Introduction
For term infants, the review addressed several issues. Five articles on infant formula [1–5] are discussed. Three of them relate to the relationship between the composition/consumption of infant formula and health outcomes later in life [1–3]; 2 of them review the evidence on the supplementation of beta-palmitate in infant formula [4] and the role of hydrolyzed rice protein formulas in infant feeding [5]. Two additional papers are devoted to probiotics, a field where the gap between basic research and clinical practice has been constantly growing over the years. A Cochrane systematic review summarizes the available data on the use of probiotics in colicky infants, a very challenging issue for pediatricians and parents [6]. New data on the restoration of normal microbiota composition in antibiotic-treated and cesarean infants are provided [7]. The influence of pregnancy and infant feeding on the intestinal microbiome is also covered [8]. The impact of complementary feeding on allergic disorders has been systematically reviewed by an expert group from the United States [9]. The main message is to confirm that the introduction of complementary foods should not be different between infants at risk or not at risk for allergy. Preliminary data show that an early introduction of egg and peanut could even be beneficial to infants with a strong family history of allergy. Another paper suggests an influence of the timing of introduction of complementary feeding on infant sleep [10]. The last 3 articles on term infants demonstrate that the use of young child formula is one of the means to better cover the nutritional needs of young children (1–3 years), especially iron and vitamin D [11–13].

For preterm infants, the focus of last year’s chapter has been on types of feeding. This year we will address 2 main issues. Both issues are important as they are related to the
actual provision of nutrients to the child, not only what is offered but also whether it is tolerated. Many observational studies have shown that undernutrition and poor growth affect neurodevelopmental and other long-term outcomes. This has been summarized in the review of Ong et al. in an elegant way. Undernutrition might be caused by a reduced or imbalanced nutrient offer or that the amount that is administered is adequate in itself but just does not reach the systemic circulation of the infant. Prevention of undernutrition is one thing; the question that also surfaces nowadays is whether additional nutrient supply beyond the stage of undernutrition proves to be beneficial. Four articles for which we were granted permission to discuss at this Yearbook are presented on this topic [14–17]. The other issue that will be addressed is on tolerance. Three articles are discussed [18–20]. The number of articles on this topic resembles the emphasis that is placed on reaching full enteral feeds as soon as possible. The reduction in time that indwelling catheters are in place, with subsequent higher risks not only of infection but also of suboptimal feeding and hepatic disturbances, is the underlying cause of the interest. In addition, when own mothers milk can be the major source of food, the risk for necrotizing enterocolitis and possibly septicemia can be reduced. It may also be of help of increasing neurocognitive development as this remains to be at risk for preterm infants, despite major advances in perinatal care.

Key articles reviewed for this chapter

Term Infants

Randomized controlled trial of iron-fortified versus low-iron infant formula: Developmental outcomes at 16 years
Gahagan S, Delker E, Blanco E, Burrows R, Lozoff B
*J Pediatr* 2019;212:124–130

Association of infant formula composition and anthropometry at 4 years: Follow-up of a randomized controlled trial (BeMIM study)
Fleddermann M, Demmelmaier H, Hellmuth C, Grote V, Trisic B, Nikolic T, Koletzko B
*PLoS One* 2018;13:e0199859

Consumption of soy-based infant formula is not associated with early onset of puberty
*Eur J Nutr* 2019;58:681–687

Palm oil and beta-palmitate in infant formula: a position paper by the European Society for Paediatric Gastroenterology, Hepatology, and Nutrition Committee on Nutrition

Efficacy and safety of hydrolyzed rice-protein formulas for the treatment of cow’s milk protein allergy
*Arch Pediatr* 2019;26:238–246

Probiotics to prevent infantile colic
Ong TG, Gordon M, Banks SSC, Thomas MR, Akobeng AK
*Cochrane Database of Systematic Reviews* 2019;3:CD012473

Probiotic supplementation restores normal microbiota composition and function in antibiotic-treated and in caesarean-born infants
*Microbiome* 2018;6:182

Diet during pregnancy and infancy and the infant intestinal microbiome
*J Pediatr* 2018;203:47–54

Complementary feeding and food allergy, atopic dermatitis/eczema, asthma, and allergic rhinitis: a systematic review
Obbagy JE, English LK, WongYP, Butte NF, Dewey KG, Fleisher DM, Fox MK, Greer FR, Krebs NF, Scanlon KS, Stoody EE

Association of early introduction of solids with infant sleep: a secondary analysis of a randomized clinical trial
Perkin MR, Bahnson HT, Logan K, Marrs T, Radulovic S, Craven J, Flohr C, Lack G
*JAMA Pediatr* 2018;172:e180739

Compared with cow milk, a growing-up milk increases vitamin D and iron status in healthy children at 2 years of age: The Growing-Up Milk-Lite (GUMLi) randomized controlled trial
Lovell AL, Davies PSW, Hill RJ, Milne T, Matsuyama M, Jiang Y, Chen RX, Woudes TA, Heath ALM, Grant CC, Wall CR
*J Nutr* 2018;148:1570–1579
A comparison of the effect of a Growing Up Milk-Lite v. cow’s milk on longitudinal dietary patterns and nutrient intakes in children aged 12–23 months: the Growing Up Milk-Lite randomized controlled trial
Lovell AL, Davies PSW, Hill RJ, Milne T, Matsuyama M, Jiang Y, Chen RX, Grant CC, Wall CR
Br J Nutr 2019;121:678–687

A multicenter, double-blind, randomized, placebo-controlled trial to evaluate the effect of consuming Growing Up Milk “Lite” on body composition in children aged 12–23 months
Wall CR, Hill RJ, Lovell AL, Matsuyama M, Milne T, Grant CC, Jiang Y, Chen RX, Wouldes TA, Davies PSW

Preterm Infants
Supplementing Enteral Intake

Improved lung function at age 6 in children born very preterm and fed extra protein post-discharge
Toftlund LH, Agertoft L, Halken S, Zachariassen G
Pediatr Allergy Immunol 2019;30:47–54

Neurodevelopmental outcome of nutritional intervention in newborn infants at risk of neurodevelopmental impairment: the Dolphin neonatal double-blind randomized controlled trial
Dev Med Child Neurol 2018;60:897–905

Improved outcomes in preterm infants fed a nonacidified liquid human milk fortifier: a prospective randomized clinical trial
Schanler RJ, Groh-Wargo SL, Barrett-Reis B, White RD, Ahmad KA, Oliver J, Baggs G, Williams L, Adamkin D

Commencing nutrient supplements before full enteral feed volume achievement is beneficial for moderately preterm to late preterm low birth weight babies: a prospective, observational study
Fan WQ, Gan A, Crane O
Nutrients 2018;10:1340

Gastric Residuals

Effect of gastric residual evaluation on enteral Intake in extremely preterm infants: a randomized clinical trial
Parker LA, Weaver M, Murgas Torrazza RJ, Shuster J, Li N, Krueger C, Neu J
JAMA Pediatr 2019;173:534–543
Randomized controlled trial of iron-fortified versus low-iron infant formula: developmental outcomes at 16 years

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J Pediatr 2019;212:124–130

Background: The objective of the study was to test differences in cognitive outcomes among adolescents randomly assigned previously as infants to iron-fortified formula or low-iron formula as part of an iron deficiency anemia (IDA) prevention trial.

Methods: Infants were recruited from community clinics in low- to middle-income neighborhoods in Santiago, Chile. Entrance criteria included term, singleton infants; birth weight of ≥3.0 kg; and no major congenital anomalies, perinatal complications, phototherapy, hospitalization >5 days, chronic illness, or IDA at 6 months. Six-month-old infants were randomized to iron-fortified (12 mg/L) or low-iron (2.3 mg/L) formula for 6 months. At 16 years of age, cognitive ability, visual perceptual ability, visual memory, and achievement in math, vocabulary, and comprehension were assessed, using standardized measures. We compared differences in developmental test scores according to randomization group.

Results: At the follow-up assessment, the 405 participants averaged 16.2 years of age and 46% were male. Those randomized to iron-fortified formula had lower scores than those randomized to low-iron formula for visual memory, arithmetic achievement, and reading comprehension achievement. For visual motor integration, there was an interaction with baseline infancy hemoglobin, such that the iron-fortified group outperformed the low-iron group when 6-month hemoglobin was low and underperformed when 6-month hemoglobin was high.
Conclusion: Adolescents who received iron-fortified formula as infants from 6 to 12 months of age at levels recommended in the US had poorer cognitive outcomes compared with those who received a low-iron formula. The prevention of IDA in infancy is important for brain development. However, the optimal level of iron supplementation in infancy is unclear.

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Comments

Iron deficiency anemia (IDA) is a global public health problem considered the most common and widespread nutritional disorder in the world. IDA in infancy is associated with negative health outcomes, including poorer cognitive, motor, and socioemotional development. The optimal level of iron fortification is controversial. There is increasing concern on iron neurotoxicity in infant and on the deleterious effects of iron exposure in early life on brain aging and neurodegenerative disease outcomes.

The American Academy of Pediatrics Committee on Nutrition recommends that formula-fed infants receive formula containing 10–12 mg/L of iron, whereas the European Society for Paediatric Gastroenterology, Hepatology, and Nutrition Committee on Nutrition recommends lower concentrations of iron in infant formula, that is, 4–7 mg/L. The European Union Commission delegated Regulation of September 25, 2015, on the essential composition of infant (IF) and follow-on formula (FOF) set an iron content of 2–8 and 4–13 mg/L for IF and FOF, respectively.

The Santiago Longitudinal Study was designed to evaluate the behavioral and developmental effects of preventing IDA in infancy. Enrollment occurred between 1991 and 1994. Infants who were already taking ≥1 bottle of milk or formula per day (≥250 mL) were randomly assigned to iron-fortified or low-iron formula from 6 to 12 months of age. At 12 months, 835 infants completed the randomized controlled trial: 430 randomized to iron-fortified formula and 405 randomized to low-iron formula [1]. At the end of the trial, 19% of infants randomized to iron-fortified formula were iron deficient and 2.8% had IDA. Among those randomized to a low-iron formula, 35% were iron deficient and 3.8% had IDA.

At 16 years of age, outcomes were assessed in 49% of the infancy sample (n = 405). There was no significant difference in attrition by randomization group. Infant background characteristics (i.e., age, sex, SES, HOME environment, formula intake, maternal age, IQ, and education) were similar in those assessed at 16 years compared with those not assessed. There were no statistically significant group differences in the hematologic or iron status measures at 16 years of age. The adolescent sample differed from the infancy sample in the proportion of males assessed (46 vs. 53% in infancy; p < 0.05). Furthermore, maternal IQ was slightly higher in those assessed compared with those not assessed (mean [SD] IQ 84.5 [0.5] vs. 83.1 [0.5]; p = 0.04). Sex and maternal IQ were adjusted for in all analyses. These differences illustrate the limitations of follow-up studies of randomized controlled trials, which should be considered as observational, thereby making it impossible to draw any causal relationship. However, the Santiago Longitudinal Study is the only study comparing iron-fortified formula with low-iron formula in humans. The results of this follow-up study do not question iron supplementation in IF and FOF. They point out the need for further research on the optimal level of iron fortification. With regard to iron supplementation in IF and FOF, the “more the better” is obviously not adequate.
Association of infant formula composition and anthropometry at 4 years: Follow-up of a randomized controlled trial (BeMIM study)

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PLoS One 2018;13:e0199859

Background: The relationships between nutrition, metabolic response, early growth and later body weight have been investigated in human studies. The aim of this follow-up study was to assess the long-term effect of infant feeding on growth and to study whether the infant metabolome at the age of 4 months might predict anthropometry at 4 years of age.

Methods: The Belgrade-Munich infant milk trial was a randomized controlled trial in which healthy term infants received either a protein-reduced infant formula (1.89 g protein/100 kcal) containing alphalactalbumin enriched whey and long-chain polyunsaturated fatty acids, or a standard formula (2.2 g protein/100 kcal) without long-chain polyunsaturated fatty acids, focusing on safety and suitability. Non-randomized breastfed infants were used as a reference group. Of the 259 infants that completed the Belgrade-Munich infant milk trial study at the age of 4 months (anthropometry assessment and blood sampling), 187 children participated in a follow-up visit at 4 years of age. Anthropometry including weight, standing height, head circumference, and percent body fat was determined using skinfolds (triceps, subscapular) and bioelectrical impedance analysis. Plasma metabolite concentration, collected in samples at the age of 4 months, was measured using flow-injection tandem mass spectrometry. A linear regression model was applied to estimate the associations between each metabolite and growth with metabolites as an independent variable.

Results: At 4 years of age, there were no significant group differences in anthropometry and body composition between formula groups. Six metabolites (Asn, Lys, Met, Phe, Trp, Tyr) measured at 4 months of age were significantly associated with changes in weight-for-age z-score between 1 and 4 months of age and BMI-for-age z-score (Tyr only), after adjustment for feeding group. No correlation was found between measured metabolites and long-term growth (up to 4 years of age). No long-term effects of early growth patterns were shown on anthropometry at 4 years of age. Conclusion: The composition of infant formula influences the metabolic profile and early growth, while long-term programming effects were not observed in this study.

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Comments: The association between both rapid weight gain and high protein intake in infancy and increased risk for overweight and obesity later in life is well known. However, there is yet no firm evidence from the available data that this relationship is causal. The influence of protein quality on longitudinal changes in body composition is less clear. This follow-up study was able to recruit at the age of 4 years 124 of the 213 infants randomized in the 2 IF groups, that is, an attrition rate of 42%. The study population at 4 years of age differed from the original study population with respect to age of mothers at delivery and percentage of mothers smoking during pregnancy. This is a limitation of the study which in any case should be considered as observational. This study found no evidence that the quality of the protein intake had an impact on the growth pattern assessed at 4 years of age. In addition, this study did not suggest an influence of early protein intake and growth from birth to 4 months of age on anthropometry at 4 years of age. It contradicts the observation by Weber et al. [2], showing
an association between early protein intake and weight gain and the risk for overweight and obesity at 6 years of age. It is still to be demonstrated that the use of low-protein infant formula early in life plays a role on the risk for overweight and obesity later in life. However, there is no need to give a protein intake far beyond the protein needs in infancy.

Consumption of soy-based infant formula is not associated with early onset of puberty

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Eur J Nutr 2019; 58: 681–687

Background: The use of soy products is common in young children with cow milk allergy (CMA). The aim was to examine prospectively the association between infantile consumption of soy-based formula, growth parameters and early pubertal signs, in comparison to cow milk-based formula.

Methods: A nested case-control study was conducted, selected from a cohort of infants prospectively followed from birth until the age of 3 years for eating habits and the development of IgE-mediated CMA. Infants who consumed only soy-based formula were included in the soy group. The control group was randomly selected from those without IgE-CMA and not receiving soy formula. Study participants were reevaluated between ages 7.8 and 10.5 years by an interview, nutritional intake by 3 days diaries, and height, weight, and pubertal signs by physical examination.

Results: The soy-fed group included 29 participants (17 males), median age 8.92 years (interquartile range 8.21–9.42). The control group included 60 participants (27 males), median age 8.99 years (interquartile range 8.35–9.42). The groups had comparable height and BMI z scores (–0.17 ± 1.08 vs. –0.16 ± 1.01, p = 0.96, and 0.67 ± 1.01 vs. 0.53 ± 1.02, p = 0.56, for soy and control groups, respectively). Four (3 males and 1 female) from the soy-group (13.8%) and 8 females from the control-group (13.3%) had early pubertal signs (p = 0.95). No association was detected between puberty and infantile nutrition, after controlling for BMI and family data. No association with puberty or differences between groups were found in current daily consumption of soy, micronutrients, energy, carbohydrates, fat, and protein.

Conclusions: This is the first prospective, physical examination-based study, demonstrating no association between infantile soy-based formula consumption and both growth and puberty parameters.

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Comments

Phytoestrogens represent a broad group of plant-derived compounds of nonsteroidal structure that have weak estrogen activity. They are present in beans in general and soybeans in particular. Lignans and isoflavones are the major classes of phytoestrogens of interest from a nutritional and health perspective. The main compounds contained in soy protein-based foods are isoflavones that can bind to estrogen receptors, interact with enzyme systems influencing estrogenic activity, and exert weak estrogenic activity. Infant formulas based on soy protein isolates
contain relatively high concentrations of isoflavones, and more information is needed on potential long-term effects of phytoestrogens. There are several reports of a positive association between soy formula exposure and sexual development. A three-fold increase in the number of patients with premature thelarche seen between 1978 and 1981 in Puerto Rico led to further investigation in a case–control study [3]. Onset of thelarche before 2 years of age was significantly associated with consumption of soy protein isolate-based infant formula and of various meats. A study was performed in the United States with telephone interviews in 811 adults aged 20–34 years who had participated as infants during the years 1965–1978 in clinical trials with soy protein-based or cow’s milk protein infant formula (n = 248; 120 males) [4]. Women-fed soy formula in infancy experienced a slightly but significantly longer duration of menstrual bleeding (by 0.37 days), with no difference in self-assessed intensity of menstrual flow. They also reported greater discomfort with menstruation (unadjusted relative risk for extreme discomfort vs. no or mild pain, 1.77; 95% CI 1.04–3.00). In a study from Israel, breast development in the first 2 years of life was associated with the use of soy infant formulas [5]. High-serum isoflavones concentrations were associated with the risk of precocious puberty in Korean girls, but their source was not obligatory from food intake [6]. Conversely, Andres et al. [7] observed no difference in ultrasonographic measures of breast bud, uterus, ovaries, prostate, and testes, in a group of 100 prepubertal children studied at 5 years of age, of whom a third were fed soy-based formula during infancy.

This study of Sinai et al. is the first prospective study, including real-time infantile data regarding both feeding habits and birth parameters, in conjunction with a physical examination and a face-to-face interview at the age of early pubertal onset. In addition, various factors known to play a role in the timing of onset of puberty (e.g., family history of early puberty, prenatal growth, obesity, nutritional habits, and physical activity) were accounted for in the study. The main weakness of the study is the small sample size (29 participants in the soy-fed group and 60 participants in the control group). The authors observed that soy consumption was not associated with early onset of secondary pubertal signs. There is a need for a large multicenter study to further assess whether or not soy protein formula should still be considered as an endocrine disruptor. In the meantime, the recommendations published in 2006 by the European Society for Paediatric Gastroenterology, Hepatology, and Nutrition to avoid the use of soy-protein formula in the first 6 months of life seem to remain appropriate [8].
Palm oil and beta-palmitate in infant formula: A position paper by the European Society for Paediatric Gastroenterology, Hepatology, and Nutrition Committee on Nutrition

Bronsky J1, Campoy C2, Embleton N3, Fewtrell M4, Fidler Mis N5, Gerasimidis K6, Hojsak I7, Hulst J8, Indrio F9, Lapillonne A10,11, Molgaard C12,13, Moltu SJ14, Verduci E15, Vora R16, Domellöf M17; ESPGHAN Committee on Nutrition

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Background: Palm oil (PO) is used in infant formulas in order to achieve palmitic acid (PA) levels similar to those in human milk. PA in PO is esterified predominantly at the SN-1,3 position of triacylglycerol, and infant formulas are now available in which a greater proportion of PA is in the SN-2 position (typical configuration in human milk). As there are some concerns about the use of PO, we aimed to review literature on health effects of PO and SN-2-palmitate in infant formulas.

Methods: PubMed and Cochrane Database of Systematic Reviews were systematically searched for relevant studies on possible beneficial effects or harms of either PO or SN-2-palmitate in infant formula on various health outcomes.

Results: We identified 12 relevant studies using PO and 21 studies using SN-2-palmitate. Published studies have variable methodology, subject characteristics, and some are underpowered for the key outcomes. PO is associated with harder stools and SN-2-palmitate use may lead to softer stool consistency. Bone effects seem to be short-lasting. For some outcomes (infant colic, faecal microbiota, lipid metabolism), the number of studies is very limited and summary evidence inconclusive. Growth of infants is not influenced. There are no studies published on the effect on markers of later diseases.

Conclusion: There is insufficient evidence to suggest that PO should be avoided as a source of fat in infant formulas for health reasons. Inclusion of high SN-2-palmitate fat blend in infant formulas may have short-term effects on stool consistency but cannot be considered essential.

Comments This is a position paper by the European Society for Paediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) Committee on Nutrition (ESPGHAN CoN). The

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systematic review performed by ESPGHAN CoN was able to appraise the available studies and to draw sound conclusions. It allows also to better estimate the possible gaps between the scientific evidence and the claims made by the manufacturers. Triacylglycerols (TAGs) in breast milk provide 45–55% of the energy intake of breast-fed infants as well as essential fatty acids and other lipids that play important roles in optimal development. Palmitate constitutes about 25% of the fatty acids of breast milk TAGs, and approximately 70% of this is at the sn-2 position. Inversely, palmitate in most infant formulas is predominantly at the sn-1 and sn-3 positions of the TAG backbone. This difference in TAG structure is of importance in palmitic acid (PA) and total lipid absorption. The pancreatic lipase – colipase system is highly selective for the sn-1 and sn-3 TAG positions, resulting in the generation of 2 free fatty acids and an sn-2 monoacylglycerol. All sn-2 monoacylglycerols are well absorbed as are saturated fatty acids of chain length <14 carbons and all unsaturated fatty acids. However, free long-chain saturated fatty acids, such as PA, form calcium soaps that are insoluble at body temperature and are excreted in the feces. Thus, PA absorption is greater in breast-fed infants than in formula-fed infants. The percentage of fed calcium that is also absorbed is greater in breast-fed than in formula-fed infants; fecal calcium – palmitate soaps are associated with hard stools, and this may, at least in part, explain the greater stool softness in breast-fed infants as compared to formula-fed infants.

A very recent randomized controlled trial including 488 infants from birth to 4 months of age not reviewed by ESPGHAN CoN demonstrated that feeding infant formulas with increased levels of sn-2 palmitate (respectively, 43 and 51% of the lipid content) and a concomitant decrease in sn-1 and sn-3 palmitate: (1) supports normal infant growth, (2) results in softer stools during the first 2 months of life, (3) increases bone mineral content at 4 months of age, and (4) is well tolerated. Thus, feeding formulas containing high sn-2 palmitate is safe and provides positive outcomes to infants in terms of stool consistency and bone mineralization during the first 4 months of life [9]. As stated by ESPGHAN CoN, there is insufficient evidence to suggest that palm oil should be avoided as a source of fat in infant formulas for health reasons. Inclusion of high SN-2-palmitate fat blend in infant formulas may have short-term effects on stool consistency because of reduced formation of calcium soaps but cannot be considered essential.
Efficacy and safety of hydrolyzed rice-protein formulas for the treatment of cow’s milk protein allergy

Bocquet A 1,2, Dupont C 3,4, Chouraqui JP 5, Darmaun D 6, Feillet F 7, Frelut ML 1,8, Girardet JP 9, Hankard R 10, Lapillonne A 11,12, Rozé JC 6, Simeoni U 13, Turck D 14, Briend A 15; Committee on Nutrition of the French Society of Pediatrics (CNSFP)

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Arch Pediatr 2019; 26:238–246

Background: Foods for special medical purposes with a protein fraction made of hydrolyzed rice protein (HRP) are on the market in Europe since the 2000s for the treatment of cow’s milk protein allergy (CMPA).

Methods: A PubMed search was performed with the objective to find studies regarding the efficacy and safety of HRP formulas (HRPFs). Eleven clinical trials on HRPFs in infants were identified and ranked according to the level of evidence of the Oxford Centre for Evidence-based Medicine (CRBM).

Results: HRPFs are proposed as a plant-based alternative to cow’s milk protein-based extensively hydrolyzed formulas beside the soy protein formulas whose use in CMPA is controversial. HRPFs do not contain phytoestrogens and are derived from non genetically modified rice. HRPFs are strictly plant-based apart from the addition of vitamin D3 (cholecalciferol). As the aminoacid content of rice proteins differs from that of human milk proteins, the protein quality of these formulas is improved by supplementation with free lysine, threonine, and tryptophan. The consumption of HRPFs has risen: for example, in France, HRPFs account for 4.9% in volume of all formulas for children aged 0–3 years. Several studies have shown the adequacy of HRPFs in treating CMPA. They ensure satisfactory growth from the 1st weeks of life for infants and toddlers, both in healthy children and in those with CMPA.

Conclusion: HRPFs can be used to treat children with CMPA either straightaway or in second intention in cases of poor tolerance to cow’s milk protein-based extensively hydrolyzed formulas for organoleptic reasons or for lack of efficacy. In France, the cost of HRPFs is close to that of regular infant or follow-on formulas.

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Comments

Rice protein allergy is rare in Western countries. Rice is considered the least allergenic cereal because it triggers undesirable reactions in <1% of children with allergies. Rice proteins can be the cause of the non-IgE-mediated food protein-induced enterocolitis (FPIES) but more rarely than cow’s milk or soy proteins. The diagnosis delay and symptom severity are greater than for cow’s milk protein allergy (CMPA). Children with rice-induced FPIES are more likely to develop the same syndrome with other foods (oats, barley, wheat, and other noncereal foods) than children whose FPIES was caused by cow’s milk or soy. HRP formulas (HRPFs) are not available in many countries, while they are widely used in others such as Italy, Spain, and France.
Evidence from clinical trials published to date shows that HRPFs are a feasible treatment option in children with CMPA, either in first intention or in case of palatability issues with cow’s milk protein-based extensively hydrolyzed formulas (CMP-eHFs). HRPFs allow a satisfactory growth from birth through the first few years of life in healthy children as well as in children suffering from CMPA. Such conclusions are, however, valid only for the products reported in the studies reviewed. Another aspect of HRPFs is a relatively low cost compared to CMP-eHFs. No data are available to draw any conclusions on the use of HRPFs in cases of allergy to CMP-eHFs, which today require the use of amino acid formulas. On the other hand, it is not currently possible to conclude on the influence of the formula used to treat infants with CMPA on the duration of the CMPA.

Inorganic arsenic intake is likely to affect long-term health. It should be kept in mind that high concentrations are found in some rice-based foods and drinks widely used in infants and young children. In order to reduce exposure, ESPGHAN CoN recommended in 2015 that rice drinks for infants and young children should be avoided and that, for all of the rice products, strict regulation should be enforced regarding arsenic content [10]. Since 2016 (EU 2015/1006 of June 25, 2015), the maximum level of inorganic arsenic for rice intended to produce foodstuffs for children under 3 years of age is 0.10 mg/kg (a limit twice as low as that for white rice) [11]. The CNSFP reiterates in this review paper its 2012 recommendations: HRPFs can be considered as an alternative to CMP-eHF as a first-line treatment for infants with CMPA because of their effectiveness, in terms of allergic symptoms and nutritional adequacy, their palatability, and their lower cost. HRPFs may therefore represent an option, either as a first intention regimen for a child with CMPA or as second intention if CMP-eHFs are either not accepted or poorly accepted for organoleptic reasons.

### Probiotics to prevent infantile colic

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**Background:** Infantile colic is typically defined as full-force crying for at least 3 h/day, on at least 3 days/week, for at least 3 weeks. Infantile colic affects a large number of infants and their families worldwide. Its symptoms are broad and general, and while not indicative of disease, may represent a serious underlying condition in a small percentage of infants who may need a medical assessment. Probiotics are live microorganisms that alter the microflora of the host and provide beneficial health effects. The most common probiotics used are of *Lactobacillus*, *Bifidobacterium* and *Streptococcus*. There is growing evidence to suggest that intestinal flora in colicky infants differ from those in healthy infants, and it is suggested that probiotics can redress this balance and provide a healthier intestinal microbiota landscape. The low cost and easy availability of probiotics makes them a potential prophylactic solution to reduce the incidence and prevalence of infantile colic. The aim of the systematic review was to evaluate the efficacy and safety of prophylactic probiotics in preventing or reducing severity of infantile colic.
Methods: In January 2018 we searched CENTRAL, MEDLINE, Embase, PsycINFO, CINAHL, 10 other databases and 2 trials registers. In addition, we handsearched the abstracts of relevant meetings, searched reference lists, ran citation searches of included studies, and contacted authors and experts in the field, including the manufacturers of probiotics, to identify unpublished trials. Randomised control trials of newborn infants < 1 month of age without the diagnosis of infantile colic at recruitment were selected. We included any probiotic, alone or in combination with a prebiotic (also known as synbiotics), versus no intervention, another intervention(s) or placebo, where the focus of the study was the effect of the intervention on infantile colic. We used standard methodological procedures of Cochrane.

Results: Our search yielded 3,284 records, and of these, we selected 21 reports for full-text review. Six studies with 1,886 participants met our inclusion criteria, comparing probiotics with placebo. Two studies examined *Lactobacillus reuteri* DSM, 2 examined multi-strain probiotics, one examined *Lactobacillus rhamnosus*, and one examined *Lactobacillus paracasei* and *Bifidobacterium animalis*. Two studies began probiotics during pregnancy and continued administering them to the baby after birth. We considered the risk of bias for randomisation as low for all 6 trials; for allocation concealment as low in 2 studies and unclear in 4 others. All studies were blinded, and at low risk of attrition and reporting bias. A random-effects meta-analysis of 3 studies (1,148 participants) found no difference between the groups in relation to occurrence of new cases of colic: risk ratio 0.46, 95% CI 0.18–1.19; low-certainty evidence; $I^2 = 72\%$. A random-effects meta-analysis of all 6 studies (1,851 participants) found no difference between the groups in relation to serious adverse effects (risk ratio 1.02, 95% CI 0.14–7.21; low-certainty evidence; $I^2$ not calculable (only 4 serious events for one comparison, 2 in each group: meconium plug obstruction, patent ductus arteriosus and neonatal hepatitis). A random-effects meta-analysis of 3 studies (707 participants) found a mean difference (MD) of −32.57 minutes per day (95% CI −55.60 to −9.54; low-certainty evidence; $I^2 = 93\%$) in crying time at study end in favour of probiotics. A subgroup analysis of the most studied agent, *Lactobacillus reuteri*, showed a reduction of 44.26 minutes in daily crying with a random effects model (95% CI −66.6 to −21.9; $I^2 = 92\%$), in favour of probiotics.

Conclusion: There is no clear evidence that probiotics are more effective than placebo at preventing infantile colic; however, daily crying time appeared to reduce with probiotic use compared to placebo. There were no clear differences in adverse effects. We are limited in our ability to draw conclusions by the certainty of the evidence, which we assessed as being low across all 3 outcomes, meaning that we are not confident that these results would not change with the addition of further research.

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Comments

Infantile colic is defined as periods of inconsolable, unexplained, and incessant crying in a seemingly healthy infant that leads to exhausted, frustrated, and concerned parents seeking to comfort their child. These episodes often occur in the evening. Colic has been included under functional gastrointestinal disorders (Rome IV diagnostic criteria), and the definition has been expanded to include paroxysms of irritability and fussiness for at least 1 week in an infant who has no failure to thrive. This condition appears to be more frequent in the first 6 weeks of life, occurring in up to 25% of newborns depending on geography and definitions employed, with prevalence often peaking at that point. Episodes of colic usually resolve by 3–4 months of age. However, about 5% of colicky, crying infants have a serious, underlying medical problem, including cow’s milk protein allergy, gastroesophageal reflux disease, or lactose intolerance. Any treatment that may improve the infant’s condition is of course more than welcome by parents. The results of this Cochrane review are of paramount importance, avoiding an excessive and expansive use of probiotics that is not supported by the available scientific evidence. Health claims made by manufacturers on the use of probiotics in general and in colicky infants in particular need to be considered with great caution.
Probiotic supplementation restores normal microbiota composition and function in antibiotic-treated and in caesarean-born infants


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Background: Infants born by caesarean section or receiving antibiotics are at increased risk of developing metabolic, inflammatory and immunological diseases, potentially due to disruption of normal gut microbiota at a critical developmental time window.

Methods: We investigated whether probiotic supplementation could ameliorate the effects of antibiotic use or caesarean birth on infant microbiota in a double blind, placebo-controlled randomized clinical trial. Mothers were given a multispecies probiotic, consisting of Bifidobacterium breve Bb99 (Bp99 2 × 10^8 CFU), Propionibacterium freudenreichii subsp. shermanii JS (2 × 10^9 CFU), Lactobacillus rhamnosus Lc705 (5 × 10^9 CFU) and Lactobacillus rhamnosus GG (5 × 10^9 CFU; n = 168 breastfed and 31 formula-fed), or placebo supplement (n = 201 breastfed and 22 formula-fed) during pregnancy, and the infants were given the same supplement. Faecal samples of the infants were collected at 3 months and analyzed using taxonomic, metagenomic and metaproteomic approaches.

Results: The probiotic supplement had a strong overall impact on the microbiota composition, but the effect depended on the infant’s diet. Only breastfed infants showed the expected increase in Bifidobacteria and reduction in Proteobacteria and Clostridia. In the placebo group, both birth mode and antibiotic use were significantly associated with altered microbiota composition and function, particularly reduced Bifidobacterium abundance. In the probiotic group, the effects of antibiotics and birth mode were either completely eliminated or reduced.

Conclusion: The results indicate that it is possible to correct undesired changes in microbiota composition and function caused by antibiotic treatments or caesarean birth by supplementing infants with a probiotic mixture together with at least partial breastfeeding.

Comments: Microbial colonization of the infant gut plays an important role in later health. In healthy newborns, the gut microbiome composition experiences longitudinal changes until the age of 2–3 years, when an adult-like anaerobic pattern is acquired. Perturbations in the microbiome are associated later in life with susceptibility to autoimmune diseases, such as diabetes, inflammatory bowel disease, and atopy, and to overweight and obesity. Colonization of the infant gut is a complex process dependent on multiple overlapping factors, including age, mode of delivery, type of feeding, presence of siblings or pets, and environmental exposures as geographical location or farm exposure [12]. As an example, cesarean section and the use of antibiotics in the neonatal period and early infancy are strongly associated with a significant gut microbiota disruption, usually named as dysbiosis. Conversely, breast milk keeps the microbiota in a state characterized by low diversity and Bifidobacte-
Diet during pregnancy and infancy and the infant intestinal microbiome

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Background: To determine the association between diet during pregnancy and infancy, including breastfeeding versus formula feeding, solid food introduction, and the infant intestinal microbiome.

Methods: Infants participating in the Vitamin D Antenatal Asthma Reduction Trial were included in this study (n = 323). Maternal and infant diets were assessed by questionnaire. Infant stool samples were collected at age 3–6 months. Stool sequencing was performed using the Roche 454 platform. Analyses were stratified by race/ethnicity.

Results: Breastfeeding, compared with formula feeding, was independently associated with infant intestinal microbial diversity. Breastfeeding also had the most consistent associations with individual taxa that have been previously linked to early-life diet and health outcomes (e.g., Bifidobacterium). Maternal diet during pregnancy and solid food introduction were less associated with the infant gut microbiome than breastfeeding status. We found evidence of a possible interaction between breastfeeding and child race/ethnicity on microbial composition.

Conclusions: Breastfeeding versus formula feeding is the dietary factor that is most consistently independently associated with the infant intestinal microbiome. The relationship between breastfeeding status and intestinal microbiome composition varies by child race/ethnicity. Future studies will need to investigate factors, including genomic factors, which may influence the response of the microbiome to diet.

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Prenatal diet influences the risk of infant and child allergy. For instance, the Mediterranean diet during pregnancy has been associated with a reduced risk of both persistent and atopic wheeze and atopy in children at 6.5 years old. High meat consumption during pregnancy is associated with an increased risk of wheeze in the first year of life, while maternal dairy intake is associated with a reduced risk of infantile wheeze. Little is known about the actual mechanisms by which maternal diet affects children’s health. Maternal diet may influence the infant gut microbiome through vertical transfer of maternal microbes to infants during vaginal delivery and breastfeeding. Diet during infancy is associated with health and disease outcomes and with the infant’s intestinal microbiome. Short-term diets composed solely of either plant or animal foods have been shown to alter the human gut microbiome. In addition, studies in humans and humanized gnotobiotic mice show that diets with reduced carbohydrates, or high in polysaccharides, alter gut microbiome composition. There are few data on the relationship between maternal diet and the developing infant gut microbiome. One study observed that fruit and dairy intake of the mother during pregnancy was associated with the gut microbial composition [13].

The present study confirms the major role of breastfeeding in the modulation of the intestinal microbiota in young infants. More information is needed to know whether the influence of breastfeeding on the microbiota persists beyond 3–6 months of age. The reasons why race/ethnicity has an impact on infant’s intestinal microbiota need further investigation. It should also be emphasized that the main weakness of this study is the fact that the included infants had a family history (father and/or mother) of asthma or allergy that may have an impact on the child microbiome. All of the data observed by Savage in this manuscript should be replicated by other investigators.

Complementary feeding and food allergy, atopic dermatitis/eczema, asthma, and allergic rhinitis: a systematic review

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Background: Nutrition during infancy and toddlerhood may influence health and disease prevention across the life span. Complementary feeding (CF) starts when human milk or infant formula is complemented by other foods and beverages, beginning during infancy and continuing to age 24 months. The aim of this study was to describe systematic reviews conducted for the USDA and the Department of Health and Human Services Pregnancy and Birth to 24 months Project to answer the following question: What is the relationship between the timing of the introduction of complementary foods and beverages (CFBs), or types and amounts of CFBs consumed, and the development of food allergy, atopic dermatitis/eczema, asthma, and allergic rhinitis?
Methods: The literature was searched using 4 databases (CINAHL, Cochrane, Embase, PubMed) to identify articles published from January 1980 to February 2017 that met predetermined inclusion criteria. For each study, data were extracted and risk of bias was assessed. The evidence was qualitatively synthesized to develop a conclusion statement, and the strength of the evidence was graded.

Results: Thirty-one included articles addressed the timing of CFB introduction, and 47 articles addressed the types and amounts of CFBs consumed.

Conclusion: Moderate evidence suggests that there is no relationship between the age at which CF first begins and the risk of developing food allergy, atopic dermatitis/eczema, or childhood asthma. Limited to strong evidence, depending on the specific food, suggests that introducing allergenic foods in the first year of life (after 4 months) does not increase the risk of food allergy and atopic dermatitis/eczema but may prevent peanut and egg allergy. There is not enough evidence to determine a relationship between diet diversity or dietary patterns and atopic disease. Research is needed to address gaps and limitations in the evidence on CF and atopic disease, including research that uses valid and reliable diagnostic measures and accounts for key confounders and potential reverse causality.

Comments: The influence of the timing of introduction of complementary foods on the occurrence and/or severity of atopic diseases is a controversial issue. Over the last 50 years, guidelines have changed several times moving from an early introduction, that is, < 2–3 months to a later introduction, that is, >6 months, with different advice in infants at risk and not at risk of allergy. Very few data were available to support these guidelines. More studies on complementary feeding are now published, even if most of them are observational and therefore do not allow to prove a causal relationship between time of introduction and health outcomes. The National Institute of Allergy and Infectious Diseases estimates that ~5% of children and ~4% of adults in the United States have ≥1 food allergies and that ~30% of the US population has atopic dermatitis. In addition, the CDC estimates that ~8% of Americans have asthma and an additional 8% have allergic rhinitis. Therefore, understanding the relationship between dietary intake during infancy and toddlerhood and atopic disease is of public health importance. An important consideration in the evaluation of the effect or association between the timing of introduction of complementary foods (CFs) and an atopic-disease-related outcome is reverse causality that may be either due to the presence of an atopic family history, on the one hand, and due to the presence of allergic symptoms before the introduction of CFs, on the other hand. In both cases, parents may decide to anticipate or postpone the introduction of CFs (depending on feeding recommendations given), while, at the same time, these children may already be at a higher risk of developing the disease, independent of the timing of introduction of CFs. Eczema and asthma-like symptoms are the most frequently investigated end points in prospective observational studies, while symptomatic food allergy was the most investigated end point in the randomized controlled trials.
Association of early introduction of solids with infant sleep: A secondary analysis of a randomized clinical trial

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Background: WHO recommends exclusive breastfeeding for 6 months. However, 75% of British mothers introduce solids before 5 months and 26% report infant waking at night as influencing this decision. The objective of the study was to determine whether early introduction of solids influences infant sleep.

Methods: The Enquiring About Tolerance (EAT) study was a population-based randomized clinical trial conducted from January 15, 2008, to August 31, 2015, that included 1,303 exclusively breastfed 3-month-old infants from England and Wales. Clinical visits took place at St Thomas’ Hospital, London, England, and the trial studied the early introduction of solids into the infant diet from age 3 months. The early introduction group (EIG) continued to breastfeed while non allergenic and then 6 allergenic foods were introduced. The standard introduction group (SIG) followed British infant feeding guidelines (i.e., exclusive breastfeeding to around age 6 months and to avoid any food consumption during this period). Secondary analysis of an a priori secondary outcome of the effect of early food introduction on infant sleep using the standardized Brief Infant Sleep Questionnaire.

Results: Of the 1,303 infants who were enrolled in the Enquiring about Tolerance study, 1,225 participants (94%) completed the final 3-year questionnaire (618 SIG [95%] and 607 EIG [93%]). Randomization was effective and there were no significant baseline differences between the 2 groups. Following the early introduction of solids, infants in the EIG slept significantly longer and woke significantly less frequently than infants in the SIG. Differences between the 2 groups peaked at age 6 months. At this point, in the intention-to-treat analysis infants in the EIG slept for 16.6 (95% CI 7.8–25.4) minutes longer per night and their night waking frequency had decreased from 2.01 to 1.74 wakings per night. Most clinically important, very serious sleep problems, which were significantly associated with maternal quality of life, were reported significantly more frequently in the SIG than in the EIG (OR 1.8; 95% CI 1.22–2.61).

Conclusions: In a randomized clinical trial, the early introduction of solids into the infant’s diet was associated with longer sleep duration, less frequent waking at night, and a reduction in reported very serious sleep problems.

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Comments

Infant sleep is an important issue for parents. It is a common belief that introducing complementary foods may help infants sleep better. In this ancillary study of the well-known enquiring about tolerance randomized controlled trial [14], infants introduced to CFs at 3–4 months of age slept on average about 7 min longer during the night (95% CI 2 to about 13 min) over the whole course of the study from birth to 3 years of age. Infants introduced to CFs at 3–4 months of age were also reported to have fewer night wakeings (mean % difference: 9.1 [95% CI 4–14%]). The infants introduced to CFs at 3–4 months of age also showed lower odds of both “very serious” and “small” sleep problems (as perceived by the parents when answering the question “do you consider your child’s sleep as a problem?”), in comparison to infants introduced to CFs at 6 months of age (OR 0.83 [95% CI 0.71–0.95] and 0.55 [0.38–0.82], respectively). It is worth men-
tioning that the severity of sleep problems was based on the perception of the parents. The observed differences in sleep duration or night wakings in this study were small in relation to an overall nighttime sleep duration of around 10–11 h at 6 months of age. They are very unlikely to be of biological relevance. Few data on the relationship between introduction of complementary feeding and infant sleep are available. The study by Bainbridge et al. [15] in which rice cereal was added to formula in the bottle in exclusively formula-fed infants at 4 vs. 6 months of age showed that infants receiving the rice cereal at 4 months slept on average 60 min longer during the night at 6 months of age (95% CI 34–154 min). This was assessed as the time that had passed between the last bottle at night and the first in the morning. The result was not statistically significant. However, the study population included 38 infants only, and thus the trial was most likely underpowered for this outcome. Three prospective studies at high risk of bias showed (1) either a longer night sleep duration [16], that is, on average 12 min at 9 and 18 months for those introduced to CFs at ≤3 vs. >3 months of age; (2) a shorter 24-h sleep duration [17], that is, on average about 24 min at 1 year and 13 min at 2 years for those introduced to CFs at ≤4 vs. >4 months of age; (3) no association between the timing of introduction of CFs and 24-h sleep duration at 6 months of age [17] or with sleep time in breastfed infants at 9 months of age [18]. The conclusion from the literature is that there is no evidence that the time of introduction of complementary foods has a relevant influence on the infant’s sleep pattern.

Compared with cow milk, a growing-up milk increases vitamin D and iron status in healthy children at 2 years of age: The Growing-Up Milk-Lite (GUMLi) randomized controlled trial

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Background: Iron deficiency and vitamin D deficiency are significant pediatric health issues in New Zealand and Australia and remain prevalent micronutrient deficiencies in young children globally. We aimed to investigate the effect of a micronutrient-fortified, reduced-energy growing-up milk (GUMLi) compared with cow milk (CM) consumed for 1 year on dietary iron and vitamin D intakes and the status of New Zealand and Australian children at 2 years of age.

Methods: The GUMLi Trial was a multicenter, double-blind, randomized controlled trial in 160 healthy 1-year-old New Zealand and Australian children conducted in 2015–2017. Participants were randomly assigned 1:1 to receive GUMLi (1.7 mg Fe/100 mL; 1.3 μg cholecalciferol/100 mL) or CM (0.02 mg Fe/100 mL; 0.06 μg cholecalciferol/100 mL) for 12 months. Secondary outcomes, reported here, included change in dietary iron and vitamin D intakes, iron status, and 25-hy-
droxyvitamin D concentrations from blood samples at age 2 years. All regression models were adjusted for baseline outcome and study center.

Results: GUMLi was a large contributor to dietary intakes of iron and vitamin D after 12 months when compared with intakes from food and CM. The adjusted mean difference between groups for serum ferritin concentrations was 17.8 μg/L (95% CI 13.6–22.0 μg/L; \( p < 0.0001 \)), and for 25-hydroxyvitamin D it was 16.6 nmol/L (95% CI 9.9–23.3 nmol/L; \( p < 0.0001 \)). After 12 months, ID was present in 16 (24%) participants in the CM group and 5 (7%) participants in the GUMLi group (\( p = 0.009 \)), and the prevalence of vitamin D deficiency in the CM group increased to 14% (\( n = 10 \)) and decreased to 3% (\( n = 2 \); \( p = 0.03 \)) in the GUMLi group.

Conclusion: In comparison with CM, GUMLi significantly improved dietary iron and vitamin D intakes and the iron and vitamin D status of healthy children at 2 years of age.

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A multicenter, double-blind, randomized, placebo-controlled trial to evaluate the effect of consuming Growing Up Milk “Lite” on body composition in children aged 12–23 months

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Background: Growing Up Milk (GUM) was developed to assist young children in meeting their nutritional requirements during the second year of life. However, there is limited evidence that GUM improves nutritional status and growth in young children. To evaluate the effect of consuming Growing Up Milk “Lite” (GUMLi; reduced protein with synbiotics and micronutrients added) compared with standard cow milk as part of a whole diet for 1 year on body composition at 2 years of age.

Methods: GUMLi Trial was a multicenter, double-blind, randomized placebo-controlled trial conducted in Auckland and Brisbane. Healthy 1-year-old were recruited and randomly assigned to receive either GUMLi or standard cow milk for 12 months as part of a whole diet. The primary outcome was percentage body fat at 2 years of age measured by bioelectrical impedance. All regression models adjusted for baseline outcome and study center.

Results: 160 children (80 per arm) were randomly assigned, and 134 (67 per arm) were included in the modified intention-to-treat analyses. The mean percentage body fat at 12 months was 23.3% (SD 7.9) in the GUMLi group and 25.7% (SD 7.2) in the cow milk group. After adjusting for baseline outcome and study location, the estimated mean difference in percentage body fat between the intervention and control at 12 months was –2.19% (95% CI –4.24 to –0.15; \( p = 0.036 \)). Per-protocol analysis showed a similar effect (mean difference: –2.09%; 95% CI –4.16 to –0.03; \( p = 0.047 \)). Both fat mass and the fat mass index were significantly lower in the GUMLi group at 12 months than in the cow milk group.

Conclusions: At 2 years of age, children who consumed a GUM with a lower protein content than cow milk over 12 months had a lower percentage of body fat.

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Comments

Early childhood (1–3 years of age) is a period of rapid growth and development, with a gain of approximately 25% in height and 50% in weight occurring during this period. While milk remains a major food, this is a transition period from weaning foods toward a family diet, rendering children vulnerable to nutrient inadequacy. Taking into account the available evidence, the European Food Safety Authority considered, in 2013, that dietary intakes of alpha-linolenic acid (ALA), docosahexaenoic acid (DHA), iron, vitamin D, and iodine (in some European countries) are low in infants and young children living in Europe, when compared to the dietary reference values [19]. European Food Safety Authority, therefore, proposed to pay particular attention to ensur-
ing an appropriate supply of ALA, DHA, iron, vitamin D, and iodine in infants and young children with inadequate, or at risk of inadequate, status of these nutrients [19]. More recently, the French Nutri-Bébé survey, covering 1,035 infants (<1 year) and young children (1–3 years) who were not breastfed at the time of the survey, revealed a high intake of protein, sodium, and vitamin A and a low intake of fat, ALA, DHA, iron, vitamin D, and vitamin E [20, 21]. These inadequacies were attributed to the early weaning and/or abandonment of milk formula, as well as to the consumption of an unbalanced diet with excessive use of semi-skimmed cow’s milk and meals intended for adults [20, 21]. Young Child Formula (YCF, so called “Growing-Up Milk”), an alternative to cow’s milk (CM) or breast milk for children 1–3 years of age, are marketed as products specifically formulated for the nutritional needs of young children aged 1–3 years [22]. They are fortified with several nutrients, including iron, vitamin D, and essential fatty acids, and they contain less protein, saturated fat, and sodium than CM. YCFs have been widely available in many countries since the early 90s. Previously classified as foods intended for a particular nutritional use (so-called “dietetic foods”) since July 2016, they have been considered common foods, fortified with certain nutrients and targeting a specific subgroup of the population (young children). There is no specific regulation on the essential composition of YCFs worldwide, including the EU. The ESPGHAN Committee on Nutrition considered, after reviewing the literature, that there were limited data on the nutrient intakes of young children consuming YCF and the potential role of YCF in their diets [23]. Therefore, in a recent position paper, the Committee considered it of interest to determine whether YCF intake could correct (and to what extent) some of these deficits, as compared to CM. The 3 abovementioned studies from New Zealand are therefore welcome to better understand what may be the role of YCFs to cover nutritional needs of young children aged 1–3 years. The supplementation of a YCF with vitamin D and iron allows to increase the status of these 2 nutrients as compared to cow’s milk in healthy children aged 2 years. Interestingly, a lower percentage of body fat was observed in 2-year-old children consuming a low-protein YCF. Finally, the consumption of a reduced protein YCF fortified with iron and vitamin D did not affect dietary patterns compared with consumption of an unfortified CM. YCF allows the most frequent nutritional inadequacies observed in several countries to be overcome, especially iron and vitamin D. YCF consumption can also improve the intake of protein and sodium. The results of these 3 studies from New Zealand study could lead to consider, with caution, the potential consequences of an unbalanced diet associated with low YCF consumption in terms of the risk of overweight, iron deficiency, and hypertension. While nutrient imbalance is common in many countries, complementary feeding regimens differ and are determined by tradition, empirical behaviors, and availability of foods, including the capacity to afford YCF. As a result, no universal instructions can be formulated. The advice of health professionals must be adapted to each family and child, taking into account the quality of their diet. The use of YCF is not a necessity if the diet provided is balanced as recommended, considering the possible nutrient deficits in each country. However, YCF is a useful tool to compensate, at least partially, for the gap between expectations and reality.
Preterm Infants

Supplementing enteral intake

Improved lung function at age 6 in children born very preterm and fed extra protein post-discharge

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Background: In very preterm-born children, alveolar maturation is challenged and lung function is often compromised during childhood. So far, very few studies have focused on type of early nutrition and lung function in children born preterm.

Methods: This study is a 6 years follow-up of 281 very preterm-born infants with a gestational age <32 + 0 weeks. Infants breastfed at discharge from hospital were randomized to unfortified (UHM) or fortified (FHM) mother’s (human) milk, whereas those not breastfed received a preterm formula (PF). The intervention lasted until 4 months corrected age. At 6 years of age fractional exhaled nitric oxide (FeNO), airway resistance and occlusion measurements with reversibility were performed. Data on predisposition to asthma and allergy as well as possible allergic symptoms of the child were obtained with questionnaires.

Results: Outcome data was fully or partially available on 160 (66.9\%) of 239 children. This included 49 (30.6\%) children fed UHM, 58 (36.3\%) fed FHM and 53 (33.1\%) fed PF. Successful FeNO measurements were obtained in 119 (74.4\%) children and airway resistance measurements in 160. FeNO results were not significantly different between feeding groups. Children fed a protein-enriched diet (FMH/PF) had the lowest, for example, best, airway resistance; FHM-fed had lower values than UHM-fed (\(p = 0.042\)) before, and PF-fed had significantly lower values than UHM-fed after beta-2-agonist inhalation (\(p = 0.050\)). The tendency of lower airway resistance when protein enriched were the same in gender-specific analyses. In SGA children, the same tendency was found between PF- and UHM-fed (\(p = 0.007\) before and \(p = 0.046\) after beta-2-agonist inhalation). All values were within reference limits.

Conclusions: Lung function in very preterm-born children may improve when fed a protein-enriched nutrition post-discharge.

Comments

Due to immaturity, respiratory support, oxidative stress, and possibly undernutrition, preterm infants may develop lung damage and sometimes bronchopulmonary dysplasia. Bronchopulmonary dysplasia is in itself a significant risk factor of a disturbed neurocognitive development [24]. The lung damage obtained during the neonatal phase extends frequently to the school age range [25, 26], and a higher asthma incidence is associated with lower gestational age [27]. The use of a high-density formula in infants with chronic lung disease in the postnatal phase did not improve growth or respiratory outcome, despite a small increase in total energy and protein intake [28]. In the present study, the authors wanted to determine whether the type of post-discharge nutrition affects lung function in 6-year-old children born very preterm by
measuring airway resistance and fractional exhaled nitric oxide (a non-invasive method to screen for airway inflammation in asthma). In this multicenter Danish trial, 320 very preterm infants were included to receive unfortified human milk, fortified human milk, or preterm formula from discharge to 4 months corrected age. Children with BPD and diseases influencing nutritional status such as necrotizing enterocolitis, chromosomal anomalies, and intraventricular hemorrhage were excluded. At age 6 years, 119–160 children were tested. Regardless of feeding group, no significant differences between feeding groups were observed. Despite earlier research showing a clear effect of preterm birth on lung function at later age, this study showed that lung function, expressed by airway resistance, was within normal range within all groups. In addition, hardly any significant differences were seen between the feeding groups. This may indicate 3 things:

1. The differences between feeding groups were too small to detect an effect of the intervention.
2. The window of modulating an effect is before the intervention started (i.e. impact is possible at the direct postnatal phase)
3. Immediate postnatal nutritional support in Denmark at around 2005 was already of such a level that lung function in the studied “healthy” preterm infants was not influenced by modest changes following discharge.

Neurodevelopmental outcome of nutritional intervention in newborn infants at risk of neurodevelopmental impairment: the Dolphin neonatal double-blind randomized controlled trial

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Aim: To investigate whether neonates at risk for neurodevelopmental impairment have improved neurodevelopment after docosahexaenoic acid, choline, and uridine-5-monophosphate supplementation versus controls.

Method: Recruitment was from UK neonatal units. Eligible for inclusion were infants born at <31 weeks’ gestation with a weight less than the ninth centile; infants born at <31 weeks’ gestation with a grade II or higher intraventricular haemorrhage/preterm white matter injury; infants born between 31 and 40 weeks’ gestation plus 28 days with a grade II or higher intraventricular haemorrhage/preterm white matter injury, moderate or severe hypoxic-ischaemic encephalopathy, or defined neuroimaging abnormalities. Treatment/control supplementation was for 2 years (double-blind, randomized, controlled design). Infants were stratified according to sex, gestation, and brain injury severity. Primary outcome was cognitive composite score of the Bayley Scales of Infant Development, Third Edition (Bayley-III at 24 months). Secondary outcomes were language composite score of the Bayley-III, motor composite score of the Bayley-III, and Vineland Adaptive Behaviour Scales, Second Edition score.

Results: Sixty-two neonates were recruited, 59 were randomized (34 males, 25 females). Fifty-three started supplementation. Most families found supplementation acceptable. The treatment group cognitive composite score-Bayley-III scores were non-significantly higher than controls (mean score difference at 24 months: 9.0; 95% CI –0.2 to 18.2). Language and Vineland Adaptive Behaviour Scales, Second Edition scores, but not motor score, were non-significantly higher in the treatment group.
Interpretation: Most families found supplementation feasible. Improved neurodevelopmental outcomes in the treatment group were not statistically significant. A larger multicentre trial exploration is warranted.

Comments

This specific trial focusses on the supplementation of docosahexaenoic acid (DHA), choline, and UMP, supplementation in neonates with neurodevelopmental impairment risk factors. The study population included neonates being born very preterm, small for gestational age infants, but also on infants born between 31 and 40 weeks any brain damage. The only study that targeted a similar population was conducted by Dabydeen et al. [29] published in 2008. They conducted a prospective, double-blind, and randomized, 2-stage group sequential study and controlled for gestation, gender, and brain lesion. Neonates with perinatal brain damage were randomly allocated to receive either a high- (120% recommended average intake) or average (100% recommended average intake) energy and protein diet. The study began at term and continued for 12 months. That study was terminated when 16 subjects had completed the protocol because the predetermined stopping criterion of >1 SD difference in occipitofrontal circumference at 12 months’ corrected age in those receiving the higher-energy and -protein diet had been demonstrated. Axonal diameters in the corticospinal tract, length, and weight were also significantly increased. They concluded that infants with significant perinatal brain damage have increased nutritional requirements in the first postnatal year and suggest that decreased postnatal brain growth may exacerbate their impairment. No study has been published since then. The present study does not provide more energy and protein but adds a specific mixture (DHA, choline and UMP, a pyrimidine) aimed to enhance the production of phosphatidylcholine, which is the most abundant brain phospholipid. In addition, DHA, choline, and uridine supplementation synergistically increases rodent brain phospholipids, synaptic components, functional brain connectivity, and cognitive performance [30]. Power calculation beforehand revealed that in total 48 infants should be included, with an additional 12 as a result of anticipated loss to follow-up. Although the results were not statistically significantly different, there was a better score in the children who received the supplementation, Bayley composite score was 9 points (nonsignificant) higher. Disappointing as this may seem, these results as well as those obtained in the trial by Dabydeen indicate that there is a potential in additional nutritional support of especially vulnerable newborns. However, the observed improvement in Bayley-III for treated infants should be replicated in a larger trial, before this will have important implications for the treatment of infants at risk of neurological impairment.
**Improved outcomes in preterm infants fed a nonacidified liquid human milk fortifier: a prospective randomized clinical trial**

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**Objective:** To compare growth, feeding tolerance, and clinical and biochemical evaluations in human milk-fed preterm infants randomized to receive either an acidified or a nonacidified liquid human milk fortifier.

**Study Design:** This prospective, controlled, parallel, multicenter growth and tolerance study included 164 preterm infants (≤32 weeks of gestation, birth weight 700–1,500 g) who were randomized to acidified or nonacidified liquid human milk fortifier from study day 1, the first day of fortification, through study day 29 or until hospital discharge.

**Results:** There was no difference in the primary outcome of weight gain from study days 1 to 29 (acidified liquid human milk fortifier, 16.4 ± 0.4 g/kg/day; nonacidified liquid human milk fortifier, 16.9 ± 0.4 g/kg/day). However, in both the intention-to-treat and the protocol evaluable analyses, infants fed nonacidified liquid human milk fortifier had significantly greater weight gain from study days 1 to 15 (17.9 vs. 15.2 g/kg/day; *p* = 0.001). Infants fed with acidified liquid human milk fortifier received more protein (4.26 vs. 4.11 g/kg/day, *p* = 0.0099) yet had lower blood urea nitrogen values (*p* = 0.010). The group fed acidified liquid human milk fortifier had more vomiting (10.3 vs. 2.4%; *p* = 0.018), gastric residuals (12.8 vs. 3.7%; *p* = 0.022), and metabolic acidosis (27 vs. 5%; *p* < 0.001) in the intention-to-treat analysis and more abdominal distension (14.0 vs. 1.7%; *p* = 0.015) in the protocol evaluable analysis.

**Conclusions:** Infants fed an acidified liquid human milk fortifier had higher rates of metabolic acidosis and poor feeding tolerance compared with infants fed a nonacidified liquid human milk fortifier. Initial weight gain was poorer with the acidified liquid human milk fortifier.

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**Comments**

The use of human milk fortifiers is widespread in neonatal units around the world. In some countries, such as the United States, liquid fortifiers are used. This was the result of several cases of infant infection and death from Cronobacter sakazakii sepsis using powdered formula and led the FDA to ban powdered formulas or fortifiers [31]. In order to achieve sterility, liquid fortifiers can be acidified or treated with heat. Acidification of the fortifier will reduce the pH of the feeding with possible disadvantages. The disadvantage of any liquid fortifier is the replacement of a certain volume of own mother’s milk, thereby reducing the amount of potential beneficial bioactive factors that are not been added by the fortifier. Fourteen sites participated in this nonblinded study, with a primary outcome of weight gain during the first 4 weeks of supplementation that started whenever the infants reached an intake of 80 mL/kg/day. In total, 160 infants participated in the intention to treat analysis; no differences were identified in the primary outcome of weight gain from study days 1 to 29 between the acidified or nonacidified liquid human milk fortifier groups in either the ITT analysis (effect size, –0.6 ± 0.6 g/kg/day) or protocol evaluable analysis (effect size, –0.8 ± 0.5 g/kg/day). Post hoc analyses did reveal some differences, for example, during the first 2 weeks and in...
groups with large amounts of donor milk or other feedings, all in favor of the nonacidic fortifier. However, other important determinants showed detrimental effects of the use of an acidic fortifier (pH and vomiting episodes). These results, together with data from other trials [32, 33], indicate that whenever nonacidic fortifiers are available, those should be used. The question whether fortifiers should be used at all is again out there. The most recent Cochrane meta-analysis, with 1,071 infants included, reached the following conclusion: “Limited available data do not provide strong evidence that feeding preterm infants with multi-nutrient fortified breast milk compared with unfortified breast milk affects important outcomes, except that it leads to slightly increased in-hospital growth rates” [34]. Therefore, long-term results are warranted.

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**Commencing nutrient supplements before full enteral feed volume achievement is beneficial for moderately preterm to late preterm low birth weight babies: a prospective, observational study**

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**Abstract:** The aim of this study was to observe after following a routine change in the feeding protocol whether the earlier introduction of nutrient supplements improved nutritional outcomes in moderately preterm to late preterm low birth weight (LBW) babies. In this prospective observational study, LBW babies between 31 and 39-weeks’ gestation admitted to a Special Care Nursery were assigned to 2 groups (F80, n = 45, F160, n = 42) upon commencing nutrient supplement at total fluid intake achievement of 80 or 160 mL/kg/day. Outcomes included weight, protein intake, biochemical markers, feeding intolerance, and length of stay. F80 nutrient supplements commenced before F160 (2.8 vs. 6.7 days, *p* < 0.0001) and lasted longer (15.2 vs. 12.2 days, *p* < 0.03). Weight gain velocity and length of stay were similar. F80 mean protein intake during the first 10 days was higher (3.38 vs. 2.74 g/kg/day, *p* < 0.0001). There were fewer infants with protein intake < 3 g/kg/day in the F80 group (8 vs. 65%, *p* < 0.001). F80 babies regained birthweight almost 2 days earlier (7.5 vs. 9.4 days, *p* < 0.01). Weight gain Z-scores revealed an attenuation of the trend towards lower weight percentiles in the F80 group. Feeding intolerance was decreased for F80 (24.4 vs. 47.6%, *p* < 0.03). There were no adverse outcomes. Earlier nutrient supplementation for LBW babies lifts mean protein intake to above 3 g/kg/day and reduces both the duration of post-birth weight loss and incidence of feeding intolerance.

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**Comments**

The previous study started fortifying human milk at an intake of 80 mL/kg/day, but the studied infants were all below a gestational age of 32 weeks. The present study addresses a much larger population, namely, those born between 31 and 39 weeks of gestation. The resultant of the earlier start of fortification was predictable; slightly higher weight gain and faster time to regain birth weight. Moreover, it was not associated with any negative outcome, including tolerance. Although the number of infants studied was relatively small, there are only a few studies addressing this group. So, the conclusion is that there is a modest benefit, and no downsides to start fortifying own mother’s milk at an intake of 80 mL/kg/day as can be done routinely in infants at lower gestational ages.
Effect of gastric residual evaluation on enteral intake in extremely preterm infants: a randomized clinical trial

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Importance: Evaluating prefeed gastric residuals is considered routine care but has little supporting evidence.

Objective: To determine the effect of omitting prefeed gastric residual evaluation on nutritional outcomes in extremely preterm infants.

Design, Setting, and Participants: This single-center randomized clinical trial compared the omission of gastric residual evaluation with prefeed gastric residual evaluation. Infants were recruited from a level 4 neonatal intensive care unit and were enrolled from October 17, 2013, to October 8, 2016, and then followed up for 6 weeks after birth. Eligible participants were infants born at 32 or fewer weeks’ gestation with a birth weight of 1,250 g or less; they were enrolled within 72 h after birth and within 24 h after feeding initiation. All participants (n = 143) were included in the modified intent-to-treat analysis, which was conducted from March to July 2018.

Interventions: The residual group underwent prefeed gastric residual evaluation; the no residual group did not. Feeding decisions were made according to nutritional guidelines, and infants received only human milk.

Main Outcomes and Measures: The primary outcome was weekly enteral nutrition intake in mL/kg for 6 weeks after birth.

Results: Of 143 infants, 74 (51.7%) were randomized to undergo gastric residual evaluation (residual group) and 69 (48.3%) to omitted gastric residual evaluation (no residual group). The residual group comprised an even number of male and female infants (37 [50.0%]) with a mean (SD) gestational age of 27.1 (2.4) weeks and a mean (SD) birth weight of 888.8 (206.6) grams, whereas the no residual group had more male infants (36 [52.17%]), a mean (SD) gestational age of 27 (1.2) weeks, and a mean (SD) birth weight of 915.2 (180) g. The no residual group had feedings that advanced more quickly compared with the residual group (mean weekly increase, 20.7 vs. 17.9 mL/kg/day; p = 0.02) and consumed more feedings at weeks 5 (137.2 [95% CI 128.6–145.8]; p = 0.03) and 6 (141.6 [95% CI 133.2–150.0]; p = 0.03). Among the secondary outcomes, the no residual group had higher mean estimated log weights (7.01 [95% CI 6.99–7.02] vs. 6.98 [95% CI 6.97–7.00]; p = 0.03), had fewer episodes of abdominal distention (0.59 [95% CI 0.34–1.01] vs. 1.79 [95% CI 1.27–2.53]; p = 0.001), and were discharged 8 days earlier (4.21 [95% CI, 4.14–4.28] vs. 4.28 [95% CI, 4.19–4.36]; p = 0.01). Odds for necrotizing enterocolitis (0.058 [95% CI 0.018–0.190] vs. 0.026 [95% CI 0.006–0.109]), death (0.004 [95% CI 0.0003–0.046] vs. 0.012 [95% CI 0.001–0.131]), late-onset sepsis (0.970 [95% CI 0.67–1.40] vs. 1.38 [95% CI 0.97–1.94]), and ventilator-associated pneumonia (0.084 [95% CI 0.033–0.214] vs. 0.056 [95% CI 0.019–0.168]) were similar between groups.

Conclusions and Relevance: Among extremely preterm infants, the omission of gastric residual evaluation increased the delivery of enteral nutrition as well as improved weight gain and led to earlier hospital discharge; these results may translate into evidence-based practice.

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Gastric residual volume in feeding advancement in preterm infants (GRIP Study): a randomized trial

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Objective: To evaluate the effect of not relying on prefeeding gastric residual volumes (GRV) to guide feeding advancement on the time to reach full feeding volumes in preterm infants, compared with routine measurement of GRV. We hypothesized that not measuring prefeeding GRV can shorten the time to reach full feeds.

Study Design: In this single-center, randomized, controlled trial, we included gavage fed preterm infants with birth weights (BW) 1,500–2,000 g who were enrolled within 48 h of birth. Exclusion criteria were major congenital malformations, asphyxia, and BW below the third percentile. In the study group, the GRV was measured only in the presence of bloody aspirates, vomiting, or an abnormal abdominal examination. In the control group, GRV was assessed routinely, and feeding advancement was based on the GRV. The primary outcome was the time to reach feeding volumes of 120 mL/kg/day. Secondary outcomes were time to regain BW, episodes of feeding interruptions, sepsis, and necrotizing enterocolitis.

Results: Eighty-seven infants were enrolled. There were no differences between the study and control groups with respect to time to reach full feeds (6 days [95% CI 5.5–6.5] vs. 5 days [95% CI 4.5–5.5]; p = 0.82), time to regain BW, episodes of feeding interruptions, or sepsis. Two infants in the control group developed necrotizing enterocolitis.

Conclusions: Avoiding routine assessment of GRV before feeding advancement did not shorten the time to reach full feeds in preterm infants with BW between 1,500 and 2,000 g.

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Comments

The presence of large or greenish gastric residual volume (GRV) often triggers bedside staff to withhold or decrease the volume of subsequent feeds. Fear for NEC, although causality or associations are never proven, is usually the common ground for such a clinical decision. Two well-designed trials have appeared last year questioning the validity of measuring gastric residuals routinely in infants at the neonatal intensive cares. The results seem contradictory at first glance. Whereas Parker et al. found a positive effect of not measuring residuals, Singh et al. did not find any advantage in clinical outcomes. Both were single-center studies, but the infants they included were quite different. Healthy preterm infants, with a mean gestational age of 32 weeks and a birth weight of 1,750 g (Singh et al.), are a different population than preterm infants with a mean gestational age of 27 weeks and a birth weight of approximately 900 g (Parker et al.). Other studies, Torrazza et al. and Riskin et al. found also clinical benefits without apparent risks with a no – residual measurement regime [35, 36]. Studies by Mihatsch et al. [37] and Shulman et al. [38] concluded that GRV were unreliable predictors of feeding intolerance and the attainment of full enteral feeds and that increased GRV is not predictive of NEC. So together these studies indicate that there seems no benefit of measuring residuals. If anything, there might be a benefit in not measuring residuals in smaller infants. Besides, the time saved by not measuring residuals may also reduce the costs of nursing.
Gastric residual volumes versus abdominal girth measurement in assessment of feed tolerance in preterm neonates: a randomized controlled trial

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Background: Preterm neonates often have feed intolerance that needs to be differentiated from necrotizing enterocolitis. Gastric residual volumes (GRV) are used to assess feed tolerance but with little scientific basis.

Purpose: To compare prefeed aspiration for GRV and prefeed measurement of abdominal girth (AG) in the time taken to reach full feeds in preterm infants.

Methods: This was a randomized controlled trial. Infants with a gestational age of 27–37 weeks and birth weight of 750–2,000 g, who required gavage feeds for at least 48 h, were included. Infants were randomized into 2 groups: infants in the AG group had only prefeed AG measured. Those in the GRV group had prefeed gastric aspiration obtained for the assessment of GRV. The primary outcome was time to reach full enteral feeds at 150 mL/kg/day, tolerated for at least 24 h. Secondary outcomes were duration of hospital stay, need for parenteral nutrition, episodes of feed intolerance, number of feeds withheld, and sepsis.

Results: Infants in the AG group reached full feeds earlier than infants in the GRV group (6 vs. 9.5 days; \( p = 0.04 \)). No significant differences were found between the 2 groups with regard to secondary outcomes.

Implications for Practice: Our research suggests that measurement of AG without assessment of GRV enables preterm neonates to reach full feeds faster than checking for GRV.

Implications for Research: Abdominal girth measurement as a marker for feed tolerance needs to be studied in infants <750 g and <26 weeks of gestation.

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Comments: Again, this study questioned the validity of measuring gastric residuals routinely. There results were in a similar direction as those of Parker et al., discussed earlier. The number of infants included was slightly above 100, with a mean gestational age of 31 weeks and a birth weight of 1,300 g. As a safety net, the researchers added the measurement of abdominal girth in the routine practice. This was well appreciated by the nurses. Measurement of abdominal girth only without checking gastric residual volume enabled preterm neonates to reach full feeds faster than routinely checking for residuals.

References


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