrease IL-2 production [46], and that high-dose retinol and RA supplementations in vitro can enhance IL-2 or IL-2 receptor expression [47], implying that RA supplementation may enhance proliferation of Th1 cells if this occurs in vivo [39]. Nonetheless, the commanding importance of vitamin A in the defense against infectious diseases is demonstrated in voluminous epidemiological evidence as summarized in the following section.

It should be noted that since the human immune system is immature during infancy, infants are dependent on maternal immune compounds transferred through breast milk [48]. Therefore the immunocompetence during infancy depends greatly on the mother's immunocompetence which in turn depends on her vitamin A status.

Epidemiological Evidence

Epidemiological studies indicate that young children in developing countries are the most vitamin A deficiency vulnerable group [3, 4, 16, 18, 49]. Recent global estimates of vitamin A deficiency among preschool-aged children are 127 million for subclinical vitamin A deficiency and 4.4 million for xerophthalmia [49]. Vitamin A deficiency claims the lives of one million young children every year [50]. Geographically, South/Southeast Asia, and Africa harbor the overwhelming majority (45% and 25–35%, respectively, or 70–80% combined) of the global cases of vitamin A deficiency while the rest are distributed in the Eastern Mediterranean, Western Pacific, and the Americas [49]. Epidemiological evidence pertinent to the role of vitamin A in the health of infants can be grouped into three major themes: The first and second involve major limiting factors on infants' vitamin A intake: (a) maternal vitamin A deficiency and (b) weaning transition. The third theme centers on the protective effect of vitamin A against infections.

Maternal Vitamin A Deficiency Compromises Infant's Vitamin A

All newborns have very low liver stores of vitamin A [51, 52], and thus are dependent on maternal milk for both managing their immediate physiological needs, and building liver stores [3, 16, 53]. Milk of a healthy mother provides an excellent source of vitamin A for neonates [52]. For example, retinol and β-carotene concentrations in the colostrum of women in developed countries are 1,524 RE/L and 130 RE/L, respectively, and 1,193 RE/L and 50 RE/L, respectively, in developing countries [3]. As well, vitamin A in human milk is also well absorbed because lipase in breast milk stimulates bile salt which helps absorption in the intestine of the infant [52, 54].

The concentrations of both retinol and β-carotene in breast milk decrease over time [3, 51, 55–60]. Still, milk of a well-nourished mother would continue to provide adequate vitamin A for months. Breastfeeding is highly protective against childhood xerophthalmia even in places where vitamin A deficiency is endemic [3, 14, 18]. The protective effect may last even after weaning probably due to infants' liver stores established before weaning [3, 18, 61].

However, maternal nutrition and other factors significantly affect vitamin A levels in human milk [3, 58]. Children's dietary intake of vitamin A in developing countries tends to be low during infancy [4]

because their mothers' milk, the sole or primary source of vitamin A, tends to be low in vitamin A content [16, 56, 61, 62] due to the low maternal vitamin A status. While mothers with subclinical vitamin A deficiency may be able to transfer enough vitamin A to satisfy the infants' immediate physiological needs, their milk may fail to facilitate infants' building body reserves that will become crucial during and after the process of weaning [3, 62] especially in places where weaning foods are low in vitamin A.

FAO/WHO [63] suggests that infants require >180 RE/day just to meet basal needs. For infants to build normal body reserves, they need a minimum intake of 350 RE/day during the first year and 400 RE/day during the second and third years [63]. According to the estimates based on studies published between the 1950s and early 1990s [3], infants of unsupplemented mothers in developing countries consumed relatively low but sufficient vitamin A (average 375–534 RE/day, compared to 500–711 RE/day in developed countries) during the first 6 months of life. However, thereafter their intake levels declined steadily to 241 RE/day between 7 and 12 months and to 161 RE/day by the second year of their life. These figures are far below the above-mentioned FAO/WHO suggested values and imply that a 7-month old infant in a developing country would begin dispensing his/her meager liver reserves to cope with their basal needs, eventually depleting their reserves [3]. Indeed it has been reported that breast-fed infants of vitamin A deficient mothers are likely to suffer subclinical vitamin A deficiency by 6 months of age [52].

Weaning Is a Risk Factor of Vitamin A Deficiency

In the process of weaning, the breast milk is gradually replaced by non-breast milk fluids and solid foods, the nutritional composition of which is usually inferior to breast milk. The successful adaptation of infants to this transition in nutrition involves modifications of energy metabolism in the vast majority of organs, such as intestine, liver, muscle, adipose tissue, and brain [22]. Nutrients play a major role in this modification as well as organ growth and functional differentiation. The adaptations of energy metabolism to the new nutritional environment can be achieved through various physiological or morphological changes, many of which ultimately involve a change of the transcription rate of the corresponding gene [22]. Nutrients such as glucose, fatty acids, amino acids, iron, and vitamins, in concert with hormones regulate the gene expression [22].

The vitamin A contents of weaning foods in many developing countries are often lower than breast milk of mothers suffering subclinical vitamin A deficiency [3, 62, 64]. Plant foods are predominant sources of vitamin A in many developing countries, especially in Asia and Africa [4]. Consequently, weaning foods for children are also of plant sources with relatively low vitamin A activity. For example, a study in rural Kenya reports that the vast majority of infants (89.5%) consumed animal sources of vitamin A less than three times a week [62]. Vitamin A-rich plant foods such as dark green leafy vegetables are often under used for weaning foods because of their blandness, bitterness, or fibrousness, often considered unsuitable for infants and young children [3, 65]. Refined rice contains no carotenoids [4] (unless artificially fortified) even though rice porridge/gruel is a foremost weaning food in many parts of Asia.

Additionally, some preparation methods of weaning food can further compromise vitamin A status, as exemplified by excessive cooking [3] commonly done to prepare gruel. Yellow maize provides provitamin A carotenoids, but its bioavailability would be reduced in maize gruel through the cooking process. Similarly, if maize gruel is prepared or given to the infant without fat and/or protein, the bioavailability and bioconversion would be impaired further.

Consumption of weaning foods coupled with poor sanitation can also expose children of weaning age to pathogens and parasites, leading to infections. During the weaning period, children in developing countries are especially vulnerable to infections due to the exposure to pathogens from non-breast milk foods [64, 66]. This vulnerability may be exacerbated by the reduction in breastfeeding and milk retinol as well as other milk constituents such as maternal anti-microbial agents [64, 67, 68].

Vitamin A Help Fight Infections

As reviewed in the previous section, vitamin A is important for the maintenance of both innate and adaptive immune responses [38, 39], as well as for the cross-regulation of cell-mediated and humoral immune responses [40]. Thus vitamin A deficiency can impair immune defense and increase susceptibility to infection (see the above section on "Immune Function").

Evidence from Vitamin A Supplement Studies

The importance of vitamin A in combating infectious mortality can be found in vitamin A intervention studies. Vitamin A supplements resulted in a 34% reduction in child mortality in Indonesia [4, 69] and a 30% reduction in Nepal [70]. Curiously, the benefit vitamin A intervention on mortality may vary by specific pathogens [4]. For example, relative risks of supplemented children in Ghana were 0.82, 0.66, and 1.0 for measles, diarrhea, and respiratory infections, respectively [71].

Measles virus can invade the eyes leading to measles kerato-conjunctivitis, and this eye pathology may be exacerbated in the presence of vitamin A deficiency [4]. In South African studies with hospitalized children, vitamin A supplementation significantly reduced both complications (pneumonia, diarrhea, post-measles croup, requirement for airway, etc.) and outcomes (durations of pneumonia, diarrhea, and for recovery) of measles [4, 72–74]. These reductions may be attributed to the enhancement of the defense against the bacterial infections or possibly the measle-specific immune function [39, 75].

Vitamin A supplementations also lead to a reduction in the incidence of severe diarrhea and diarrhea-related mortality. However, mild diarrhea (3–4 stools/day) does not appear to be affected [4, 76].

Vitamin A deficiency is associated with respiratory infections, such as various forms of bronchitis or pneumonia diagnosed by the presence of fever, cough, rhonchi or rales (the abnormal sounds heard by stethoscope) [4]. Unlike measles complications or severe diarrhea, vitamin A intervention studies fail to provide evidence for clear reduction of respiratory infections mortality and morbidity except for some possible reduction in the severity of symptoms [39]. However, symptoms of respiratory infection such as coughs can be viewed as a strategy of human body to rid of pathogens. Viewed this way it is difficult to dismiss the possibility that vitamin A may still help fight respiratory infections.

In Tanzanian children of 6 months to 5 years of age, vitamin A supplements reduced diarrhea- and AIDS-related mortality in HIV infected children [39, 77] although in a U.S. study no improvement was seen in immune function parameters [39, 78].

Vitamin A may also play a role in the severity of malaria infections although its exact role is not fully understood [79]. A study with young children (6 months to 5 years) in Papua New Guinea [80] demonstrated that vitamin A supplementation decreased number of febrile episodes, parasite density, and the proportion of subjects with enlarged spleen, especially for younger children (12–36 months). The observation that younger children benefited more than older children may be related to the role of vitamin A in boosting the development of immunity among infants and young children because antibody response involved in diminishing the severity of infection develops rapidly in young children during their first year or two of malaria exposure [39].

Evidence from Food Fortification

Food fortification with vitamin A is an efficient and cost-effective strategy [81] to ensure adequate vitamin A intake, as the process tends to be socially acceptable and does not interfere with normal food choices or eating patterns [82]. Fortification of staple foods or condiments such as salt, sugar, seasonings, cooking oil, margarine and wheat and corn flours has been popular in addressing vitamin A

deficiency in several countries. Other foods such as tea, instant noodles, fish sauce and traditional meal accompaniments such as *Inkomazi* in South Africa [82] have also been fortified though to a lesser degree. Fortifiable foods are penetrating the markets, providing means to passively supplement high-risk populations with the required amounts of vitamin A on a daily basis. One of the challenges of food fortification is identifying commodities that are widely consumed in constant amounts by the target population [81].

A growing body of literature suggests tangible benefits from fortified foods. For example, Chen et al. [83] evaluated the effectiveness of different combinations of nutritional fortified diet to improve the blood levels of vitamin A and other micronutrients in the preschool population of Banan District of Chongqing, China. They discovered that a daily serving of a micronutrient fortified seasoning powder for 6 months was effective in improving the levels of hemoglobin, serum retinol, and RBP [83]. Similar results were found in 2002 in a study conducted in North East Thailand [84].

Vitamin A Assessment Methods

This section reviews biochemical vitamin A assessment technologies originally recommended by the WHO [85] and some newer methods useful in non-clinical settings. Serum retinol is the most commonly used while serum RBP is a useful surrogate measure of serum retinol. These serum concentrations do not always represent the body reserves of vitamin A, and since body reserves of vitamin A has crucial implications for infants' health, we also review methods to assess body reserves, including the relative-dose response (RDR) test and the modified relative-dose response (MRDR) test. Table 31.2 summarizes strengths and limitations of these methods.

Serum Retinol

The WHO [85, 86] recommends serum retinol as the main indicator for classifying the public health problem of vitamin A deficiency. However, serum retinol is a valid indicator of body reserves only when severely depleted (<20 μg/g liver) or extremely high (>300 μg/g liver), between which the concentrations of serum retinol may not reflect total body reserves due to the body's homeostasis [87]. Only when liver reserves are nearly depleted do plasma levels of retinol fall significantly [1, 4]. The WHO [85] defines a serum retinol level <0.7 μmol/L as subclinical deficiency and a level <0.35 μmol/L as clinical deficiency, and proposes the following prevalence cut-off values to assess the public health significance of subclinical vitamin A deficiency: 2–10% mild; 10–20% moderate; >20% severe.

Examples of serum retinol assessment methods are high-performance liquid chromatography (HPLC), fluorometry, and UV spectrophotometry, among which the first is preferred due to its high

Table 31.2 Vitamin A status assessment methods

Markers	Strengths	Limitations
Serum retinol	Considered the gold standard and widely used	Unstable and requires stringent handling; concentrations may not reflect body reserves
Serum RBP	Stable and require less stringent handling than retinol	May not reflect body reserves
Relative-dose response test (RDR)	Assesses body reserves as sufficient vs. deficient	Requires two repeated blood sampling hours apart; invasive; requires a mature and healthy liver
Modified RDR	Assesses body reserves as sufficient vs. deficient	Costly

specificity and sensitivity. Retinol is relatively unstable, requiring stringent conditions for specimen collection, processing, and transportation [88]. For example, for HPLC methods, blood samples should be centrifuged in a timely manner and stored frozen at cryonic temperatures free from light, oxygen, and desiccation until analysis [85].

In some non-clinical settings, venous blood collection from infants can be difficult or undesirable. Relatively recently, the HPLC methods to measure retinol in dried blood spots of capillary blood on filter paper have been developed [89, 90]. Dried blood spots from finger pricks are less invasive and easier to collect, store, and transport than venous blood samples. Dried blood spots have been successfully applied for numerous analytes [91, 92]. In healthy individuals, dried blood spots retinol and serum retinol correlate well (e.g. $r^2=0.88$) [93, 94]. The correlation at lower concentrations is still unclear.

One must be cautious in interpreting low serum concentrations of retinol because they may be a result of acute phase response to infection instead of vitamin A deficiency. RBP is a negative acute phase protein, and its hepatic synthesis and secretion of the retinol-RBP complex into the serum is reduced in the presence of infection [95], consequently reducing the plasma concentrations of retinol [1, 96–98]. Likewise, a low concentration may be attributable to impaired synthesis of RBP caused by both protein-energy malnutrition and zinc deficiency [1]. Potential misclassifications of vitamin A deficiency due to acute phase response can be statistically corrected to some extent by a use of biomarkers of acute phase proteins [96, 97] such as α1-antichymotrypsin, α1-acid glycoprotein, and C-reactive protein (CRP).

Serum Retinol-Binding Protein

As the transport protein specific to retinol, serum RBP is a well-accepted surrogate measure for serum retinol, based on the observation that the relative proportions of the two parameters have an approximately 1:1 molar relationship, except in certain conditions (see below for these conditions) [4, 99]. Main methods used to quantify serum RBP levels include HPLC, radial immunodiffusion (RID), and enzyme immunoassay (EIA), among which the latter two are simpler and more economical than HPLC [88, 100].

Based on the assumption of the 1:1 molar ratio, WHO [85] defines both serum retinol and RBP levels of <0.7 μmol/L as a cut-off for subclinical deficiency. Some researchers proposed that different cut-off values may apply to different populations. For example, Gamble et al. [101] estimated 0.77 μmol/L (16.2 mg/L) for children under 5 years old in the Marshall Islands. Also, Gamble et al. [101] reported that percent saturation of RBP with retinol varied by retinol concentration: 79 ± 25%, 90 ± 14%, and 96 ± 13% for children with retinol level ≤0.35, 0.36–0.70, and >0.7 μmol/L, respectively. de Pee and Dary [91] thus argue that RBP can only be used with those populations for which the relationship with serum retinol concentration has been established in a subsample.

The use of serum RBP is advantageous over serum retinol in several respects [91]. Being a protein, RBP can be detected with immunologic assays, which are simpler and more economical than HPLC of retinol. More importantly, RBP is more stable than retinol and can better withstand exposure to light and temperature variations. RBP in dried blood spots has been reported to be stable for at least 4 weeks at 30 °C if stored in a sealed bag with desiccant [102]. Finally, RBP analysis can be done with a fraction of serum volume (10–20 μL) than HPLC analysis of retinol (>100 μL) [91].

When the 1:1 molar relationship between retinol and RBP is disturbed, the usefulness of RBP levels as surrogate measure of retinol decreases, especially with immunologic assays which cannot distinguish holo-RBP (RBP bound to retinol) and apo-RBP (RBP not bound to retinol), and thus have potential to overestimate the vitamin A level if a large amount of apo-RBP is present in the serum or plasma [91]. Kidney malfunction appears to be one such condition that can potentially disproportionally

increase apo-RBP in the circulation. A study in patients with acute renal failure showed that vitamin A levels were significantly decreased relative to healthy controls, but RBP levels were normal in these patients [103]. It is likely that the kidney was not successfully filtering apo-RBP that has completed its job of delivering retinol to target tissues, thus contributing to increased levels of apo-RBP. In healthy individuals, kidneys clear out such apo-RBP from serum circulation. Another condition to violate the 1:1 molar ratio between RBP and retinol is obesity. Obese individuals tend to have higher serum RBP concentrations than in non-obese individuals [104], likely due to greater adipocyte synthesis of RBP [105].

Serum RBP shares the same limitations as serum retinol. Serum RBP concentrations may misclassify vitamin A deficiency, especially in the presence of an acute phase response, under which both retinol and RBP levels decrease [99]. Similarly, other factors such as protein-energy malnutrition, liver disease, and chronic renal failure also affect RBP levels irrespective of vitamin A status [99]. Additionally, in women, there may be menstrual cycle phase, oral contraceptive use, and lactation effects. These possible biases on RBP need to be adjusted statistically or controlled via careful study designs and sampling procedures.

Relative-Dose Response Test as an Indicator of Body Reserves

The RDR test is a test for estimating the liver stores of vitamin A at the population level. The principle of RDR is based on the observation that apo-RBP accumulates in the liver in vitamin A deficiency, and that following a dose of vitamin A, the relative excess of apo-RBP in the liver binds to vitamin A and the resulting holo-RBP is released to the circulation. In individuals with vitamin A deficiency, a small dose of vitamin A leads to a rapid, sustained increase in serum retinol [6]. Data indicate that this occurs when the vitamin A liver stores are below 0.07 μmol/g liver [85]. The RDR test involves (1) initial collection of fasting blood sample via venipuncture to assess fasting serum retinol (A0), (2) a dose of 450–1,000 μg of retinyl ester in an oily solution (either straight or absorbed in an appropriate food, i.e. bread), and (3) a second blood collection and measurement of serum retinol 5 h after the oral dose (A5) [85]. The RDR value is determined by the percentage of change between the baseline serum retinol level and that from the second sample (RDR = {(A5 − A0)/A5}*100). An RDR value of ≥20 (%change) is considered due to inadequate liver reserves (<0.7 μmol/g liver).

WHO [85] classifies that a moderate public health problem exists when a 20–30% of a population show the RDR value of ≥20%, and a severe problem exists when 30% or more of a population show this value. It should be noted that RDR values and liver stores may not have a linear relationship above or below the critical level because sometimes negative RDR values can occur among individuals without vitamin A deficiency. Thus RDR should not be used for the assessment of individual's vitamin A status diagnosis. For the assessment of the degree of vitamin A deficiency in a population using RDR, a study must use a statistically adequate, representative number of subjects, along with the serum-distribution curves which are randomly obtained from the sample to help overcome the problems [85].

RDR is more sensitive than serum retinol levels for identifying marginal vitamin A status [6]. However, the RDR test shares similar limitations of a serum retinol assessment. These include the reductions of its specificity and sensitivity with malabsorption, underdeveloped liver, liver disease, and severe protein-energy malnutrition. Other limitations are related to the requirement of two blood samplings within a 5-h interval. This increases the invasiveness of the test and lowers the compliance for the second sample collection [85]. These problems may be eased by designing a procedure in which subjects are offered benefits during the wait time such as health examinations and educational workshops [85]. Adoption of DBS prepared using finger pricks instead of venous blood draws for RDR would reduce the invasiveness and be more tolerable for infants. However, the response in the capillary

blood may be different from that in the venous blood (possibly slower or smaller response in the capillary), and this difference has not been characterized. The use of DBS-RBP in lieu of serum retinol for RDR has been examined using DBS prepared from venous blood [106] but not in capillary blood.

Modified Relative-Dose Response Test

MRDR is another method to estimate the liver stores based on the same principle of biological response as RDR, but it requires only one blood sampling. First, an oral dose (100 μg/kg body weight, or a 1.5 mg standard dose) of 3,4-didehydroretinyl acetate (DR) is given. DR binds to RBP and appears in the serum after the dose if liver vitamin A stores are low. After 4–6 h, a venous blood sample is taken to assess the levels of the serum DR and the serum retinol. MRDR is determined by the molar ratio of serum DR over serum retinol (MRDR = serum DR/Serum retinol). The MRDR of >0.06 is defined as inadequate liver stores [85].

Acceptability of MRDR is higher than RDR thanks to a single blood collection [85]. Another advantage of MRDR is that subjects can take the DR dose at home and come only once for blood collection 4–6 h later. MRDR, however, has some limitations. For example, free DR is unstable as an analyte, and must be analyzed immediately upon extraction by HPLC, protected from light. Moreover, DR is not commonly available commercially, so it must be either synthesized or extracted from freshwater fish liver oils for the purpose of the test. Thus the cost of obtaining DR can be prohibitive (e.g. US$2,000 for 1.5 g) [85].

Other Indicators

In addition to the above biochemical methods, cytological and functional indicators may be used to assess individuals' or population's vitamin A status. Conjunctival impression cytology examines histologic abnormalities on the bulbar conjunctiva [107]. Functional indicators of vision include those based on dark adaptation time [107], pupillary dark adaptation [107, 108], and night blindness interview [85, 109].

Summary

Young children are the most vulnerable to vitamin A deficiency and deficiency-related morbidity and mortality. Vitamin A plays an important role in a multitude of biological functions including normal vision, growth and development, and immune defense. Prevention of vitamin A deficiency would improve the health of infants, particularly through improvements in their resistance against and recovery from infectious diseases. Improving maternal vitamin A status is crucial for increasing vitamin A in breast milk in addition to improving the mother's health. Weaning children in developing countries are very vulnerable to severe vitamin A deficiency and susceptible to infectious mortality. This may be ameliorated by improving maternal vitamin A (and hence milk vitamin A) which would better prepare children to survive the period of weaning with sufficient liver vitamin A reserves. Improving vitamin A content in weaning foods is also important. We reviewed biochemical vitamin A status indicators aimed at estimating serum circulating vitamin A concentrations and the levels of body reserves. We discussed the notion that serum concentrations may not always reflect body reserves of vitamin A and touched on some major factors contributing to this discrepancy.

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Index

R.R. Watson et al. (eds.), *Nutrition in Infancy: Volume 1*, Nutrition and Health,
DOI 10.1007/978-1-62703-224-7, © Springer Science+Business Media New York 2013