

The right infant nutrition: do nutrition and growth matter in the 6 to 24 month period?

Carlo Agostoni

Neonatal-Pediatric Area, Fondazione IRCCS Cà Granda – Ospedale Maggiore Policlinico, Department of Clinical Sciences and Community Health, University of Milan, Italy

Proceedings

Proceedings of the 10th International Workshop on Neonatology · Cagliari (Italy) · October 22nd-25th, 2014

The last ten years, the next ten years in Neonatology

Guest Editors: Vassilios Fanos, Michele Mussap, Gavino Faa, Apostolos Papageorgiou

Abstract

In the last decades several studies tested the hypothesis that at early developmental stages certain foods or nutrients, in specific amounts, fed during limited sensitive periods, may lead to clinical alterations that take place decades later (*early nutritional programming* of long term health). In spite of suggestions from different early dietary habits, epidemiologic data show that episodes of rapid growth (growth acceleration hypothesis), whichever the dietary habits, are associated with later unfavorable health conditions and should be prevented. Early fast weight gain may be associated with increased likelihood of developing insulin resistance, dyslipidemic conditions, obesity, elevated blood pressure, and endothelial dysfunction. Accordingly, infant's growth pattern may represent the interaction between genetic background and environment, inclusive of nutrition. The branch of science focusing on these aspects is known as *epigenetics*. Different studies have shown on the other hand a reduced growth in infants with specific disorders (milk allergy, HIV) even before the overt clinical symptoms of the disease. Within this context the nutritionist's task is the prevention of deficiencies, but intervention strategies to prevent malnutrition should emphasize improvements in linear growth in the first 2-3 years of life rather than aim at gaining weight, to prevent the event of rapid early weight gain. The present constraints of the global economic crisis require cost/benefit analyses for all the interventions to optimize nutrition and growth in early years. Recent indications for complementary feeding indicate the beneficial effects of introducing earlier food items such as egg and fish,

together with breastfeeding continuation through the first year, in reducing the later risk of immune allergic disorders and metabolic impairments.

Keywords

Nutritional programming, early nutrition, growth acceleration, malnutrition, dietary interventions, cost/benefit analyses.

Corresponding author

Carlo Agostoni, Neonatal-Pediatric Area, Fondazione IRCCS Cà Granda – Ospedale Maggiore Policlinico, Department of Clinical Sciences and Community Health, University of Milan, Via della Commenda 9, 20121 Milan, Italy; phone +39 02 55032497; email: carlo.agostoni@unimi.it.

How to cite

Agostoni C. The right infant nutrition: do nutrition and growth matter in the 6 to 24 month period? *J Pediatr Neonat Individual Med.* 2014;3(2):e030229. doi: 10.7363/030229.

Introduction

In the last decades several studies tested the hypothesis that at early developmental stages certain foods or nutrients, in specific amounts, fed during limited sensitive periods, may determine an endocrine metabolic asset leading to clinical alterations that take place decades later (*early nutritional programming* of long term health). Observational studies indicate that breastfeeding, relative to formula feeding, if continued through the complementary feeding period may reduce the risk for obesity at school age even after adjustment for biological and sociodemographic confounders. Moreover, prolonged breastfeeding is associated with increased neurodevelopmental scores up to early adulthood, while its outcome in terms of delayed decay of brain function is still unknown. Besides the environment surrounding breastfeeding, specific nutrients within human milk may play a direct role. With the introduction of solids the major changes in diet are represented by the sudden decrease of fat intake from 50% to 30% of total energy. A protein excess, commonly found throughout all European countries, has been associated to a higher risk of adiposity in early childhood, as confirmed by first reports from a large European trial [1]. The amount of fat does not seem to be associated with later adiposity, while its

quality may affect blood lipoproteins, blood pressure and neurodevelopmental performance. Early intake of dietary fibers might also have beneficial effects. Epidemiologic data show that episodes of rapid growth (growth acceleration hypothesis), whichever the dietary habits, are associated with later unfavorable health conditions and should be prevented.

The major difficulty in considering the associations of a given macronutrient with diseases of adulthood is represented by the capacity to disentangle its immediate effects from those of the other nutrients, and then relate them to later clinical outcomes (the symptoms and signs of non-communicable disorders) or to earlier biochemical and/or anthropometrical surrogates. The experience of the STRIP project shows the positive effects of a modified-fat diet not limited to early phases but, rather, extended throughout adolescence with periodical counseling interventions [2]. There are data suggesting that the quality of fats may be more relevant than their absolute amount, particularly considering the development of brain and the programming effect on its later performances. Few data indicate that the infant's physiology is oriented towards storing fat, as a possible consequence of the high-glucose supply during the foetal life, and supported by the high supply of fat by human milk. This evolutionary acquisition might be protective towards the extremes ranges of fat intake, by maximizing the resources for survival during periods of depletion. Today, it seems difficult to separate the metabolic effects of fats from those of different protein levels, both converging towards the major issue of body fat storage and its functional consequences. Although fats are the most interesting nutrients in relation to later untoward consequences, no association has been found either between intake profile (including periods of growth acceleration), nor with measurements of adiposity, present or future [3]. Recent evidence raised concern on the potential adverse long-term consequences of early rapid child growth (growth acceleration hypothesis). Accordingly, early fast weight gain may be associated with increased likelihood of developing insulin resistance, dyslipidemic conditions, obesity, elevated blood pressure, and endothelial dysfunction. This hypothesis is consistent with epidemiologic data and with the observations of a lower risk of overweight and obesity in breastfed infants, consistent with their slower growth rates. The concept matches also the observations of increased prevalence of the metabolic syndrome

in infants born small for gestational age (growth restricted, thrifty phenotype hypothesis) [4]. Barker and coworkers have reported that growth patterns with rapid catch-up through childhood strongly relate with later cardiovascular disorder [5]. A “catch-up fat” phenotype across the life cycle is a risk factor for obesity and insulin-related complications not only in infants and children who experienced catch-up growth after earlier foetal or neonatal growth retardation, but also in adults who show weight recovery after substantial weight loss, whichever the cause (famine, disease-cachexia or even dieting) [6]. This interpretation is fully consistent with the increasing and alarming prevalence of chronic-degenerative disorders and their prodromic conditions (obesity, high blood pressure, insulin resistance) in developing countries [7].

Growth patterns as expression of genetics and nutrition

As derivable from the previous paragraph, it seems that infant’s growth pattern, as expression of the interaction between genetic background and environment, inclusive of nutrition, may be particularly relevant starting as early as the first months of life, since it may be associated with later health outcomes. The branch of science focusing on these aspects is known as *epigenetics*. Different studies have shown a reduced growth in infants with symptomatic allergy to cow’s milk (expressed with atopic eczema) during the first year of life. Differences in weight and length progression between atopic infants and healthy children are significant from the second month of age onward, and become marked in the second 6 months of life. The growth faltering starts even before the clinical expression of the disease, maybe indicating a more general unbalance in energy metabolism and disposal [8]. No adverse long-term effect on anthropometric development up to age 10 years was found for infants fed partially hydrolyzed whey, extensively hydrolyzed whey, extensively hydrolyzed casein, or cow-milk formula, whether comparisons were made between formula groups or with respect to breastfed children [9]. Temporary limited delays in growth achievements have been found with the use of extensively hydrolyzed formulas, and either taste characteristics or intrinsic characteristics of absorption and nutrient utilization have been advocated to explain these observations [10]. Even more clear growth delays

before the appearance of clinical symptoms have been found in infants born to HIV-seropositive mothers [11]. Early symptomatic children showed impairments in growth progression starting as early as 2 months of age [12]. Differences towards non-infected counterparts through the first year of life were evident for later symptomatic vs non-infected ones too. In this last subgroup, at two years of age negative differences in length achievement vs infant born to non-infected mothers were found [13]. It is recommended that timely growth monitoring should be used to improve the clinical course and the quality of life of these children [14].

From these two examples we may therefore derive that growth is a general indicator of health status in any case, and even more sensitive than previously believed in children. Since growth (besides genetics and ethnic backgrounds) is also closely connected to nutrition patterns, we may easily derive that nutrition, growth and health outcomes are closely connected in children. The primary role of adequate nutrition in the perspective of health outcomes remains the immediate threat to children in resource-poor environments in developing countries where child morbidity and mortality remain high. Children with evidence of poor prior growth are at greater risk of morbidity and mortality from common infectious diseases, including lower respiratory infections and diarrhoea. In these settings, failure to promote compensatory growth may have negative short-term consequences. Within this context the nutritionist’s task is the prevention of deficiencies, in order to leave the individual the full possibility of expression of its genetic potential, while allowing for recovery of early secondary functional deficiencies. Combined interventions have the greatest chance of success. At the same time, the rapid passage to better economic conditions has generated contrasting situations. In transitional countries, stunting (shortness for age) and micronutrient deficiencies (iron, vitamin A, and zinc) in children coexist with obesity and non-communicable disorders originating the double burden of nutritional disease [15, 16]. Specific patterns of prenatal and postnatal growth are also potential contributors, and intervention strategies to prevent malnutrition should emphasize improvements in linear growth in the first 2-3 years of life rather than aim at gaining weight. In any case, in considering the costs and benefits of promoting catch-up growth, we must not lose sight of the immediate health threats to children in resource-poor environments [17]. The positive effects of compensatory growth is associated with

improvements in neurocognitive development and intellectual achievements. Nutrition interventions aimed at women and children under 2 years are among the key strategies for the millennium development goal of universal primary education by 2015 [18]. As a consequence, health outcomes in developing and transition countries are immediate (survival vs infections and acute diseases), intermediate (neurocognitive achievement) and at long-term (prevention of the early manifestations of non-communicable disorders). Finally, a preliminary warning points out an increasingly and alarming prevalence of chronic-degenerative disorders and their prodromic signs (obesity, high blood pressure, insulin resistance) in developing and transition countries, since rapidly improved economic conditions allow for an easier availability of energy-dense food and rapid gains in growth, mainly weight, instead than just compensatory height gain [15, 16]. Once more, the event of rapid early weight gain seems to be the most identifiable alarming starting point for later disorders, in either those born at term and adequate for gestational age, or those who have been growth restricted during their intrauterine life. Understanding these mechanisms may have an enormous preventive potential, given major public health implications. The early consequences of an accelerated growth may be investigated through some biochemical markers, or indicators, also called “surrogates”, since they cannot stand for the overt disease [19]. Recently, techniques allowing for the detection of early anatomical and functional changes have shown possible higher degrees of associations with the possible disease conditions [20].

The future: a nutrieconomic approach?

The present constraints of the global economic crisis require a transformation into cost/benefit analyses for all the interventions performed at the stadium of preventive medicine. Optimistically, this type of analysis would help in selecting the best diagnostic-therapeutic approaches, while optimizing the interventions on conditions recognized “at high risk”. In the last years, costs have been figured out in terms of DALYs (Disability-adjusted life years) or QALYs (quality-adjusted life years) [21].

Cost-utility studies have progressively increased in recent years in all subspecialty of Paediatrics, and, within this context, the field of nutrition has been object of reappraisal in either developed or underdeveloped countries [22]. The prevention and

treatment of malnutrition on one hand, and population programmes for the prevention of overweight and obesity on the other, have been thoroughly considered. Programmes of home food fortification by the addition of Sprinkles (micronutrients) have been evaluated, considering that only the combined supplementation of multiple micronutrients with lipid-based supplements improves growth in young children [23]. Home fortification of complementary foods reduces the prevalence of anaemia in infancy, and zinc supplementation is associated with a reduction in diarrhoea and respiratory disease morbidity while improving linear growth. Also vitamin A supplementation decreases the incidence of diarrhoea and measles. Measures of cost effectiveness were calculated, such as, the cost per death averted, the cost per DALYs saved, the gain in earnings due to higher cognitive functioning for each dollar spent. The estimated cost per death averted is dollars 406 (273-3,248), the cost per DALY saved is dollars 12.2 (8-97) and the present value of the gain in earnings is dollars 37 (18-51) for each dollar spent on the Sprinkles program [24]. These estimates are developed for a low-income country (GDP per capita = dollars 417) with a high infant mortality rate (IMR = 83/1,000), high prevalence of anaemia (93%), and high mean longitudinal prevalence of diarrhoea (17%). In this setting, interesting all individuals, the focus of outcomes of growth is to individualise cost and benefits of any intervention, with a common expression in terms of QALYs and DALYs, as a sort of common exchange, in a way similar to z scores for the evaluation of anthropometric indices. Accordingly, unfavorable long term effects of accelerated growth in early stages need to be prevented (through follow-up measures, and referring to functional and/or anatomic indicators). Cost/benefit analyses of interventions (DALYs, QALYs) on growth should be expanded on population basis and extended to different type of disorders in order to create bases for agreed indications on the optimal macronutrient supply in the 6 to 24 month period. Recent findings suggest that an early exposure to dietary antigens may be more protective towards allergy than a later introduction even in high-risk infants [25]. The consequent earlier introduction of traditionally believed “pro-allergenic” food items such as egg and fish, together with breastfeeding continuation through the first year, could contribute to reducing protein and increasing fat supply, with a potential role in the overall prevention of non-communicable disorders of adulthood such as

immune allergic diseases and the metabolic syndrome in either Western and rapidly emerging transition countries [26, 27].

Declaration of interest

The Author declares that there is no conflict of interest.

References

- Weber M, Grote V, Closa-Monasterolo R, Escribano J, Langhendries JP, Dain E, Giovannini M, Verduci E, Gruszfeld D, Socha P, Koletzko B. Lower protein content in infant formula reduces BMI and obesity risk at school age: follow-up of a randomized trial. *Am J Clin Nutr.* 2014;99(5):1041-51.
- Niinikoski H, Lagstrom H, Jokinen E, Siltala M, Ronnema T, Viikari, Raitakari OT, Jula A, Marniemi J, Nanto-Salonen K, Simell O. Impact of repeated dietary counseling between infancy and 14 years of age on dietary intakes and serum lipids and lipoproteins: the STRIP study. *Circulation.* 2007;116(9):1032-40.
- Agostoni C, Caroli M. Role of fats in the first two years of life as related to later development of NCDs. *Nutr Metab Cardiovasc Dis.* 2012;22(10):775-80.
- Singhal A, Kattenhorn M, Cole TJ, Deanfield J, Lucas A. Preterm birth, vascular function, and risk factors for atherosclerosis. *Lancet.* 2001;358(9288):1159-60.
- Barker DJ, Osmond C, Forsen TJ, Kajantie E, Eriksson JG. Trajectories of growth among children who have coronary events as adults. *N Engl J Med.* 2005;353(17):1802-9.
- Dulloo AG, Jacquet J, Seydoux J, Montani JP. The thrifty 'catch-up fat' phenotype: its impact on insulin sensitivity during growth trajectories to obesity and metabolic syndrome. *Int J Obes.* 2006;30(Suppl 4):S23-35.
- Popkin BM, Adair LS, Ng SW. Global nutrition transition and the pandemic of obesity in developing countries. *Nutr Rev.* 2012;70(1):3-21.
- Agostoni C, Grandi F, Scaglioni S, Gianni ML, Torcoletti M, Radaelli G, Fiocchi A, Riva E. Growth pattern of breastfed and non-breastfed infants with atopic dermatitis in the first year of life. *Pediatrics.* 2000;106(5):e73.
- Rzehak P, Sausenthaler S, Koletzko S, Reinhardt D, von Berg A, Kramer U, Berdel D, Bollrath C, Grubl A, Bauer CP, Wichmann HE, Heinrich J. Long-term effects of hydrolyzed protein infant formulas on growth—extended follow-up to 10 y of age: results from the German Infant Nutritional Intervention (GINI) study. *Am J Clin Nutr.* 2011;94(6 Suppl):1803S-1807S.
- Mennella JA, Ventura AK, Beauchamp GK. Differential growth patterns among healthy infants fed protein hydrolysate or cow-milk formulas. *Pediatrics.* 2011;127(1):110-8.
- Agostoni C, Riva E, Gianni ML, Silano M, Giovannini M, Zuccotti GV. Anthropometric indicators of human immunodeficiency virus infection in infants with early and late symptoms in the first months of life. *Eur J Pediatr.* 1998;157(10):811-3.
- Agostoni C, Zuccotti GV, Gianni ML, D'Auria E, Giovannini M, Riva E. Body mass index development during the first 6 months of life in infants born to human immunodeficiency virus-seropositive mothers. *Acta Paediatr.* 1998;87(4):378-80.
- Agostoni C, Zuccotti GV, Giovannini M, Decarlis S, Gianni ML, Piacentini E, D'Auria E, Riva E. Growth in the first two years of uninfected children born to HIV-1 seropositive mothers. *Arch Dis Child.* 1998;79(2):175-8.
- Isanaka S, Duggan C, Fawzi WW. Patterns of postnatal growth in HIV-infected and HIV-exposed children. *Nutr Rev.* 2009;67(6):343-59.
- Uauy R, Kain J, Mericq V, Rojas J, Corvalan C. Nutrition, child growth, and chronic disease prevention. *Ann Med.* 2008;40(1):11-20.
- Popkin BM, Adair LS, Ng SW. Global nutrition transition and the pandemic of obesity in developing countries. *Nutr Rev.* 2012;70(1):3-21.
- Adair LS. Developing world perspective: the importance of growth for short-term health. *Nestle Nutr Workshop Ser Pediatr Program.* 2010;65:71-9.
- Martorell R, Horta BL, Adair LS, Stein AD, Richter L, Fall CH, Bhargava SK, Biswas SK, Perez L, Barros FC, Victora CG. Weight gain in the first two years of life is an important predictor of schooling outcomes in pooled analyses from five birth cohorts from low- and middle-income countries. *J Nutr.* 2010;140(2):348-54.
- Yudkin J, Lipska K, Montori V. The idolatry of surrogate. *BMJ.* 2011;343:d7995.
- McNeal CJ, Wilson DP, Christou D, Bush RL, Shepherd LG, Santiago J, Wu GY. The use of surrogate vascular markers in youth at risk for premature cardiovascular disease. *J Pediatr Endocrinol Metab.* 2009;22(3):195-211.
- Airolidi M, Morton A. Adjusting life for quality or disability: stylistic difference or substantial dispute? *Health Econ.* 2009;18(11):1237-47.
- Griebsch I, Coast J, Brown J. Quality-adjusted life-years lack quality in pediatric care: a critical review of published cost-utility studies in child health. *Pediatrics.* 2005;115(5):e600-14.
- Imdad A, Sadik K, Bhutta ZA. Evidence-based prevention of childhood malnutrition. *Curr Opin Clin Nutr Metab Care.* 2011;14(3):276-85.
- Sharieff W, Horton SE, Zlotkin S. Economic gains of a home fortification program: evaluation of "Sprinkles" from the provider's perspective. *Can J Public Health.* 2006;97(1):20-3.
- Palmer DJ, Metcalfe J, Makrides M, Gold MS, Quinn P, West CE, Loh R, Prescott SL. Early regular egg exposure in infants with eczema: A randomized controlled trial. *J Allergy Clin Immunol.* 2013;132(2):387-92.e1
- Rolland-Cachera MF, Deheeger M, Maillot M, Bellisle F. Early adiposity rebound: causes and consequences for obesity in children and adults. *Int J Obes.* 2006;30(Suppl 4):S11-7.
- Agostoni C, Laicini E. Early exposure to allergens: a new window of opportunity for non-communicable disease prevention in complementary feeding? *Int J Food Sci Nutr.* 2014;65(1):1-2.