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Milk feed osmolality and adverse events in newborn infants and animals: a systematic review

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ABSTRACT

Background High feed osmolality (or osmolarity) is often suggested to be linked with adverse gastrointestinal events in preterm infants.

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

Methods 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. Only full-text, English-language papers were included.

Results Ten human and six animal studies met the inclusion criteria. Of human studies, seven reported no differences in adverse events with varying feed osmolalities; one reported delayed gastric emptying with feed osmolarity of 539 mOsm/L compared with lower levels; one reported higher necrotising enterocolitis (NEC) incidence with feed osmolarity of 650 mOsm/L compared with 359 mOsm/L; one found higher NEC incidence with the lowest feed osmolality (326 mOsm/kg compared with 385 mOsm/kg). Of animal studies, two reported delayed gastric emptying with feed osmolarity >624 mOsm/L, one reported decreased survival due to dehydration with dietary osmolarities ≥765 mOsmol/L and none reported increased NEC incidence with differing feed osmolalities. No clear mechanisms were found, and diet composition differences limited the interpretations regarding the independent impact of osmolality.

Conclusions 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.

Definitions

- Osmolality: the concentration of a solution in terms of osmoles of solute per kilogram of solvent. Expressed as mOsm/kg.
- Osmolarity: the concentration of a solution in terms of osmoles of solute per litre of solution. Expressed as mOsm/L.

INTRODUCTION

Better neonatal care has improved short-term clinical outcomes, including overall survival. However, long-term outcomes, especially neurodevelopment, remain a big concern.[1] Poor postnatal growth of preterm and low birthweight infants is associated with adverse short-term and long-term clinical outcomes.[2] Enteral feeding is the cornerstone of nutritional management and growth, but feeding tolerance impacts on the rate of feed advancement. Due to the high nutritional and caloric needs of preterm infants, enteral nutrition of preterm infants, either fortified human milk or preterm formula, has a higher osmolality (or osmolarity) than unfortified human milk. High feed osmolality is often suggested to be linked with adverse events, particularly gastrointestinal dysfunctions and necrotising enterocolitis (NEC) in preterm infants. The osmolality of mammalian/human milk is approximately 300 mOsm/kg[3] but is often increased to levels above 400 mOsm/kg by addition of human milk fortifiers (HMFs), nutritional supplements and medications.[3–5] The nutrients that most affect feed osmolality include: monosaccharides and disaccharides, minerals and electrolytes, amino acids, hydrolysed proteins and medium-chain triglycerides.[6] Recent feeding guidelines for preterm infants do not include an upper recommended level of feed osmolality/osmolarity.[7–9] The only recommendation is from 1976 by the American Academy of Pediatrics,[10] which advises that formulas for normal infants should have an osmolarity no greater than 400 mOsm/L (approximately 450 mOsm/kg). As yet, this recommendation remains without clear substantiation based on relevant trials.

In 2013, Pearson *et al*[11] reviewed the subject of feed osmolality and considered the plausibility of osmolality in the causation of NEC, but to date, there has been no systematic review of the literature to examine this area in detail. Therefore, we performed a systematic literature review on human and animal studies to investigate whether there is a link between high milk feed osmolality and adverse gastrointestinal events, including feeding intolerance and NEC. Due to the challenge in performing randomised well-controlled studies on different osmolality diets in humans and the difficulties in assessing underlying mechanisms, we also included animal studies with relevant gastrointestinal endpoints. We included all relevant studies on the topic that measured feed osmolality regardless of differences in formula composition.

MATERIALS AND METHODS

Search strategy

Six databases (MEDLINE, Embase, CAB Abstracts, Current Contents, BIOSIS Previews and SciSearch) were searched from inception to 16 May 2018

to identify potentially relevant studies (online supplementary appendix A). The search yielded a total of 2072 records. Inclusion criteria were: (1) human and animal studies investigating the effects of milk-based and elemental feeds that differ in osmolality/osmolarity; (2) randomised controlled trials (RCT) and observational studies; (3) published full-text articles, (4) for human studies: infants up to 28 days old and (5) for animal studies: outcome measures related to gut function. Exclusion criteria were: (1) non-English records; (2) studies involving medications, vitamin supplements and mineral solutions; (3) studies involving postpyloric feeds; (4) studies not reporting on osmolality/osmolarity levels of feeds; and (5) studies involving infants with other morbidities (eg, hypernatraemia).

Data collection and analysis

HSGT screened titles and abstracts of the 2072 records and selected potentially relevant records. ZME and HSGT then assessed the abstracts of the selected records for eligibility based on the inclusion and exclusion criteria. Full-text articles of human studies were assessed by four authors (ZME, HSGT, NDE and RMvE) and animal studies by three authors (ZME, HSGT and PTS). Eligibility of each article was based on the prespecified inclusion and exclusion criteria.

Assessment of risk of bias

Two authors (ZME and HSGT) assessed risk of bias of included studies. Human RCTs were assessed using the criteria of the Cochrane Handbook for Systematic Reviews of Interventions, observational cohort studies were assessed using the Newcastle-Ottawa Quality Assessment Scale for cohort studies and animal studies were assessed using SYRCLE's risk of bias tool for animal intervention studies.[12] Disagreements were solved after discussion with the other authors (RMvE and NDE for human studies; PTS for animal studies).

Data extraction, management and analysis

Data were extracted by two authors (ZME and HSGT) using a data collection form. Data extracted included study population characteristics, adverse outcomes, composition of feeds administered and osmolality/osmolarity. Disagreements were solved after discussion with a third author (RMvE). If reported data were insufficient, we contacted authors for further information. No attempt was made to synthesise the data numerically due to variability in osmolality and osmolarity. Findings of the studies were summarised narratively.

RESULTS

Study selection

Fifty-eight of the 2072 publications met our inclusion criteria. After reading the full texts, 42 were excluded. Figure 1 shows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of the search strategy. Of the 10 included human studies,[13–22] eight were RCTs of which three were cross-over design and two were observational studies (table 1). Table 2 presents details of the six included animal RCT studies.[23–28] We received additional information from Ramirez *et al*[14] on feed osmolality.

Risk of bias

Risk of bias of human and animal studies varied and almost all studies had methodological limitations (figures 2 and 3). As reporting of experimental details in animal studies is not yet standard, evaluation of their methodological quality remains

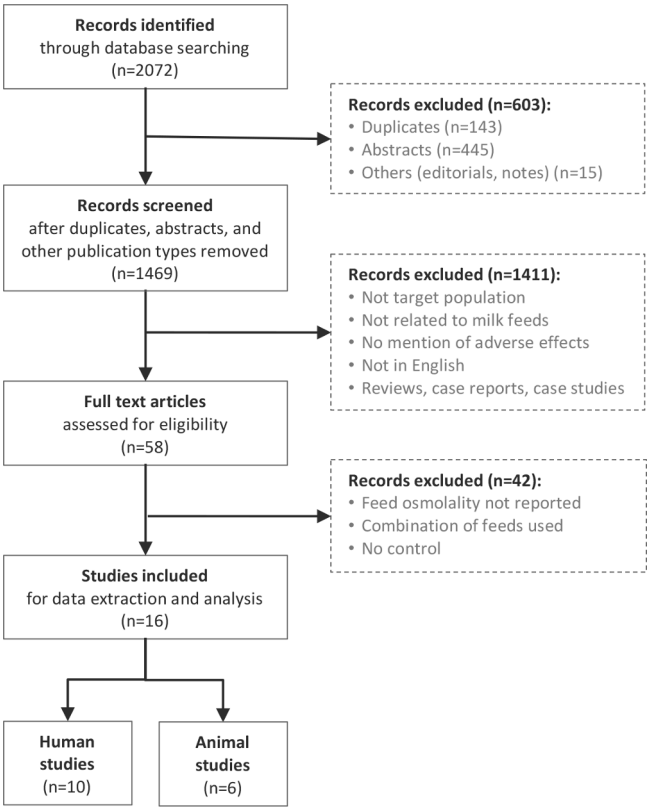

Figure 1 Flow diagram of the literature search process.

difficult. For human RCTs and animal studies, methods of blinding, randomisation and allocation concealment were frequently not clearly described. Incomplete outcome data was judged as having low risk of bias for all studies. For observational studies, high risk of bias was identified for Singh *et al*[19] and low risk of bias for Thoene *et al*[22] (online supplementary appendix B).

Human studies

Gastric emptying

Five studies reported effects of feed osmolality/osmolarity on gastric emptying.[13–17] In one study, a mean gastric residual of 30% was found in infants 3 hours after feeding a casein hydrolysate formula (539 mOsm/L), whereas no gastric residual after feeding an 80% casein and 20% soy formula (204 mOsm/L) and 3.7% gastric residual with a casein formula (211 mOsm/L) were found.[13] Another study found no change in gastric emptying with a feed osmolality of 310 versus 155 mOsm/kg.[14] However, gastric emptying was accelerated by decreasing osmolality from 310 to 155 mOsm/kg while increasing feed volume from 10 mL/kg to 20 mL/kg. Yigit *et al*[16] found no significant difference in gastric residuals after feeding different feeds with an osmolarity ranging from 275 mOsm/L to 576 mOsm/L. Similarly, Siegel *et al*[15] reported no significant difference in gastric emptying between feeding a soybean formula containing sucrose (279 mOsm/kg) or containing glucose (448 mOsm/kg). Kanmaz *et al*[17] also reported no significant difference in gastric residuals after feedings with osmolarities ranging from 340 mOsm/L to 380 mOsm/L.

Feeding intolerance

Four studies assessed the influence of dietary osmolality/osmolarity on feeding tolerance.[17–20] The definition of feeding

Table 1 Characteristics of included human studies and overview of findings

Outcome measures	References* (country)	Study design	Birth weight	Gestational age	Number of participants	Type of feed	Osmolality/ osmolarity†	Osmolality/ osmolarity measured	Outcomes
Gastric emptying	Pascale (1978)[13] (USA)	RCT	<2000 g	Not reported	8	Intact protein formula (Isocal)	204 mOsm/L	No	Greater delay in gastric emptying in infants fed higher osmolarity formula.
					6	Intact protein formula (Portagen)	211 mOsm/L		
					13	Hydrolysed protein formula (Pregestimil)	539 mOsm/L		
Gastric emptying	Ramirez (2006)[14] (USA)	Cross-over RCT	<1570 g	25–30 weeks	10	Half strength human milk or formula‡	155 mOsm/kg	Yes	No change in gastric emptying with a higher diet osmolality.
						Half strength human milk or formula‡	310 mOsm/kg		
						Half strength human milk or formula‡	310 mOsm/kg		
						Full strength human milk or formula‡	310 mOsm/kg		
					7	Full strength human milk or formula‡	155 mOsm/kg	Yes	Accelerated gastric emptying with decreased osmolality and increased feed volume.
						Full strength human milk or formula‡	310 mOsm/kg		
Gastric emptying	Siegel (1982)[15] (USA)	Cross-over RCT	Not reported	26–34 weeks	10	With sucrose (Neo-Mull-Soy)	279±12 mOsm/kg	Yes	No significant difference in gastric emptying.
						With glucose (Cho-Free with glucose)	448±11 mOsm/kg		
Gastric emptying	Yigit (2008)[16] (Turkey)	Cross-over RCT	600–1470 g	Mean 29.8 weeks	20	Human milk	319±19 mOsm/§	Yes	No significant increase in gastric emptying time for full strength fortification.
						Half strength HMF (Eoprotin)	365±25 mOsm/L§		
						Full strength HMF (Eoprotin)	440±44 mOsm/L§		
Tolerance; Gastric emptying	Kanmaz (2013)[17] (Turkey)	RCT	≤1500 g	≤32 weeks	26	Standard fortification (Eoprotin)	340 mOsm/L	No	No significant difference in feeding intolerance, residuals and abdominal distension.
					29	Moderate fortification (Eoprotin)	360 mOsm/L		
					29	Aggressive fortification (Eoprotin)	380 mOsm/L		
Tolerance; Overall morbidity	Kim (2015) [18] (USA)	RCT	700–1500 g	≤33 weeks	63	Powdered intact protein HMF (Similac)	385 mOsm/kg	No	No significant differences in overall morbidity, and both fortifiers were well tolerated.
					66	New liquid hydrolysed protein HMF	450 mOsm/kg		
Tolerance; NEC	Singh (2017)[19] (India)	Prospective observational	<1500 g	Not reported	15	Higher carbohydrate HMF (Lactodex)	378±34 mOsm/kg	Yes	No significant difference in episodes of feeding intolerance or NEC.
					15	Higher fat HMF (HIJAM)	420±31 mOsm/kg		
					15	Higher carbohydrate HMF (FM-85)	451±39 mOsm/kg		
Tolerance; NEC	Rigo (2017)[20] (France, Belgium, Germany, Switzerland and Italy)	RCT	≤1500 g	≤32 weeks	76	New partially hydrolysed protein HMF (with higher protein and micronutrients)	390 mOsm/kg	Yes	No significant difference in feeding tolerance and NEC.
					74	Extensively hydrolysed protein HMF (FM-85)	441 mOsm/kg		

Continued

Table 1 Continued

Outcome measures	References* (country)	Study design	Birth weight	Gestational age	Number of participants	Type of feed	Osmolality/ osmolarity†	Osmolality/ osmolarity measured	Outcomes
NEC	Book (1975)[21] (USA)	RCT	<1200 g	24–32 weeks	8	Cow milk formula (premature formula)	359 mOsm/L	No	Significantly higher incidence of NEC in the elemental formula group (87.5%) compared with cow milk formula group (25%).
					8	Elemental formula (Pregestimil)	650 mOsm/L		
NEC	Thoene (2016)[22] (USA)	Retrospective observational	<2000 g	Not reported	23	Acidified liquid hydrolysed protein HMF	326 mOsm/kg	No	Significantly higher incidence of NEC in the feed group with lowest osmolality.
					46	Powdered intact protein HMF	385 mOsm/kg		
					51	Non-acidified liquid intact protein HMF	385 mOsm/kg		

*References indicated with first author and year.
† Osmolality/osmolarity values were rounded up.
‡Formula used in Ramirez *et al*[14] were either Enfamil 24 or Neosure.
§Range of values also reported in Yigit *et al*[16] (275–371 mOsm/L, 310–411 mOsm/L and 344–576 mOsm/L).
HMF, human milk fortifier; NEC, necrotising enterocolitis.

intolerance varied among the studies but frequently included presence of abdominal distension, vomiting and delayed/withheld feedings. None of these studies found significant differences in feeding tolerance with feed osmolalities up to 451 mOsm/kg.[17–20]

NEC and overall morbidity

Five studies reported the effects of dietary osmolality/osmolarity on NEC and overall morbidity.[18–22] One study reported a significantly higher NEC incidence in infants after receiving an elemental formula (650 mOsm/L) compared with a cow milk-based formula (359 mOsm/L) (87.5% vs 25%, respectively; $p<0.02$).[21] Thoene *et al*[22] reported a significantly higher NEC incidence in infants receiving an acidified liquid HMF (326 mOsm/kg) compared with those receiving a powdered HMF (385 mOsm/kg) and a non-acidified liquid HMF (385 mOsm/kg) (13%, 0% and 0%, respectively; $p=0.0056$). Rigo *et al*[20] found no significant difference in NEC incidence comparing one HMF (441 mOsm/kg) with a new HMF with higher protein and micronutrient content (390 mOsm/kg). Similarly, Singh *et al*[19] found no significant difference in NEC incidence with different feed osmolalities (451 mOsm/kg, 420 mOsm/kg and 378 mOsm/kg). Furthermore, Kim *et al*[18] reported no significant difference in overall morbidity (NEC and sepsis) in infants fed either a liquid HMF (450 mOsm/kg) or a powder HMF (385 mOsm/kg).

Animal studies

Adverse events and paraclinical endpoints

Six studies evaluated the mechanistic effects of feeds with different osmolalities/osmolarities,[23–28] although not necessarily the main aim of these studies. Goldblum *et al*[23] found no significant difference in intestinal luminal osmolality of the proximal and distal intestine after feeding neonatal dogs with a hyperosmolar feed (710 mOsm/kg) compared with iso-osmolar feeds. Gastric content could only be recovered in the group fed hyperosmolar feed, implying delayed gastric emptying. Similarly, Miller *et al*[24] found prolonged gastric emptying time and increased water in the intestine in neonatal rats with increased dietary osmolality.[24] Miyake *et al*[25] reported similar mucosal injury scores in neonatal mice in two NEC-induced groups fed hyperosmolar feeds and both had higher scores than a control human milk fed group. Szabo and Fewell[27] and Szabo *et al*[28] concluded that a single hyperosmolar feed did not induce intestinal motor dysfunction, differences in gastrointestinal hormone concentration, bacterial proliferation or intestinal mucosal damage in neonatal piglets. In preterm piglets, Sun *et al*[26] found no differences in gut permeability after feeding human milk with different fortification, resulting in osmolalities from 289 mOsm/kg to 460 mOsm/kg. However, differences were found in several structural, functional and immune parameters in the intestine and blood in the group receiving human milk with a formula-based fortifier (460 mOsm/kg) compared with those receiving human milk with bovine colostrum (408 mOsm/kg). Gastric residuals were also significantly higher in this group compared with groups fed donor human milk with or without fortifier ($p<0.05$).

Three studies evaluated the effects of a hyperosmolar feed on clinical outcomes.[24–26] Miller and Czajka[24] reported decreased survival in neonatal rats after feeds with a dietary osmolarity ≥765 mOsmol/L. In a mice study by Miyake *et al*,[25] NEC was induced by giving hypoxia and gavage administration of lipopolysaccharide and formula feeding. NEC incidence was similar in groups that received a lower (325 mOsm/kg) versus

Table 2 Characteristics of included animal studies and overview of findings

Outcome measures	References* (country)	Study design	Study population	Number of animals	Type of feed	Osmolality/ osmolarity†	Osmolality/ osmolarity measured	Outcomes
Intestinal osmolality and gastric content	Goldblum[23] (1981) (USA)	RCT	Neonatal dogs	4	Breast milk	300 mOsm/kg	Yes	No significant difference in intestinal osmolality in proximal and distal intestine with high osmolality feed. Gastric content recovered only in hypertonic-fed group.
				8	Cow milk formula (Similac)	298 mOsm/kg		
				14	Elemental formula (Pregestimil)	710 mOsm/kg		
Survival and gastric emptying	Miller[24] (1967) (USA)	RCT	Neonatal rats	40	Rat's breast milk	352 mOsm/L	Yes	Decreased survival with dietary osmolarity ≥765 mOsmol/L. Prolonged gastric emptying and increased water in the intestine with increasing dietary osmolarity.
				20	Hyperosmolar skim milk feed with glucose	624 mOsm/L		
				20	Hyperosmolar skim milk feed with glucose	765 mOsm/L		
				20	Hyperosmolar skim milk feed with glucose	975 mOsm/L		
				20	Hyperosmolar skim milk feed with glucose	1308 mOsm/L		
NEC and mucosal injury	Miyake[25] (2016) (Canada)	RCT	Neonatal mice	4	Breast milk	Not reported	Yes	Same incidence of NEC (80%) and similar mean mucosal injury score in the hyperosmolar feed groups. No incidence of NEC, low mean mucosal injury score and low intestinal inflammatory response in breastfed control group.
				10	Diluted hyperosmolar feed (Similac lower Iron+Esbilac Puppy Milk Replacer)	325 mOsm/kg		
				10	Hyperosmolar feed (Similac lower Iron+Esbilac Puppy Milk Replacer)	849 mOsm/kg		
Diarrhoea, NEC, gut permeability, inflammatory condition and gastric residual	Sun[26] (2018) (Denmark)	RCT	Preterm piglets	9	Unfortified donor pig milk (A)	312 mOsm/kg	Yes	Significantly more diarrhoea with highest osmolarity feed (D). No difference in incidence of NEC and gut permeability between feed groups (A–D). Several structural, functional and immune parameters in the intestine and blood differed with feeds C and D. Gastric residual significantly higher with feed C than feeds B and D.
				19	Donor human milk (B)	289 mOsm/kg		
				19	Donor human milk+bovine colostrum (C)	408 mOsm/kg		
				16	Donor human milk+formula based fortifier‡ (D)	460 mOsm/kg		
Intestinal motor dysfunction	Szabo (1990)[27] (USA)	RCT	Neonatal piglets	8	Commercial pig milk formula	482±35 mOsm/kg	Yes	No significant intestinal motor dysfunction indicated by pattern of small intestinal myoelectric activity (after single meal).
				9	Hyperosmolar pig milk formula with sorbitol	874±30 mOsm/kg		
GI hormones, bacterial proliferation and mucosal damage	Szabo (1990)[28] (USA)	RCT	Neonatal piglets	10	Commercial pig milk formula	481±41 mOsm/kg	Yes	No significant difference gastrointestinal hormone concentration, bacterial proliferation and no intestinal mucosal damage (after a single meal).
				10	Hyperosmolar pig milk formula with sorbitol	872±32 mOsm/kg		

*References are indicated only with first author and year.
†Osmolality/osmolarity values were rounded up.
‡Fortifiers used in Sun *et al*[26] were Nutrilon Nenatal or Enfamil HMF.
GI, gastrointestinal; HMF, human milk fortifier; NEC, necrotising enterocolitis; RCT, randomised controlled trial.

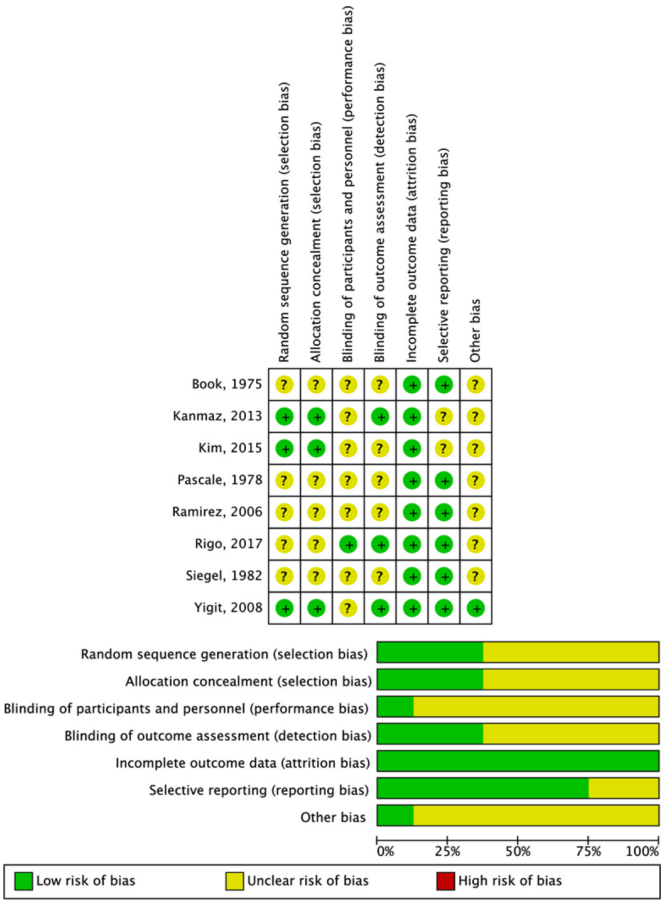

Figure 2 Assessment of the risk of bias in included human randomised controlled trials and the review authors' judgements about each risk of bias item presented as percentages.

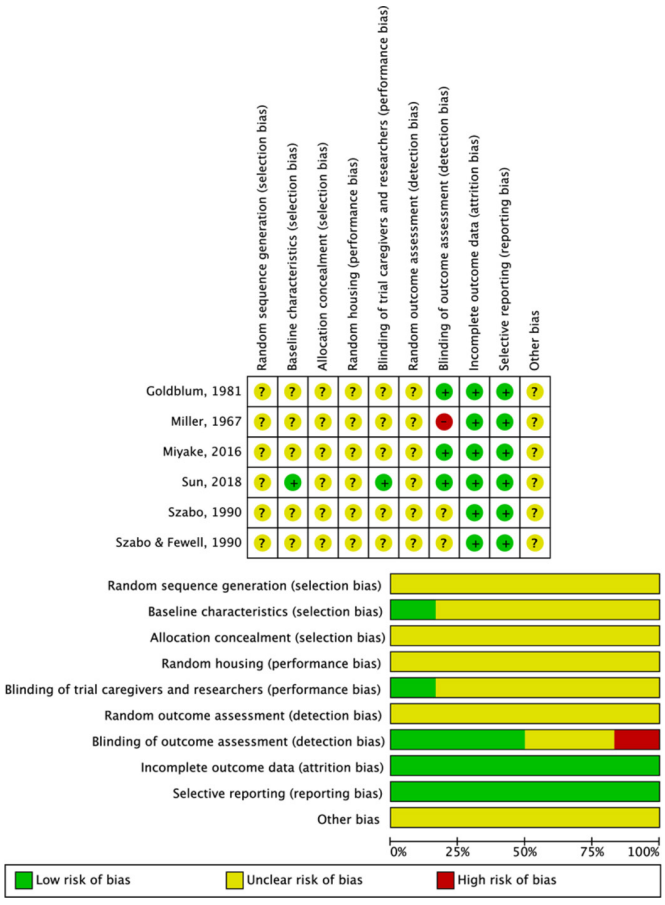

Figure 3 Assessment of the risk of bias in included animal studies and the review authors' judgements about each risk of bias item presented as percentages.

higher (849 mOsm/kg) osmolality feed. There were no NEC cases in the control breastmilk fed group without lipopolysaccharide or hypoxia. Sun *et al*[26] found significantly more diarrhoea in preterm piglets fed donor human milk with a formula-based fortifier (460 mOsm/kg) compared with groups receiving unfortified donor human, sow's milk or donor human milk with bovine colostrum (312–408 mOsm/kg) ($p<0.05$). There was no significant difference in NEC incidence between the groups receiving different feed osmolalities (289–460 mOsm/kg).

DISCUSSION

Based on the 10 included human studies with 618 infants, we found no consistent evidence that feed osmolality/osmolarity is associated with any adverse gastrointestinal events especially feeding intolerance, except at very high levels (eg, >539 mOsm/L). Below this level, we found no difference in feeding intolerance when infants were fed differing feed osmolalities (up to 450 mOsm/kg). As delayed gastric emptying is often regarded a major determinant of feed intolerance, we expected similar results for this outcome, and indeed we found no changes in gastric emptying with differing feed osmolarities (up to 440 mOsm/L). Only one human study[13] found a greater delay in gastric emptying with a feed osmolarity of 539 mOsm/L. However, significant differences in protein, fat and carbohydrate composition, besides differences in feed osmolarities in the studied formula, limit the interpretation of this result. Siegel *et al*[15] subsequently performed a study where similar feed compositions were used and found that feed osmolality did not significantly influence gastric emptying. However, the feed osmolalities tested in this study (up to 448 mOsm/kg) were much lower than in the study by Pascale *et al*.[13]

In comparison, some animal studies found that increasing feed osmolarities >624 mOsm/L, regardless of feed composition, delayed gastric emptying.[23 24] The exact mechanisms for delayed gastric emptying are not clear from these studies. However, Goldblum *et al*[23] reported a reduction in osmolarity in the contents of the proximal intestine in neonatal dogs after a hyperosmolar feed, indicating dilution occurring in the stomach. This dilution may have occurred through osmoreceptors in the duodenum initiating a delay in gastric emptying through direct interactions with the stomach.[29] In preterm piglets,[26] higher gastric residuals were found in piglets fed with an osmolality of 408 mOsm/kg compared with an osmolality of 460 mOsm/kg; however, the feed compositions in this study differed markedly (different fortifiers to human donor milk).

In a study published after our literature search was completed,[30] three fortifiers with varying feed osmolalities (320 mOsm/kg, 379 mOsm/kg and 498 mOsm/kg) added to human donor milk fed to preterm piglets were compared. Gastric residuals were similar among groups, but NEC incidence and gut inflammatory reactions were highest in the group fed fortified human milk with the highest osmolality. Furthermore, in another recently published piglet study by one of the authors (PTS),[31] a free amino acid-based formula diet showed adverse effects on digestion and growth compared with three diets consisting of 70% intact proteins and 30% essential amino acids. This effect

could have been due to the higher osmolality in the free amino acids groups compared with the other groups (580 mOsm/kg vs 470–480 mOsm/kg, measured but not described in the paper). Together, the results of the animal and human studies raise the question whether there is a certain level of feed osmolality where diets start to delay gastric emptying and create adverse intestinal reactions. However, it is important to acknowledge that most studies did not have osmolality/osmolarity as the principal dietary factor that varied and many other nutritional components (eg, fat, protein, calcium, magnesium and phosphate) varied between the diet groups, which may influence outcomes.

The most severe clinical manifestation of feeding intolerance in neonates is NEC. We found no evidence in human studies that milk feed osmolalities (up to 450 mOsm/kg) increased the incidence of NEC. Only one small human study found a significantly higher NEC incidence with a feed osmolarity of 650 mOsm/L.[21] However, significant differences in formulae compositions make it impossible to determine whether the higher NEC incidence was directly attributed to the high feed osmolarity or due to the specific formula composition (i.e. casein hydrolysate with high medium-chain triglycerides and glucose content) or a combination of both. The specific role of formula composition is illustrated by Thoene *et al*,[22] reporting a higher NEC incidence in infants fed an acidified HMF with the lowest feed osmolality (326 mOsm/kg). In the animal studies, we found no significant difference in the incidence of NEC with differing feed osmolalities (up to 849 mOsm/kg). NEC was induced in neonatal mice by Miyake *et al*[25] through gavage formula feeding (regardless of osmolality) combined with lipopolysaccharides and hypoxia. This is a method frequently adopted by others in rodents,[32 33] suggesting that other factors than solely feed osmolality play a role in the development of NEC, at least in rodents. In piglets, however, infant formula feeding alone can induce spontaneous NEC-like symptoms without exposure to hypoxia, gavage and lipopolysaccharide.[34] Lower osmolality diets, such as unfortified human, bovine or porcine milk or colostrum, clearly result in lower NEC sensitivity and less adverse intestinal reactions than formula in preterm piglets.[26 35–38] However, it remains unclear if this is due to lower feed osmolality or to composition of nutrients and protective bioactive factors in natural milk diets.

Besides adverse gastrointestinal events, neonatal rats fed a diet ≥765 mOsmol/L had increased mortality due to dehydration.[24] Compared with adult rats, newborn rats have reduced kidney function and difficulty conserving water in the body.[24 39] The impaired ability to maintain fluid homeostasis coupled with hyperosmolar feeds may lead to severe dehydration. Although it is inappropriate to directly extrapolate the results of this animal study to humans, neonatal infants also have reduced kidney function and difficulty regulating fluid balance increasing the risk of overhydration and dehydration,[40] thus feeds with a very high osmolality may also have other adverse effects in preterm infants.

Strengths and weaknesses of the review

To our knowledge, this is the first systematic review to investigate the link between feed osmolality and adverse gastrointestinal events. The strength of this review is the systematic approach of searching the literature with no restriction to year of publication and selection of studies based on prespecified inclusion and exclusion criteria. The PRISMA checklist was used to assist with the reporting of the review (online supplementary appendix C). Each full-text article was reviewed by three or more researchers independently. The limitations of this review include that only one reviewer screened the titles and abstracts of all search records and excluded obvious ineligible studies. The remainder were reviewed by at least two reviewers to select all eligible studies for inclusion. Furthermore, we restricted the review to only include studies published as full-text articles in English and that reported on osmolality/osmolarity. The included studies varied in methodological quality, mainly limited by unclear blinding, and no or unclear randomisation and allocation concealment. Feed osmolarity, when measured, was frequently highly variable and in some studies not measured but assumed, limiting the interpretation of any cut-off values that could influence outcomes. Although we acknowledge that it is necessary to alter at least one aspect of a feed to change the osmolality/osmolarity, significant differences in formula composition in the studies make it difficult to evaluate the independent effect of feed osmolality/osmolarity on specific adverse outcomes. An additional limitation was the relatively small number of neonates in each study included in this review, limiting the interpretation of the results. The interpretation of animal studies may be limited as the actual level by which osmolality adversely affects the infant versus animal intestine could differ; however, findings from the animal studies support the findings in human studies. Future RCTs would need to enrol >1000 infants to be powered to determine effects on key morbidities such as NEC or sepsis. It will remain difficult to investigate the specific effect of feed osmolality, independently of associated changes in dietary ingredients. Well-designed animal studies, using serial dilutions of osmolality, may help to identify mechanisms related to adverse gastrointestinal and metabolic effects of hyperosmolar diets. Until further scientific evidence is available, an upper maximum for osmolality/osmolarity in milk diets, especially for vulnerable groups such as preterm infants, are based on the pragmatic conclusions from existing infant and animal studies.

CONCLUSIONS

In conclusion, we found no consistent evidence that feed osmolality of 300–500 mOsm/kg poses a safety risk to newborn infants. In the available studies, significant differences in feed composition among diets with different osmolality levels limit the interpretation of results regarding the independent impact of osmolality.

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Competing interests Z-ME, HSGT and RMvE are employees of Danone Nutricia Research, Utrecht, The Netherlands. NDE has previously conducted research with support from manufacturers of infant formula including Nestec SA (Switzerland), Wyeth UK and Nutricia UK but did not receive any payment, support or benefit in kind for contribution to this manuscript and has no ongoing personal, consultancy or financial relationships with Nutricia or other relevant commercial interest. PTS has nothing to declare.

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