

PRETERM NUTRITION RESEARCH

Selected Study Summaries



SELECTED STUDY SUMMARIES DEMONSTRATING NUTRICIA'S COMMITMENT TO PRETERM NUTRITION RESEARCH IN FOUR CLINICAL BENEFIT AREAS

For over >60 years Nutricia has been developing expertise in preterm nutrition research and, in collaboration with external academic and/or clinical partners, has conducted research in this arena. This has resulted in over 300 publications advancing knowledge in preterm nutrition in four clinical benefit areas:

- Growth & metabolism
- Cognitive development
- Gastrointestinal health
- Immune health

This document provides a highlight of recently published papers demonstrating Nutricias commitment to preterm care research. This gives an indication of the breadth and depth of Nutricia's research in preterm nutrition from preclinical to clinical work which is relevant to the preterm infant in hospital through to their discharge home.

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A close-up photograph of a newborn baby lying in a hospital bed. The baby is wearing a white hospital gown and has their eyes closed. A hand is gently resting on the baby's forehead. The background is slightly blurred, showing a blue hospital bed sheet. The overall tone is calm and professional.

GROWTH & METABOLISM

FEEDING PRETERM INFANTS AFTER HOSPITAL DISCHARGE: GROWTH AND DEVELOPMENT AT 18 MONTHS OF AGE

Cooke RJ *et al.* *Pediatr Res* 2001;49:719-22.

BACKGROUND

These authors had previously reported that preterm infant boys fed a preterm formula after initial hospital discharge until 6 months corrected age had increased body weight (Cooke *et al.* 1998) and increased linear growth and head growth (Cooke *et al.* 1999) when compared with boys fed a term formula. This has led the same authors to hypothesise that improved early growth would be associated with better later growth and development at 18 months corrected age.

AIM

To determine whether improved growth seen at 6 and 12 months corrected age in preterm infant boys fed a preterm formula following hospital discharge led to improved growth and development at 18 months corrected age.

STUDY DESIGN

One hundred and twenty nine infants (<1750g, <34 weeks gestation) were randomised into one of the following 3 feeding groups immediately before hospital discharge:

- A Preterm formula to 6 months corrected age.
- B Term formula to 6 months corrected age.
- C Preterm formula to term age and then term formula to 6 months corrected age.

Subjects were stratified according to their birthweight, <1250g and >1250g. During the study infants were seen at 12 weeks, 6, 12 and 18 months corrected age. Weight, length and head circumference were determined at each visit. Bayley MDI and PDI assessments were performed at 18 months corrected age. Investigators were blind to the formula group of individual subjects.

RESULTS

- At 18 months corrected age weight, length and head circumference (OFC) were greater ($P < 0.0001$) for boys in group A than groups B and C (see table).

(Mean \pm SD)	A	B	C
Weight (kg)	10.7 \pm 1.5	9.7 \pm 0.7	9.4 \pm 1.4
Length (cm)	81 \pm 3.4	79 \pm 2.7	77 \pm 4.7
OFC (cm)	49 \pm 1.7	48 \pm 2.0	48 \pm 1.5

- No differences were detected in weight, length or head circumference (OFC) between groups for the girls.
- Boys fed the preterm formula were 600g heavier and 2cm longer than girls fed the preterm formula.
- No differences were detected in MDI and PDI between the groups.

Additional Note

Whilst this study was unable to show that better growth led to better development, MDI and PDI scores were close to normal suggesting an overall improvement in care in these high-risk infants. It is a concern that boys who received the term formula had the lowest OFC and MDI. The authors also comment that because of the small sample size the data cannot exclude the possibility that infants fed a term formula after hospital discharge are developmentally at risk when compared to those fed a preterm formula.

Cooke RJ *et al.* *Pediatr Res* 1998; 43: 355-360

Cooke RJ *et al.* *Pediatr Res* 1999; 46: 461-464

CONCLUSION

This study is the first to suggest that more rapid and more complete 'catch up' as was noted in infants fed with the nutrient enriched formula, is not associated with altered adiposity but is paralleled by an increase in fat free mass and peripheral fat mass.

ADIPOSIITY IS NOT ALTERED IN PRETERM INFANTS FED WITH A NUTRIENT ENRICHED FORMULA AFTER HOSPITAL DISCHARGE

Cooke RJ *et al.* *Pediatr Res* 2010;67:660-4.

BACKGROUND

These authors have previously reported that preterm infant boys fed a preterm formula after initial hospital discharge until 6 months corrected age had increased body weight (Cooke *et al.* 1998), increased linear growth (Cooke *et al.* 1999) and remained heavier, longer and had a greater head circumference at 18 months (Cooke *et al.* 2001) when compared with boys fed a term formula.

As there has been some concern about 'catch up' growth and the subsequent development of insulin resistance and central adiposity in preterm infants, the same authors hypothesised that differences in body weight would not be associated with increased or altered adiposity in infants fed with a nutrient enriched formula when compared with those fed with a term formula or those who were breastfed.

AIM

To determine whether the use of a nutrient enriched formula altered the adiposity of preterm infants compared to a term formula at 12 months corrected age.

STUDY DESIGN

One hundred and thirty eight infants (<1750g, <34 weeks gestation) were randomised into one of the following 3 feeding groups immediately before hospital discharge and were followed up at 12 months corrected age:

- A Preterm formula to 6 months corrected age.
- B Term formula to 6 months corrected age.
- C Preterm formula to term age and then term formula to 6 months corrected age.

A breastfeeding group was also followed (group D).

Subjects were stratified according to their birthweight, <1250g and >1250g. During the study infants were seen at the outpatient clinic every 2 weeks between discharge and term and monthly between term and 6 months. Intake was determined at each visit. Body composition was measured at discharge, term, 12 weeks, 6 and 12 months corrected age. Body composition was measured by dual energy x-ray absorptiometry (DEXA).

RESULTS

- All infants underwent 'catch up', but weight and length were greater in infants fed the preterm formula compared with the other formulas ($p < 0.001$).
- At 12 months corrected age weight (A>B,C,D: $p < 0.05$, $p < 0.001$, $p < 0.05$ respectively), fat free mass (A>B,C,D: $p < 0.05$, < 0.001 , < 0.05 , respectively) and fat mass (g), (A>B $p < 0.05$ and A>C, $p < 0.005$) though not percentage fat mass were significantly increased in the preterm group compared to the other groups (see table).

(Mean ± SD)	A	B	C	D
Weight (g)	9203 ± 1213	8649 ± 943	8476 ± 1337	8604 ± 1209
Fat free mass	6872 ± 806	6592 ± 738	6399 ± 881	6451 ± 746
Fat mass (g)	2332 ± 679	2058 ± 477	2077 ± 623	2153 ± 645
Fat mass (%)	25 ± 5.3	24 ± 4.4	24 ± 4.5	25 ± 4.8

- Leg fat mass (peripheral fat) was greater in group A than in groups B ($p < 0.005$), C ($p < 0.001$) or D ($p = 0.09$). No differences were detected in central fat mass between infants in group A when compared with those in groups B or D at 12 week 6 months or 12 months.
- No differentiation was made between boys and girls.

Additional Note

Growth in infants fed with the preterm formula followed by term formula (group C), is disconcerting. As between discharge and term when infants were fed the preterm formula weight and length improved. But after term, when infants received the term formula, their weight 'faltered' and their length no longer continued to 'catch back'. This can be directly related to the changes in nutrient intake during this time. It took 8 weeks for infants to upregulate their intake of the term formula to ensure an isocaloric intake when compared with the other formula groups. In the interim, infants were underfed and growth 'faltered'.

Cooke RJ *et al.* *Pediatr Res* 1998; 43: 355-360

Cooke RJ *et al.* *Pediatr Res* 1999; 46: 461-464

Cooke RJ *et al.* *Pediatr Res* 2001; 49: 719-722

CONCLUSION

This study is the first to suggest that more rapid and more complete 'catch up' as was noted in infants fed with the nutrient enriched formula, is not associated with altered adiposity but is paralleled by an increase in fat free mass and peripheral fat mass.

GROWTH OF VERY LOW BIRTH WEIGHT INFANTS AFTER INCREASED AMINO ACID AND PROTEIN ADMINISTRATION

Loui A & Buhner C, Journal of Perinatal Medicine, 2013;41:735-41.

BACKGROUND

In preterm infants with birth weights less than 1500g achieving intrauterine accretion rates of nutrients via parenteral and enteral nutrition is an important treatment strategy. There appears to be a critical window from birth to 3 months corrected age where inadequate nutrition has a detrimental effect on later outcomes. Current feeding guidelines aim to achieve fetal weight gain of 15g/kg/day but meeting protein requirements with fortified mother's milk or donor milk is challenging, and often not achieved.

AIM

Investigate if enriching mother's or donor breast milk with a protein powder in addition to breast milk fortifier, could improve growth of very low birthweight (VLBW) infants during their hospital stay.

STUDY DESIGN

Retrospective study of a cohort of VLBW infants born in 2010 a year after the protein powder was introduced in the neonatal unit to supplement the milk for some infants. Details of the advancement of parenteral and enteral nutrition, amount of nutrients ingested, weight gain, length and head circumference were studied, in addition to retrospective laboratory parameters to rule out the occurrence of metabolic side effects. The feeding protocol was that parenteral nutrition was started on the first day of life concurrent with enteral nutrition; on day 7 supplementation of breast milk with the fortifier and protein supplement should be commenced and progressed according to the feeding protocol.

RESULTS

Data on 43 VLBW infants were collected and details of the main parameters collected are shown in the table below.

Parameter	Median (interquartile range)
Gestational age (weeks)	27+6 (26+0/29+6)
Birth weight (g)	984 (675/1130)
Parenteral nutrition duration (days)	16 (14/18)
Protein intake (g/kg/day)	4.3 (4.0/4.4)
Weight gain from days 8-35 (g/kg/day)	17.6 (14.9/20.5)
Head growth from days 1-35 (cm/week)	0.70 (0.50/0.80)
Length growth from days 1-35 (cm/week)	1.0 (0.8/1.2)

Fortified breast milk was supplemented by protein powder at the level of 0.5-2.3g/kg/day and was added on average from days 11 to 45 of life. The target for protein intakes was reached and growth which was close to intrauterine growth was achieved. No increased incidence of metabolic acidosis was found.

CONCLUSION

The data support the ESPGAN nutritional guidance published in 2009. High protein nutrition achieved by rapid advancement of parenteral protein, and an additional protein supplement added to fortified breast milk, promotes weight gain and head growth which is similar to foetal growth.

GROWTH AND BONE MINERALISATION IN PRETERM INFANTS FED PRETERM FORMULA OR STANDARD TERM FORMULA AFTER DISCHARGE

Picaud JC *et al.* J Pediatr 2008;153:616-21.

BACKGROUND

During the last trimester mineral accretion of the fetus is at its highest. Rapid bone growth in preterm infants without sufficient mineral intake can lead to osteopenia. Enriched postnatal nutrition after discharge could help improve bone mineralisation and growth.

AIM

To evaluate growth and bone mineralisation in very low birth weight (VLBW) infants fed preterm formula (PF) or term formula (TF).

STUDY DESIGN

In a double-blind prospective study, 49 preterm infants of gestational age 33 weeks or less were randomly fed PF or TF for 2 months after discharge, then all of the infants were fed TF for the next 2 months. Anthropometric and dual-energy x-ray absorptiometry data were collected at discharge and at 2 months and 4 months after discharge. Anthropometric data was also collected at 12 months corrected age.

RESULTS

Four months after discharge, both body weight ($6139 \pm 1254\text{g}$ vs. $5540 \pm 863\text{g}$; $p=0.03$) and bone mineral content ($104.4 \pm 29.2\text{g}$ vs. $87.5 \pm 17.1\text{g}$; $p=0.01$) were significantly higher in the PF group compared with the TF group. At 12 months corrected age, mean body weight, length and head circumference remained higher in the PF group than in the TF group, and body mass index was similar and within the normal range in the 2 groups.

CONCLUSION

At 4 months after discharge, growth and mineralisation were better in the VLBW infants who were fed PF during the first 2 months after discharge compared with those who were fed TF, suggesting that PF may be particularly valuable at this early stage of development.

POST-DISCHARGE FORMULA FEEDING IN PRETERM INFANTS: A SYSTEMATIC REVIEW MAPPING EVIDENCE ABOUT THE ROLE OF MACRONUTRIENT ENRICHMENT

Teller IC *et al.* Clin Nutr 2015;<http://dx.doi.org/10.1016/j.clnu.2015.08.006>.

BACKGROUND

Nutritional deficits are common among hospitalised preterm infants and as a consequence they are at risk of being discharged with accumulated growth deficits. It is being recommended that infants with poor growth at discharge receive enriched feeding, preferably fortified maternal milk or –if not available– an enriched formula. However, evidence for the benefits of such practice is controversial due to the complexity of making comparisons between heterogeneous studies.

AIM

Investigating the role of feeding macronutrient enriched formulae to preterm infants at high risk for growth faltering at home using a systematic ‘evidence mapping’ approach.

STUDY DESIGN

A comprehensive literature review following recognised methodological guidelines was undertaken. Outcomes of all available studies comparing an enriched formula after discharge to a less enriched comparator were mapped and visualised following the principle of variation in Participant population- Intervention-Comparator-Outcomes (PICO). This method of systematic review is an emerging concept to assess heterogeneous clinical evidence as alternative to meta-analyses.

RESULTS

Thirty one studies met the eligibility criteria, of which 17 allowed extraction of growth data in relation to protein:energy ratio. High variation in birth weights, gestational age, duration of intervention, formula composition and study design were captured and visualised. The main findings were as follows:

- Nutrient enriched diets generally seemed to affect growth outcomes favourably in the course of the study, especially in male subjects. Negative effects were not identified in any but one study.
- Most differences in growth parameters were seen within the first six months but half of studies did not publish results beyond this time point.
- Volume intake seems to depend on formula energy density and raises importance for protein to energy or nutrient to energy ratios above each parameter alone.
- When enough energy is provided, a higher protein concentration increased length and HC at one year as well as supported increased lean but not fat mass accretion.
- Neurodevelopmental outcomes, measured by standard tools, were not affected by any but two interventions¹ raising the question whether tools designed to capture abnormal development are sensitive enough capturing differences in what is considered a normal developmental range.

1. The reported differences in these two studies were explained by the authors of the original studies by insufficient iodine concentrations in the comparator formula and the importance of increased LCPUFA concentrations in an otherwise comparable post-discharge formula, respectively.

The evidence mapping process identified a number of research gaps including the definition of healthy post-discharge growth, the optimum window of opportunity for intervention and besides protein, whether there are any key nutrients further supporting healthy growth and neurodevelopment.

CONCLUSION

When maternal milk is not available, feeding preterm infants experiencing growth faltering at discharge a formula with a high protein:energy ratio up to 6 months (under medical supervision) appears beneficial, especially in males. Given the heterogeneity of the data currently available, consistent monitoring of at least length and weight is advisable until proportional growth recovery has been established and a normal feeding is sufficient to support further growth and development.



COGNITIVE DEVELOPMENT

HIGHER EFFICACY OF DIETARY DHA PROVIDED AS A PHOSPHOLIPID THAN AS A TRIGLYCERIDE FOR BRAIN DHA ACCRETION IN NEONATAL PIGLETS

Liu L *et al.* Journal of Lipid Research, 2014, 55:531-9.

BACKGROUND

Docosahexaenoic (DHA) is the most abundant omega fatty acid in the mammalian brain. In humans, DHA accumulates with momentum from mid-gestation and continues at a rapid pace in the first months of life until well past the achievement of brain weight, until it reaches a plateau at 18 years. The de novo synthesis of DHA from its precursor fatty acids is not reliable in preterm and term infants and the benefits of providing preformed DHA in infancy is well established. DHA and other long chain polyunsaturated fatty acids (LCPUFAs) occur in foods as either triacylglycerols (TAGs) or phospholipids (PLs). In breast milk, DHA is predominately present in PLs but most DHA is delivered via TAG because of their overwhelming presence. TAG-DHA is the common form of DHA in infant milk.

AIM

To investigate the relative efficacy of providing DHA as a dose of C-DHA bound to either (1)TAG or (2) phosphatidylcholine (PC) a PL, on brain DHA accretion, in newly born piglets.

STUDY DESIGN

On Day 16 of life, piglets (n=16 out of n=20 initially selected), were randomly assigned to receive a dose of one of two piglet milk formula. Both of the test formulae contained DHA which had been labelled with a stable isotope, C labelling, and the C- DHA was bound to (1) TAG or (2) PC (a PL). The study ended a few days later, and the piglet brain, retina and other organs were analysed for C-DHA and other fatty acid metabolites.

RESULTS

The fatty acid profile of neural tissues showed that DHA concentrations were greatest in the retina followed by the grey and then white matter of the brain. The DHA bound to PC was 1.9 times more efficacious for brain grey matter accretion than the DHA bound to TAG. The superiority of PC-C-DHA was also apparent in the accretion of DHA in the retina, liver and red blood cells. Brain weight increased during the study indicating the advantage of PC perinatally.

CONCLUSION

The provision of DHA by a phospholipid, PC is highly effective and is consistent with previous studies of DHA and arachidonic acid, the two major LCPUFAs found in breast milk.

ACADEMIC TRAJECTORIES OF VERY PRETERM BORN CHILDREN AT SCHOOL AGE

Twilhaar ES *et al.* Disease in Childhood - Fetal and Neonatal Edition 2019;104:F419-23.

BACKGROUND

Very preterm birth is associated with academic difficulties, which is known to subsequently impact health and life chances. Close monitoring of academic development is key to identify those with difficulties and prevent academic failure, however knowledge of academic trajectories of very preterm infants is scarce. Whether very preterm infants academic development is characterised by persisting deficits, delay with catch up at a later age, or deficits that become more apparent with time is not yet understood. Whilst cross-sectional studies provide valuable insights on functioning at a specific time during development they do not provide information on development trajectories. Longitudinal studies however, have the capability to study individual change over time providing information on the expected developmental trajectory of very preterm children and potentially identifying time points where issues may become apparent or worsen.

AIM

To characterise the developmental trajectories of arithmetic, reading comprehension and spelling abilities of very preterm and full-term born children during primary school

STUDY DESIGN

This study performed a longitudinal analysis of academic performance data of 52 very preterm and 58 full-term born children. Academic performance was assessed in grade 1-6 of primary school using a pupil monitoring system, with 11 measurements of arithmetic and spelling performance and 7 measurements of reading comprehension.

RESULTS

No group-by-time interactions were found for any of the academic domains, indicating no differences in progress between groups. However the study demonstrated that very preterm infants scored on average 0.53 SD lower on arithmetic ($p < .001$), 0.31 SD on reading comprehension ($p < .001$), and 0.21 SD on spelling ($p = .01$) compared to full-term peers through the course of primary school. This relationship was stable over time, implying intact learning abilities, but also that deficits apparent in the first grade of primary school do not improve or worsen with progression through later grades. Academic difficulties in very preterm children were indicated by increased educational assistance and grade repetition, and lower secondary education levels. With the present education, including special assistance and grade repetition, very preterm infants in general were not able to reach similar academic performance levels as full-term peers.

CONCLUSION

This longitudinal study demonstrated for the first time the academic development trajectory of very preterm children. Very preterm children showed difficulties in arithmetic, reading and spelling that persisted throughout primary school. However, they showed a similar progression to full-term children suggesting intact learning abilities providing potential opportunities for intervention. More research is needed to identify risk factors that may be target of preventive strategies for poor academic outcomes, clarify which skills and neurocognitive functions can be trained in what way, at which time in development, and in which children to minimise this academic performance gap.

ADDITIONAL NOTE

This is the first longitudinal study showing academic difficulties in very preterm born infants persist during primary school.

COGNITIVE OUTCOMES OF CHILDREN BORN EXTREMELY OR VERY PRETERM SINCE THE 1990S AND ASSOCIATED RISK FACTORS: A META-ANALYSIS AND META-REGRESSION

Twilhaar ES *et al.* JAMA Pediatrics 2018;172(4):361-7.

BACKGROUND

Increasing preterm birth and survival rates have led to a growing number of children surviving preterm birth. However, despite progress in perinatal care long term morbidity rates have not decreased. Extremely or very preterm (EP/VP) birth (<32 weeks gestation) is particularly associated with cognitive impairment, which can place a significant burden on individuals, families, and society, whilst providing challenges for education and health care professionals. Understanding the contributing factors to cognitive outcomes in this population is key for improving outcomes and infant development following EP/VP birth.

AIMS

To examine the cognitive abilities of children of EP/VP birth (EP/VP children) and the role of perinatal and demographic risk factors.

STUDY DESIGN

This meta-analysis and meta-regression studied cognitive outcomes of children born extremely or very preterm since 1990 and the perinatal and demographic factors predicting cognitive outcomes. PubMed, Web of Science, and PsycINFO were searched without language restriction with key search terms including preterm, low birth weight, and intelligence. A total of 71 peer reviewed studies reporting intelligence scores were included in the analysis, comprising of 7,752 EP/VP infants and 5,155 controls. Median gestational age was 28.5 weeks and the mean age of assessment ranged from 5 to 20.1 years.

RESULTS

Children born extremely or very preterm had a significantly lower IQ compared to controls (0.86-SD lower IQ; 95% CI, -0.94 to -0.78, $P < 0.001$), which was stable in children born between 1990 and 2008. Results were heterogeneous across studies ($I^2 = 74.13$; $P < .001$). This heterogeneity could not be explained by birth year of the cohort. Multivariate meta-regression analysis with backwards elimination demonstrated that bronchopulmonary dysplasia (BPD) explained 65% of the variance in intelligence across studies. Each percent increase in BPD rate across studies was associated with a 0.01-SD decrease in IQ (0.15 IQ points; $P < 0.001$).

CONCLUSION

This robust evidence shows large deficits in intelligence in children born EP/VP, which have not improved between 1990 and 2008 despite advancing perinatal care. This emphasizes that improving outcomes after EP/VP birth remains a major challenge, however lowering the high incidence of BPD may be key to improving long-term cognitive outcomes after EP/VP birth.

ADDITIONAL NOTE

Potential strategies to manage BPD may include an optimal ventilation strategy and oxygen concentration, anti-inflammatory agents, antioxidant therapy, and adequate nutritional support.

ACADEMIC PERFORMANCE OF CHILDREN BORN PRETERM: A META-ANALYSIS AND META-REGRESSION

Twilhaar ES *et al.* Archives of Disease in Childhood: Fetal and Neonatal Edition 2018;103:F322-30.

BACKGROUND

Advances in neonatal healthcare have resulted in decreased mortality after preterm birth but have not led to parallel decreases in morbidity. Impaired growth and immature physiology impact functional organ development, in particular the brain. Academic performance provides insight in the outcomes and specific difficulties and needs of preterm children.

AIMS

To study academic performance in preterm children born in the antenatal steroids and surfactant era and possible moderating effects of perinatal and demographic factors

STUDY DESIGN

PubMed, Web of Science and PsycINFO were searched for peer-reviewed articles. Cohort studies with a full-term control group reporting standardised academic performance scores of preterm children (<37 weeks of gestation) at age 5 years or older and born in the antenatal steroids and surfactant era were included.

RESULTS

17 eligible studies included 2390 preterm children and 1549 controls. Preterm children scored 0.71 SD below full-term peers on arithmetic ($p < 0.001$), 0.44 and 0.52 SD lower on reading and spelling ($p < 0.001$) and were 2.85 times more likely to receive special educational assistance (95% CI 2.12 to 3.84, $p < 0.001$). Bronchopulmonarydysplasia explained 44% of the variance in academic performance ($p = 0.006$).

CONCLUSION

This meta-analysis on academic performance provides insight in the outcomes, difficulties and needs of preterm infants. Preterm children born in the antenatal steroids and surfactant era show considerable academic difficulties in reading, spelling, and arithmetic. Preterm children with bronchopulmonarydysplasia are at particular risk for poor academic outcome and may be a crucial target for (nutritional) interventions to improve outcomes.

IMMUNE HEALTH



NEUTRAL AND ACIDIC OLIGOSACCHARIDES IN PRETERM INFANTS: A RANDOMIZED, DOUBLE-BLIND, PLACEBO CONTROLLED TRIAL

Westerbeek EAM *et al.* American Journal of Clinical Nutrition, 2010,91:679-86.

BACKGROUND

Preterm infants are at a high risk of serious infections due to bloodstream infections and also those caused by endogenous bacteria which originate in the gastrointestinal (GI) tract. It has been shown that the number of bifidobacteria and Lactobacillus found in the GI tract of the preterm infant is lower than that found in a term infant. Breast milk contains oligosaccharides that have immunomodulatory, anti-adhesive and antimicrobial effects; the latter two effects are due to the presence of acidic breast milk oligosaccharide. It is hypothesised that enteral supplementation of prebiotics may reduce the incidence of infections related to the GI tract.

AIM

Determine the effect of enteral supplementation of a prebiotic mixture of neutral and acidic oligosaccharides (AOS) on serious infectious morbidity in preterm infants. The neutral component of the prebiotic mixture contained short-chain galacto-oligosaccharides (scGOS) & long-chain fructo-oligosaccharides (lcFOS).

STUDY DESIGN

Double blind randomised placebo controlled trial in infants with a gestational age < 32 weeks and/or a birthweight <1500g, assigned to one of three birth weight groups, and then randomly allocated to an intervention or placebo feeding group. The intervention group received a formula containing 80% scGOS & lcFOS and 20% AOS between days 3-30 of life. The primary outcome was serious infectious morbidity; a new serious infectious episode was defined as a new positive culture after adequate antibiotic treatment. Secondary outcomes included feeding tolerance and growth.

RESULTS

Initially 208 infants were recruited to the study with n=114 infants progressing to randomisation (n=55 intervention group; n=59 placebo group) with n=43 infants completing in the intervention group and n=51 completing in the placebo group. Baseline and nutritional characteristics did not differ between groups. An intention-to-treat analysis was undertaken; there was no significant difference in the incidence of ≥ 1 serious infection, ≥ 1 serious endogenous infection, or ≥ 2 serious infectious episodes between the two groups. The per-protocol analysis showed a trend towards a lower incidence of ≥ 1 serious endogenous infection and ≥ 2 serious infectious episodes in the scGOS/lcFOS and AOS supplemented group when compared to the placebo group ($p=0.09$ and $p=0.07$ respectively). There were no differences between groups in the secondary outcomes measured.

CONCLUSION

Although supplementation with a formula containing a mixture of scGOS/lcFOS and AOS did not significantly reduce the incidence of severe infectious morbidity in preterm infants, there was a trend toward a lower incidence of infections, especially those resulting from endogenous bacteria. The findings in this study should be further investigated in a larger study.

SUPPLEMENTATION OF A BOVINE MILK FORMULA WITH AN OLIGOSACCHARIDE MIXTURE INCREASES COUNTS OF FAECAL BIFIDOBACTERIA IN PRETERM INFANTS

Boehm G *et al.* Arch Dis Child Fetal Neonatal Ed. 2002;86:F178-81.

BACKGROUND

Preterm infants are particularly vulnerable to intestinal infections; therefore the establishment of a balanced microflora that may protect against infection is desirable in such infants. One external factor that is important for the quality of intestinal colonisation is the diet.

AIM

The aim of this study was to investigate the effect of a preterm formula milk supplemented with a mixture of oligosaccharides (a mixture of 90% galacto-oligosaccharides and 10% fructo-oligosaccharides in a concentration of 1 g/100ml) on the stool flora (with particular respect to bifidobacteria concentration) and stool characteristics of preterm infants.

STUDY DESIGN

30 preterm infants (maximum gestational age 32 weeks) were randomised to receive a non prebiotic containing preterm formula (control) or preterm formula containing prebiotic OS (1g/100ml) for 28 days. 12 breastfed infants were also studied. On day 1, 7, 14 and 28, faecal flora, stool characteristics, any side effects and body weight were recorded. The crown heel length was measured at the start and end of each feeding period.

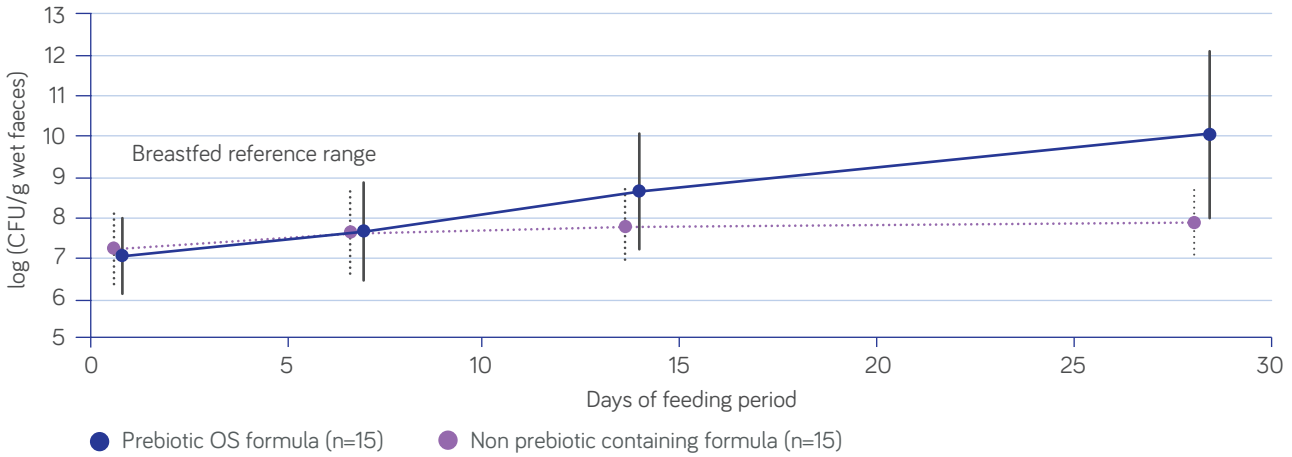
All infants started feeding with pasteurised breast milk. When the neonatologist decided to start formula feeding, the infants were randomised to one of the two intervention groups.

RESULTS

Effects on stool flora

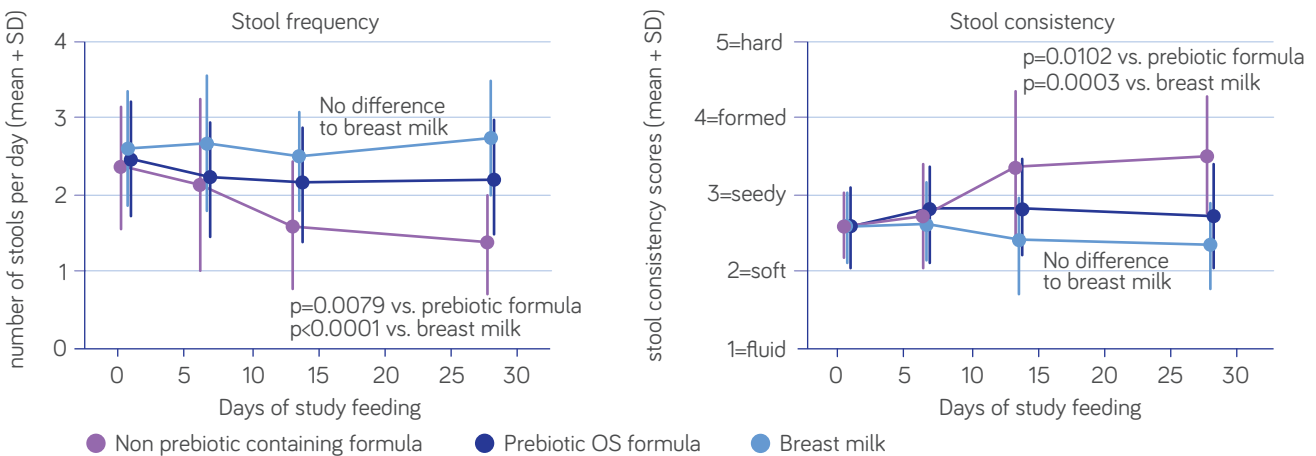
- At the initiation of treatment, the numbers of bifidobacteria present did not differ between intervention groups.
- The number of bifidobacteria was significantly higher on day 28 in infants receiving the prebiotic OS supplemented formula milk compared to the control group ($p=0.0008$).
- At day 28 the number of bifidobacteria in the prebiotic OS group was in the upper range of the reference breastfed group.

NUMBER OF BIFIDOBACTERIA



EFFECTS ON STOOL CONSISTENCY AND FREQUENCY

- The stool consistency of infants receiving the prebiotic OS formula milk was similar to that of the infants receiving breast milk.
- Infants in the control group developed significantly harder stools than the prebiotic OS group ($p=0.0102$) and the breast milk group ($p=0.0003$).
- The stool frequency in the prebiotic OS formula group and breastfed group were similar. The stool frequency after 28 days was significantly higher in the reference breastfed group than in the control group ($p<0.0001$).



WEIGHT AND LENGTH

- Weight and length gain did not differ between intervention groups.
- There was no effect of the oligosaccharides (prebiotics) on the incidence of side effects (crying, regurgitation or vomiting).

CONCLUSION

Supplementation of a preterm formula with a mixture of galacto- and fructo-oligosaccharides (prebiotics) stimulates growth of bifidobacteria and results in a stool frequency and consistency similar to those found in preterm infants fed breast milk. Thus prebiotic mixtures such as those studied here may help to improve intestinal tolerance to enteral feeding.

INCREASE OF FECAL BIFIDOBACTERIA DUE TO DIETARY OLIGOSACCHARIDES INDUCES A REDUCTION OF CLINICALLY RELEVANT PATHOGEN GERMS IN THE FAECES OF FORMULA-FED PRETERM INFANTS

Knol J *et al.* Acta Paediatr. 2005;94(Suppl 449):31-3.

BACKGROUND

Preterm infants are particularly vulnerable to intestinal infections, therefore the establishment of a balanced microflora that may protect against infection is desirable in such infants. One external factor that is important for the quality of intestinal colonisation is the diet.

AIM

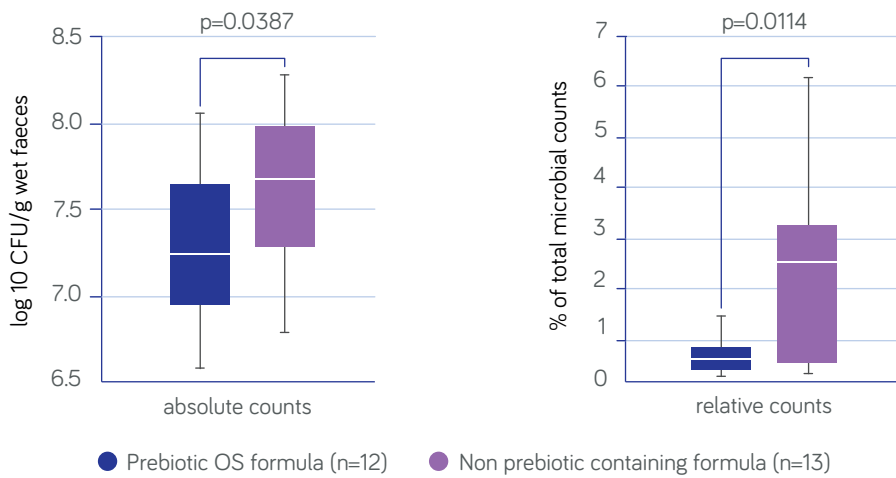
In a previous study on formula-fed preterm infants (Boehm *et al.* 2002), we were able to demonstrate that dietary oligosaccharides (a mixture of 90% galacto-oligosaccharides and 10% fructo-oligosaccharides in a concentration of 1g/100ml) stimulate the growth of faecal bifidobacteria. In the present explorative analysis of this study, we focus on the effect of the dominance of bifidobacteria on the presence of clinically relevant pathogens (Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus haemolyticus, Pseudomonas aeruginosa, Enterobacter, Klebsiella, Proteus, Streptococcus group B, Clostridium difficile, Bacillus subtilis and Acinetobacter).

STUDY DESIGN

The study involved 25 preterm infants with a maximum gestational age of 32 weeks. All infants started with pasteurized breast milk. When the neonatologist decided to start formula feeding the infants were randomised to one of two groups; preterm formula supplemented with 1g/100ml prebiotic OS (90% GOS, 10% FOS) or a non prebiotic containing preterm formula (control). Faecal pathogens were recorded on days 1 and 28. The formulas were identical except for the addition of oligosaccharides.

RESULTS

At the start of the study the sum of the studied pathogens was not significantly different between the two groups (log CFU/g stool: 7.34 ± 0.62 vs 7.24 ± 0.31 ; $p=0.87$). At the end of the study period the sum of the studied pathogens was significantly lower in the group fed the preterm formula supplemented with prebiotic OS compared to the control group (7.24 ± 0.31 log CFU/g stool vs 7.67 ± 0.58 ; $p=0.039$). When expressed as a percentage of total bacteria, the sum of the studied pathogens in the prebiotic group was also significantly lower than in the control group (0.52 ± 0.66 vs $2.58 \pm 3.07\%$; $p=0.011$). Boehm G *et al.* Arch Dis Child Fetal Neonatal Ed. 2002; 86: F176-F181



CONCLUSION

The data demonstrate that stimulation of bifidobacteria by prebiotic OS reduces the presence of clinically relevant pathogens in the faecal flora, indicating that prebiotic substances might have the capacity to protect against enteral infections.

GASTROINTESTINAL HEALTH



PREBIOTIC OLIGOSACCHARIDES REDUCE STOOL VISCOSITY AND ACCELERATE GASTROINTESTINAL TRANSPORT IN PRETERM INFANTS

Mihatsch W *et al.* Acta Paediatr. 2006;95:843-8.

BACKGROUND

In preterm infants formula feeding is often associated with hard stools, delayed gastrointestinal transport and constipation. As these problems can hamper tolerance to enteral feeding it is desirable to attain a reduction of stool viscosity and acceleration of gastrointestinal transport.

AIM

To investigate whether a mixture of prebiotic OS (a mixture of 90% galacto-oligosaccharides and 10% fructo-oligosaccharides) would improve feeding tolerance in preterm infants on full enteral formula feeding. The hypotheses was that prebiotic OS would: (1) reduce stool viscosity and (2) accelerate gastrointestinal transport.

STUDY DESIGN

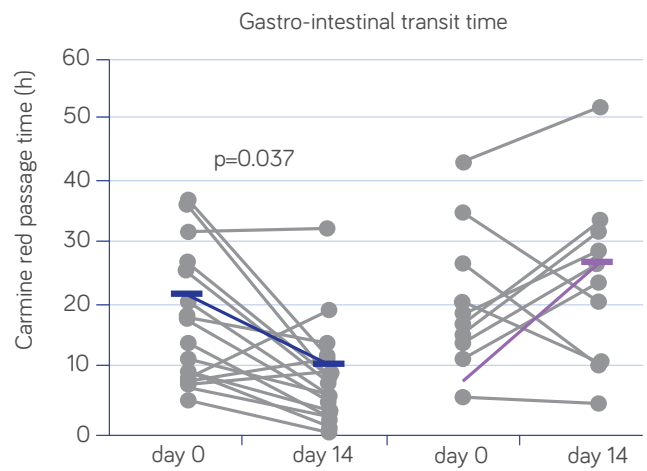
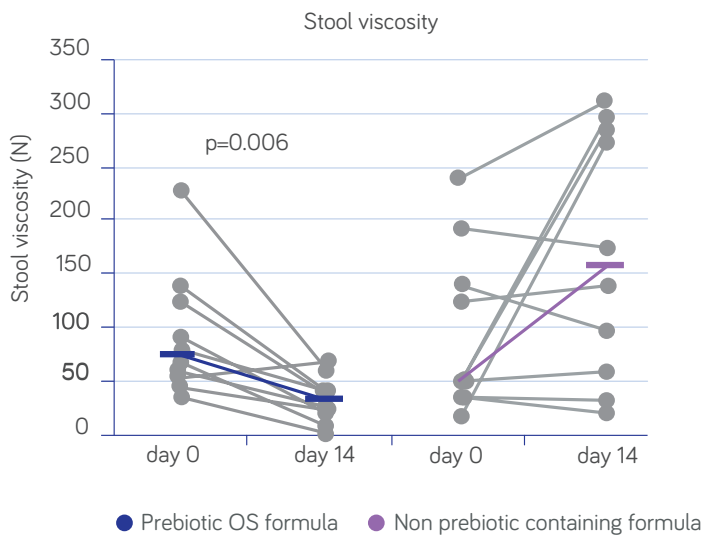
In a placebo-controlled double-blind trial 20 preterm infants on full enteral nutrition were randomly allocated to have their feedings supplemented with either prebiotic OS (1g/100ml) or a placebo for 14 days.

The mean gestational age was 27 (range 24-31) weeks, postnatal mean age 42 (range 11-84) days, and weight at study entry was 1570 (range 1080-2300) grams. Stool viscosity was measured by high-pressure capillary rheometry. Gastrointestinal transport time was assessed as the time from feeding carmine red to its appearance in the nappy.

RESULTS

Birth weight, gestational age, postnatal age, and weight at study entry did not differ between groups. In the group receiving the prebiotic OS supplemented formula, stool viscosity was significantly decreased at day 14 compared to the placebo group (32 (2-67) versus 158 (24-314) N; $p=0.006$).

The prebiotic OS supplemented group also showed a higher proportion of soft stools compared to the placebo group at day 14. The difference in gastrointestinal transit time between baseline and day 14 was significantly shortened in the prebiotic supplemented group ($p=0.037$) whereas no significant difference was observed in the placebo group. No adverse effects were observed.



CONCLUSION

Formula supplementation with prebiotic OS reduced stool viscosity and accelerated gastrointestinal transport. Further trials are required to investigate whether prebiotic OS facilitate enteral feeding advancement and early enteral nutrition thereby eventually reducing the incidence of catheter-related nosocomial infections and improving longterm outcome.

A RANDOMISED, DOUBLE-BLIND CONTROLLED TRIAL OF THE EFFECT OF PREBIOTIC OLIGOSACCHARIDES ON ENTERAL TOLERANCE IN PRETERM INFANTS

Modi N *et al.* *Pediatr Res* 2010;68:440-445.

BACKGROUND

Enteral feeding rather than parenteral (intravenous) feeding is preferred in preterm babies. Many factors make establishing and maintaining feeds difficult in pre-term babies; colonisation with probiotic bacteria improves feed tolerance and breast milk is a rich source of prebiotic OS. Breastfeeding should be promoted and encouraged in neonatal units but many mothers struggle to provide sufficient milk.

AIM

To test the hypothesis that a preterm formula containing 0.8g prebiotic OS per 100ml (at a 9:1 ratio of galacto-oligosaccharides to fructo-oligosaccharides) improves enteral tolerance in preterm babies.

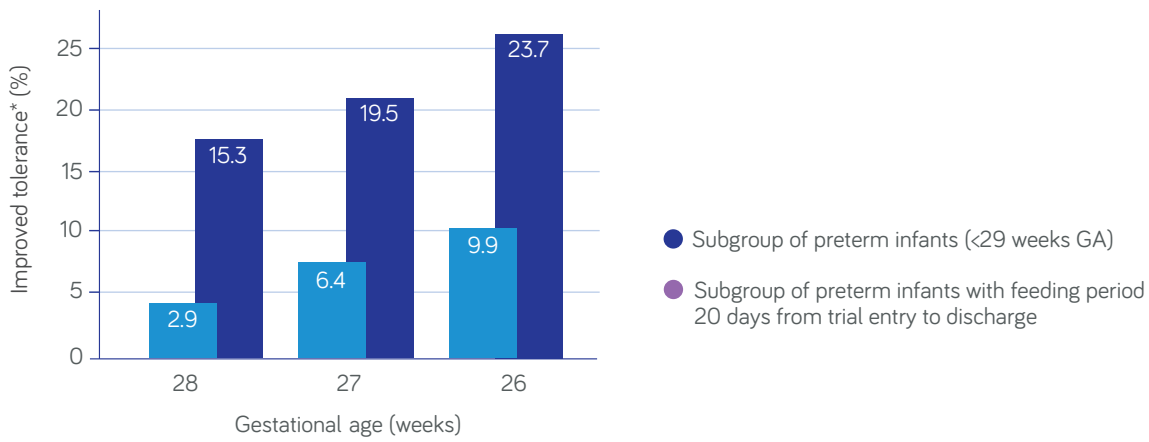
STUDY DESIGN

A UK multicentre double blind randomised controlled trial comparing a prebiotic OS containing preterm formula with a non prebiotic containing preterm formula on enteral tolerance. Formula was only used when there was insufficient breast milk. Infants were randomised within 24 hours after birth.

The primary outcome was the number of days from birth to establish a total daily enteral intake of 150ml/kg/day. The principal secondary outcome was the proportion of days between birth and 28 days or discharge that a total daily milk intake of at least 150ml/ kg/day was tolerated.

RESULTS

- Final data available for 150 babies for the primary outcome and 154 for the principal secondary outcome.
- There were no significant differences between the groups in the primary or secondary outcomes.
- After covariate adjustment there was improved enteral tolerance:
 - 2.9% higher in prebiotic OS group for infants at 28 weeks, 9.9% higher in those born at 26 weeks
 - in subgroup of infants in prebiotic OS group in hospital >20 days



*Improved enteral tolerance (=maintenance of enteral milk supply of >150ml/kg/day) compared to non prebiotic containing preterm formula

CONCLUSION

A formula with prebiotic OS may improve enteral tolerance in very preterm infants <29 weeks versus a non prebiotic containing preterm formula.

MOTILIN AND GASTRIN SECRETION AND LIPID PROFILE IN PRETERM NEONATES FOLLOWING PREBIOTIC SUPPLEMENTATION: A DOUBLE-BLIND RANDOMISED CONTROLLED STUDY

Dasopoulou M *et al.* Journal of Parenteral and Enteral Nutrition 2015;39(3):359-68.

BACKGROUND

Gut maturation as a response to feeding develops slower in preterm infants compared to term infants. Gastrin exerts a trophic effect on the neonatal intestine and relatively high levels are observed in the first 2-3 weeks of life. Motilin also reaches high levels at this time before the development of cyclic responses to feeding which is associated with maturation of migrating motor complexes and enhancement of intestinal motility. Prebiotics have been shown to positively impact on gastrointestinal motility although the mechanism is still to be determined. Furthermore, in adults prebiotics have been shown to reduce cholesterol, triglycerides and low density lipoproteins.

AIM

Investigate the effects of feeding infants a formula containing a prebiotic mixture of short chain galacto-oligosaccharides and long chain fructo-oligosaccharides on motilin and gastrin secretion and lipid profile.

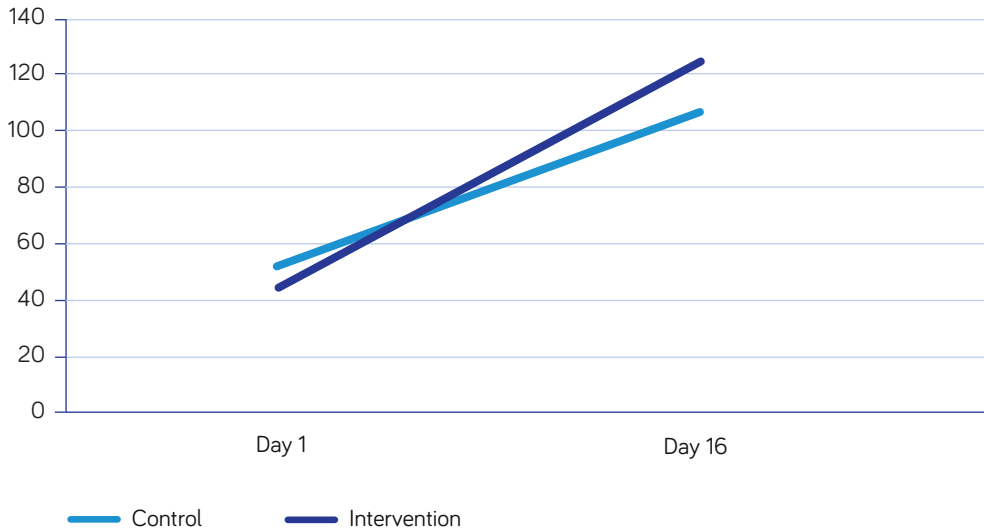
STUDY DESIGN

Randomised controlled study where preterm neonates were randomised at birth to receive either a prebiotic containing formula (the intervention) or a standard formula (the control) between days 1 and 16 of life. The prebiotic mixture was present at 0.8g/100ml and had a ratio of 90% short chain galacto-oligosaccharides and 10% long chain fructo-oligosaccharides. Basal circulating levels of plasma motilin and gastrin were measured on day 1 and again on day 16 along with cholesterol (HDL and LDL) and triglycerides. Feeding tolerance was assessed along with details about stool production. Anthropometric measurements were also undertaken.

RESULTS

Two hundred neonates were randomised and n=85 neonates completed the intervention arm of the study and n=82 the control arm which was within the power calculation for sample size. The mean motilin increase and levels at day 16 were significantly higher in the intervention group compared to the control ($p=0.001$, $p=0.005$ respectively). Gastrin levels remained high in both groups. Mean cholesterol and LDL rises were significantly greater in the control group ($p=0.037$, $p=0.001$). Mean weight was greater in the control group; gastric residue was less and stool frequency was greater in the intervention group.

MEAN MOTILIN LEVELS (PMOL/FL)



CONCLUSION

A preterm formula containing prebiotics resulted in significantly higher levels of motilin in the first 16 days of life which was related to a reduction in gastric residue. Mean cholesterol levels and LDL cholesterol were lower in the intervention group.

MILK FEED OSMOLALITY AND ADVERSE EVENTS IN NEWBORN INFANTS AND ANIMALS: A SYSTEMATIC REVIEW

Ellis ZM *et al.* Archives of Disease in Childhood - Fetal and Neonatal Edition 2019;104:F333-40.

BACKGROUND

Due to the high nutritional and caloric needs of preterm infants both fortified breast milk and preterm formula has a higher osmolality than breast milk alone. Recent feeding guidelines for preterm infants do not include an upper recommended level of feed osmolality/osmolarity, however in 1976 the American Academy of Pediatrics recommended that formulae for all infants should have an osmolarity no greater than 400 mOsm/l (approximately 450 mOsm/kg). This recommendation remains without clear substantiation based on relevant trials, however it has led to high feed osmolality being considered to impact adverse events – particularly gastrointestinal dysfunctions and necrotising enterocolitis (NEC) – in preterm infants. Therefore this systematic review assessed if there is a link between high milk feed osmolality and adverse gastrointestinal events, including feeding intolerance and NEC.

AIMS

To systematically review the literature on milk feed osmolality and adverse gastrointestinal events in newborn and low birthweight infants and animals.

STUDY DESIGN

MEDLINE, Embase, CAB Abstracts, Current Contents, BIOSIS Previews and SciSearch were searched from inception to May 2018 to identify potentially relevant studies. Inclusion criteria: randomised controlled or observational studies of newborn and low birthweight infants or animals investigating the effects of milk-based feeds with different osmolalities.

RESULTS

Based on 10 included human studies with 618 subjects no consistent evidence was found that feed osmolality is associated with any adverse gastrointestinal events except at very high levels. Seven studies reported no differences in adverse events with varying feed osmolalities/osmolarities. One study reported delayed gastric emptying with feed osmolarity of 539 mOsm/l compared to lower levels, however significant compositional differences between the feeds limit the interpretation of this result. The most severe clinical manifestation of feeding intolerance is NEC, and no consistent evidence was found that higher milk feed osmolalities impact this. One study reported higher NEC incidence with feed of osmolarity of 650 mOsm/l compared to 359 mOsm/l, however again significant differences in formulae composition make it impossible to determine if this is attributable to increased osmolality. In addition, 1 study found higher NEC incidence with the lowest feed osmolality (326 mOsm/kg) compared to feeds with higher osmolality (385 mOsm/kg) with acidified vs non acidified products, highlighting the role of formulae composition. Of animal studies, two reported delayed gastric emptying with feed osmolarity >624mOsm/L, one reported decreased survival due to dehydration with dietary osmolarities ≥765mOsmol/L and none reported increased NEC incidence with differing feed osmolalities. No clear mechanisms supporting a role of osmolality in feed intolerance were found.

CONCLUSION

There is no consistent evidence that differences in feed osmolality in the range 300–500 mOsm/kg are associated with adverse gastrointestinal symptoms in neonates.

