Lessons Learned from Clinical Studies on Infant Nutrition

Hania Szajewska

Department of Pediatrics, Medical University of Warsaw, Warsaw, Poland

Abstract

Currently, one of the scientific concepts is that maternal, fetal, and infant nutrition may have implications for infant size and growth and subsequently for the risk of developing chronic diseases later in life, in addition to genetic, environmental, and behavioral factors. As a consequence, the interest of scientists and policy makers is now focused on characterizing the optimal dietary patterns and patterns of prenatal and postnatal size/growth. The objectives of this paper were to briefly review/summarize: (1) evidence of the importance of size and growth as well as early nutrition for health and development, (2) methodological issues associated with current scientific approaches that evaluate the impact of early nutrition/growth on later outcomes, (3) recent regulations and guidelines developed by various expert groups or scientific organizations, and (4) ways to solve some unresolved issues.

Growth is a complex process defined as ‘a regulated increase in the dimensions, mass and functional complexity of tissues and organs’ [1]. It is affected directly or indirectly by a number of factors, including nutrition that may affect growth both before and after birth. Currently, one of the scientific concepts is that maternal, fetal, and infant nutrition may have implications for infant size and growth and for the risk of developing chronic diseases later in life, in addition to genetic, environmental, and behavioral factors. As a consequence, the interest of scientists and policy makers is now focused on characterizing the optimal dietary patterns and patterns of prenatal and postnatal size/growth. This paper briefly reviews: (1) evidence on the infant size/growth and early nutrition on disease in adulthood, (2) methodological issues associated with current scientific approaches that evaluate the impact of early nutrition/growth on later outcomes, (3) recent regulations and guidelines developed by various expert groups or scientific organizations, and (4) ways to solve some unresolved issues.
Summary of Evidence

Infant Size and Growth and Disease in Adulthood
At least one systematic review aimed to determine whether there is an association between infant size or growth and leading chronic diseases in adulthood [2]. The literature search covered a range of sources (MEDLINE, EMBASE, CINAHL, PsycINFO, and bibliographies of included trials, all up to 2005) and included unpublished material. Studies that assessed the relationship between infant size or growth during the first 2 years and leading causes of diseases in adulthood were included. Nineteen studies relating to 10 outcomes were included in the review. The inclusion criteria for the outcomes had been prespecified and based on the Global Burden of Disease Study. The authors concluded that no single optimal pattern of infant growth was associated with beneficial adult health outcomes. Larger infant size was associated with a reduced risk of ischemic heart disease, but also with an increased risk of type 1 diabetes. Very few or no studies associating infant size or growth with diseases such as cancer, mental illness, chronic obstructive disease, and type 2 diabetes were found. The authors identified a number of methodological limitations in the included trials. Furthermore, the authors stated that most of the evidence related to infant size, not to infant growth or actual size that is associated with the disease risk.

Early Nutrition and Disease in Adulthood
Recently, the Scientific Advisory Committee on Nutrition (SACN) reviewed evidence of the impact of early nutrition (maternal, fetal and infant) on the development of chronic disease in adulthood [1]. Observational and experimental studies were summarized. Based on the evidence available, the SACN concluded that both compromised and excessive nutrient supply during early fetal and infant life raise concerns with regard to the later health consequences of compromised or excessive nutrient supply during early fetal and infant life. The SACN pointed out that while a number of studies indicate that variation in nutrient supply early in life is associated with later outcomes and that there are studies to explain potential mechanisms, the evidence is often inconsistent. Also, the SACN stated that it is difficult to detect and quantify meaningful effect sizes for these associations.

Methodological Issues
Evidence of the associations between infant size/growth and the influence of early nutrition on growth and later development comes from studies performed in both animals and humans. Each study design has its strengths and limitations, mainly in relation to the potential to establish causality.
Animal Research
One advantage of animal trials is that they allow one to study a greater variety of nutritional interventions than is possible in human studies. They also allow for diverse interventions, some of which are impossible to perform in humans. Further advantages come from the possibility of investigating putative mechanisms of nutritional programming and identifying the precise developmental windows in which early nutritional imbalances contribute to later disease. Also, lifetime studies can be done. The major limitation is that the results of animal studies cannot be extrapolated to humans. In addition, the clinical contribution of animal research is being questioned. Recently, it was stated that much of animal research into potential treatments for humans is wasted, because it is poorly conducted and not evaluated through systematic reviews [3, 4].

Clinical Research
Retrospective Cohort Studies
The major advantage of retrospective (historical) cohort studies comes from them being very time efficient and allowing rapid results. Also, this study design often allows investigation of early life factors and disease outcomes. Large sample sizes are possible. The disadvantages of retrospective cohort studies include potential confounders and suboptimal quality of data from early life (pregnancy, infancy, and childhood), particularly with regard to nutritional exposures, since the initial data collection was for a different purpose. In addition, while many of these studies often consider birth size or weight as proxy measures of nutritional exposure during pregnancy, this may not be valid. The generalizability of the historical data to present-day populations and conditions may be questioned. Finally, this study design does not allow one to establish causality [5].

Prospective Cohort Studies
Subjects in a prospective cohort study have chosen their exposure prior to the study. No allocation is made by the investigator. Prospective cohort studies have a high accuracy of data collection with regard to exposures, confounders, and outcomes. The major disadvantage is that these studies are expensive and time-consuming (due to a long follow-up). Another disadvantage is that it is not possible to establish causal effects. Like retrospective cohort studies, they do not allow one to establish causality [5].

Systematic Reviews of Nonrandomized Trials
In general, a systematic review is better than an individual study. The Cochrane Handbook for Systematic Reviews of Interventions [6] describes 3 principle reasons for undertaking a systematic review of nonrandomized trials. These reasons are as follows: (1) to examine the case for undertaking a randomized trial by providing an explicit evaluation of the weaknesses of available nonrandomized trials, (2) to
provide evidence regarding an intervention that cannot be randomized, or which is extremely unlikely to be studied in randomized trials, and (3) to provide evidence of effects that cannot be adequately studied in randomized controlled trials (RCTs), such as long-term and rare outcomes.

**Randomized Controlled Trials**

Evidence-based medicine recommends performance of randomized controlled trials (RCTs) when addressing questions regarding the effects of prophylactic or therapeutic interventions. Such a model, if designed, conducted and analyzed properly, provides the strongest evidence for causation. Other advantages of RCTs include a low risk of selection bias and an unbiased distribution of confounders. RCTs may be blinded and blinding reduces the risk of performance and measurement bias. Some of the limitations are that RCTs might be expensive, time consuming, and do not allow for a lifetime of follow-up. For some interventions (e.g. investigation of the effects of breastfeeding), RCTs may be unethical [7].

**Systematic Reviews of RCTs**

Systematic reviews, with or without a meta-analysis, are a well-established means of reviewing existing evidence and integrating findings from various studies, including those related to infant nutrition. Although systematic reviews, in particular those compared with traditional review articles (narrative reviews), are generally well accepted, a meta-analytic approach has been the subject of much controversy. The reasons to perform a meta-analysis are as follows: (1) To increase power (i.e. the chance to reliably detect a clinically important difference if one actually exists). The problem with many individual studies is that they are too small to detect small effects, which can only be detected if the data from several trials are combined. (2) To improve precision in estimating effects (i.e. narrow the CI around effects). (3) To answer questions not raised by individual studies. (4) To resolve controversies that arise from studies with conflicting results or generate new hypotheses for future studies. Well-known problems and limitations of a meta-analysis include failure to identify all relevant studies, whether or not to include unpublished data, variable quality of included trials, inconclusive systematic reviews, opposite conclusions, and discrepancies between the results of a meta-analysis and a large RCT (discussed in detail elsewhere) [8, 9].

**Integrated Approach**

Ideally, one should look at all of the evidence available to answer a question. Thus, at the moment, an integrated approach, i.e. the combination of animal and human research (both observational and experimental), seems the most appropriate [10].
Existing Guidelines and Regulations

A number of scientific organizations and/or expert groups have published guidelines and regulations for evaluating early nutritional interventions, including modifications of infant formula. Some of them are discussed below.

ESPGHAN Committee on Nutrition

Two position papers related to nutrition trials performed in infants were published by the ESPGHAN Committee on Nutrition (CoN). The first one [11], published in 2001, concluded that modifications of infant feeding regimens and dietary products need to be evaluated in clinical trials meeting accepted standards of scientific methodology. In 2003 [12], the committee proposed, for general discussion, a list of core data that should be recorded in nutrition trials and suggested principles for the identification of data required for studies with different outcome measures. It was stated that the choice of measures of efficacy and safety is determined by the nature of the study and the hypothesis being tested. With regard to growth, the CoN suggested that growth measures be recorded in all nutrition trials involving infants and children, as safety if not as outcome measures. Examples of factors that may affect growth or body composition were summarized. These included birth weight for gestation (g and SD score for gender and gestation), gender of the infant, parental heights and weights, maternal smoking, and maternal alcohol, drug or substance abuse.

Institute of Medicine of the National Academies

More recently, the Institute of Medicine of the National Academies published a report, which was prepared at the request of the FDA and Health Canada [13]. This report focuses on infant formulas only and reviews methods used for assessing the safety of new ingredients.

- The committee recommends that growth studies, including measures of weight, length, and head circumference as well as body composition, should continue to be a centerpiece of the clinical evaluation of infant formulas.
- The committee recommends that clinical growth studies follow the study participants for the entire period when infant formula remains a substantial source of nutrients in the diets of the infants. In 1996, the FDA proposed a 120-day growth study. According to the committee, this may not be of sufficient length. The rationale behind this conclusion is that exclusive human milk feeding is recommended for 4–6 months. In the absence of human milk, the feeding of infant formula, intended as a human milk substitute, is recommended for the same period of time. Thus, the committee considers that, ideally, formula should be tested for the entire period for which it is intended to be fed as the sole source of infant nutrition (up to 6 months or \( \approx 180 \) days, consistent with breastfeeding guidelines) rather than the currently proposed 120-day period. Furthermore, the
committee considers that a 120-day growth study may not be of sufficient length either to determine delayed effects or to understand longer-term effects of early perturbations in growth.

- The committee recommends the development of specific guidelines that define normal growth and establish a level of difference in growth that represents a safety concern. Specifically, the committee recommends that any addition of an ingredient new to infant formulas should be judged against 2 controls (i.e. the previous iteration of the formula without the added ingredient and human milk).

The proposed rule does not define ‘normal’ growth, nor does it identify what represents a biologically meaningful level of difference in growth among groups of infants consuming different formulas. The Committee recognized that there is very little scientific evidence to establish a level of difference in growth associated with long- or short-term health consequences. However, the Committee concluded that any systematic and statistically significant difference in size and growth rate among infants fed a formula with the new ingredient versus human milk or an already approved formula should be a safety concern.

Current Clinical Studies – Lessons Learned

Despite these documents and numerous existing RCTs, the efficacy and/or safety of many modifications of infant feeding remain(s) questionable [14]. This is mainly due to the methodological limitations of many of the trials. One such example could be infant formulas supplemented with probiotics and/or prebiotics. In the position paper recently published by the ESPGHAN Committee on Nutrition [15], it was noted that interpreting studies on the effects of probiotic supplementation of infant formula on growth is difficult due to the limited number of studies that analyzed the effects of a given probiotic strain. The studies were often too small with insufficient power to identify relevant effects on growth, and the follow-up periods in the trials were short. Although, in general, it was concluded that a few probiotic strains used to supplement infant formula support normal growth in healthy term infants, this conclusion needs to be considered with caution. The same caution applies to other outcomes.

What Could Be Done?

In March 2011, the representatives of academia, the infant food industry, and a regulatory agency met during the workshop in Tutzing (Germany). The main goal of the workshop participants was to improve outcome measurements used in pediatric nutrition trials, as presented in detail elsewhere [16]. With regard to growth, the following concepts were discussed [16]:
• Growth is one of the key outcomes in the documentation of functional and clinical effects of infant nutrition.
• Growth is typically addressed by anthropometric measurements (i.e. weight, length, and head circumference).
• In RCTs, the growth of the study population could be compared with growth curves from standard populations such as the WHO Child Growth Standards. However, the legitimacy of this strategy would all depend on the research question being asked. For example, if the question relates to the suitability of a particular novel ingredient, an RCT with a control population fed the same formula but without the reference ingredient would be required. On the other hand, formula modification aimed at matching the growth rate of breastfed populations might cause growth in the formula-fed population that can be compared to the WHO Child Growth Standards.
• There are scientific and ethical considerations in comparing populations with different ethnic cultures and lifestyles, such as those from developing countries and less-privileged segments of the population. Different genetic and lifestyle/backgrounds may mean that outcomes such as growth curves could not always be extrapolated to studies in Europe.
• Clinical studies that assess parameters such as growth, as well as safety and efficacy of an infant formula, may provide the most informative results when the formula is fed as the sole source of nutrition from birth. This is the period with the most rapid growth, the highest nutrient requirements per kg of body weight, and the highest sensitivity to an unbalanced supply. However, in Europe, it is difficult to enroll infants fed formula from birth, since most infants are, fortunately, breastfed after birth.
• The established approach for an infant growth study is to power it to detect differences in growth using 0.5 SD in a study starting from birth with a duration of 3 months. If enrollment into the study has to be started at a later time point after an initial period of breastfeeding, e.g. during the second or third month of life, studies may need to be powered to detect smaller effect sizes to document potential effects of food components on growth at an age with lower nutrient needs than those required immediately after birth.
• There is no scientific rationale to support a strict distinction between infants younger and older than 6 months of age with respect to the effects of factors such as nutrients on growth and development. If so, the question is to what extent can data collected at 0–6 months of age be extrapolated to infants aged 6–12 months? The workshop participants agreed that this should be decided on a case-by-case basis.
• The workshop participants suggested that perhaps growth studies are not always necessary when functional effects are being investigated, and perhaps growth studies are only needed under certain circumstances (e.g. the modification of protein content or quality, or the addition of complex carbohydrates that might modify the bioavailability of other formula compounds).
Six working groups, including one on growth, were established during the Tutzing workshop. It is expected that these working groups will prepare the conclusions and recommendations for future pediatric nutrition trials as a publishable written report by the end of 2012.

Conclusions

- No single optimal pattern of infant size and growth was associated with beneficial adult health outcomes.
- Compromised or excessive nutrient supply is associated with some chronic disease outcomes; however, evidence is often inconsistent.
- The evidence of the association between nutrition in early life and later risk of diseases comes from both animal and human studies. Each of them has a number of advantages and disadvantages. At present, an integrated approach seems to be the most appropriate.
- A number of guidelines and regulations for evaluating early nutritional interventions exist; however, many issues are still open to discussion.

References

Lessons from Clinical Studies


Hania Szajewska, MD
Department of Pediatrics, Medical University of Warsaw
Dzialdowska 1
PL-01-184 Warsaw (Poland)
E-Mail hania@ipgate.pl