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The Effect of Additives for Reflux or Dysphagia Management on Osmolality in Ready-to-Feed Preterm Formula: Practice Implications

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Abstract

BACKGROUND—A common osmolality threshold for feedings are to stay below 450 mOsm/kg for normal infants. Preterm formulas are frequently modified to improve growth, modify nutrition, and to manage gastroesophageal reflux (GER) or dysphagia. Relationships between osmolality and additives to ready-to-feed preterm formulas are unclear. Our aims were to evaluate and compare the effects of caloric density, thickening agent recipes, and supplements to ready-to-feed preterm formula on osmolality.

METHODS—A freezing point osmometer was used to measure the osmolality of 47 preterm infant formula combinations with varying caloric densities (ready-to-feed 22 cal/oz and 30 cal/oz), thickening agents (rice vs oatmeal cereal), thickener amounts (0.0, 0.5, 1.0, 1.5, 2.0, 2.5, and 3.0 tsp/oz), and combinations of supplements (saline, iron, vitamin D, or multivitamin). Ten samples per combination were tested using a 10 µl pipette. Comparisons were made using ANOVA and t-tests for group and pair-wise comparisons respectively.

RESULTS—A total of 470 osmolality samples were analyzed. 1) Raters had high agreement ($r=0.98$, $p<0.001$). 2) For every 0.5 tsp/oz of thickener, the osmolality increases by 30 mOsm/kg ($p<0.001$). 3) Osmolality was higher with the oatmeal (vs rice) thickening agent ($p<0.001$). 4) Vitamin and electrolyte supplement combinations increase osmolality.

CONCLUSIONS—Alteration of ready-to-feed preterm formulas may significantly increase osmolality and have unintended consequences. Caution and monitoring should be exercised with modifying ready-to-feed preterm formulas for regurgitation, rumination, GER, dysphagia, feeding

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intolerance, or emesis. This study supports the concept of achieving volume tolerance prior to further manipulation of additives.

Keywords

Infant Feeding; Thickening; Supplements; Preterm Formula; Osmolality

INTRODUCTION

Osmolality is the ratio of solutes in a given concentration of the solvent (particles dissolved in a fluid, measured in milliosmoles/kg, mOsm/kg)[1]. In utero, the fetal gastrointestinal mucosa is exposed to lower osmolality values[2]. Upon birth, infants are frequently exposed to human milk, the gold standard for infant feeding due to its benefits on immunological, gastrointestinal, and neurodevelopmental functions. Human milk is approximately 300 mOsm/kg and increases upon fortification[1,3]. When human milk is not available due to limited supply or parental preference, powdered or liquid formulas are substituted. In the acute neonatal setting, liquid or ready-to-feed formulas are standard practice to minimize infection in this high risk population due to the risk of bacterial contamination in powdered infant formulas[4]. Numerous ready-to-feed formulas are available albeit with wide variation in osmolality. As a reference, Table 1 describes the osmolality values of commonly used formulas in the neonatal setting.

Based on human milk norms and historical consensus in 1976, the American Academy of Pediatrics (AAP) Committee on Nutrition cautioned against infant feeds over 400 mOsm/L [450 mOsm/kg] without a warning statement on the label until more evidence was obtained, due to hyperosmolality and safety reasons[1,5,6] Currently, although there are no osmolality limits for preterm infants, care should be taken to not exceed the AAP threshold. Additives, such as thickeners or supplements, to small volumes of milk may significantly increase osmolality and should be avoided if possible[1,5,6].

In the convalescing preterm infant population, providers frequently supplement and modify the nutrient composition of feedings with additives to enhance caloric density and ensure proper growth and nutrition[7–11]. Additionally, modifications to the feeding thickness are frequently used to treat premature infants presenting with gastroesophageal reflux disease (GERD) or dysphagia (immature sucking ability, sucking-swallowing-breathing incoordination, aspiration, feeding intolerance)[12–23]. However, thickening feeds also comes with risks such as necrotizing enterocolitis (NEC) or infection [22–31]. Common thickening agents are rice cereal or oatmeal cereal, with the oatmeal becoming more common due to concerns of arsenic levels in rice[32,33]. However, the effect of oatmeal on osmolality in ready-to-feed preterm formula is not known.

Our aims were to examine the relationships between osmolality and common additives to ready-to-feed liquid preterm formulas. Specifically, we characterized and compared the osmolality of 1) thickener (rice vs oatmeal from 0-3 tsp/oz) or 2) liquid supplements (saline, iron, vitamin D, or multivitamins) added to ready-to-feed liquid preterm formulas (with caloric density of 22 cal/oz and 30 cal/oz). We hypothesized the osmolality of ready-to-feed preterm formula is significantly altered with thickening agents and amounts, and supplements.

MATERIALS/METHODS

Experiments were performed at The Research Institute at Nationwide Children's Hospital in Columbus, Ohio, USA by two separate testers (WH, KAH). The following materials were used based on our current NICU feeding practices: 1) ready-to-feed preterm formulas with caloric densities of 22 cal/oz (Similac® Neosure®, Abbott Laboratories, Chicago, IL) and 30 cal/oz (Similac® Special Care®, Abbott Laboratories, Chicago, IL), 2) thickening agents: rice cereal (Gerber® Single-Grain Rice Cereal, Nestle Infant Nutrition, Florham Park, NJ) or oatmeal cereal (Gerber® Single-Grain Oatmeal Cereal, Nestle Infant Nutrition, Florham Park, NJ), 3) supplements: saline (sodium chloride compounded by Nationwide Children's Hospital pharmacy at a concentration of 2.5 mEq/mL, Columbus, OH, USA), liquid ferrous sulfate (15 mg/1 mL, Rx Choice, Hi-Tech Pharmacal Co., Inc, Amityville, NY, USA), liquid vitamin D (400 IU/mL, Aqueous Vitamin D Oral Drops, Silarx Pharmaceuticals, Inc, Carmel, NY, USA) and liquid multivitamin (Enfamil Poly-Vi-Sol® with iron, Mead Johnson & Company, LLC, Evansville, IN, USA), and 4) a freezing point depression osmometer (Osmette III, Model 5010, Precision Systems Inc., Natick, MA, USA) with a measurement range of 0-2000 mOsm/kg. Samples were extracted using a 10μl pipette (Precision Systems Inc., Natick, MA, USA) with disposable tips. Prior to testing, the osmometer was calibrated using standard testing solutions of 100, 500 and 1500 mOsm/kg (Precision Systems Inc., Natick, MA, USA), and calibration retested periodically.

Sample Preparation and Osmolality Testing

Thickener recipes were formulated by adding the specified amount (0, 0.5, 1.0, 1.5, 2.0, 2.5, or 3.0 tsp/oz) of agent (rice or oatmeal) to the ready-to-feed preterm formula (22 cal/oz or 30 cal/oz) container (Figure 1). The tester used a standard measuring spoon with thickening agent leveled off, and shaking with the dominant hand for 30 seconds to mix. Measurements were taken immediately after the batch was created.

Supplements were chosen based on and AAP recommendations and current trends with preterm infants[7–11]. Supplements were tested in their pure form (no alterations) and in combination with the ready-to-feed preterm formulas. Doses were: 0.4 mL/1 fl oz formula for saline, 0.3 mL/1 fl oz formula for ferrous sulfate, 0.5 mL/1 fl oz formula for vitamin D, and 0.5 mL/1 fl oz formula for multivitamin. Combinations tested were ready-to-feed preterm formula (22 cal/oz or 30 cal/oz) plus 1) saline, 2) ferrous sulfate, 3) vitamin D, 4) multivitamin, 5) vitamin D + ferrous sulfate, 6) vitamin D + ferrous sulfate + saline, and 7) multivitamin + saline. The tester used a 1 mL syringe for doses added to the formula in a disposable nurser bottle with a lid (Similac VoluFeed, Abbott Nutrition, Columbus, Ohio) and mixed the specific combination by shaking with the dominant hand for 30 seconds to mix. Measurements were taken immediately after the batch was created. Doses were mixed in 1 fl oz (30mL) of formula which would be the equivalent of 150 mL/kg/day for a hypothetical 1.6 kg infant if they were fed every 3 hours. The NaCl dose used was 1 mEq which would be about 0.6 mEq/kg for that same sized infant.

Raters measured the osmolality of 5 individual samples from each batch created. Samples were extracted by the tester's dominant hand using the 10 μl pipette and inserted into the osmometer for a reading.

Statistical Analysis

Statistical analysis was performed using SAS v 9.3 (SAS Institute, Cary, NC). ANOVA and T-tests were used to compare between the combinations of thickener agent and formula type. T-tests were used to compare the 22 cal/oz and 30 cal/oz supplement combinations. Linear regression models were used to measure increase in osmolality per unit increase in formula. Rater agreement was tested using Pearson correlation. P-values <0.05 were considered significant.

RESULTS

Overall, there were 470 total osmolality measurements. Raters had high agreement ($r=0.98$, $p<0.001$). The osmolality values (median, range) of the ready-to-feed formula without any additives were 268 (257-276) mOsm/kg for the 22 cal/oz, and 407 (389-429) mOsm/kg for the 30 cal/oz formulas.

Effects of Cereal Thickener in Ready-to-feed Preterm Formula with Differing Caloric Densities

Each rater-1 (KAH) and rater-2 (WH) created 28 formula recipe combinations or batches with varying caloric density, thickener agents, and thickener amounts for a total of 280 osmolality measurements. Rater agreement was high ($r=0.99$, $p<0.001$). The effects of thickening agents can be observed (Table 2). Per each 0.5 tsp/oz increase in the thickening recipe, the osmolality increased by 29.9 mOsm/kg. Comparisons between the thickening agents and caloric density can be observed in Figure 2.

Effects of Supplementation

Each rater-1 (KAH) and rater-2 (EO) created 19 supplement combinations with varying caloric density and supplements for a total of 190 osmolality measurements ($r=0.99$, $p<0.0001$). Osmolality was not measured for all supplements in their pure form (0.4 mL saline, 0.3 mL ferrous sulfate, 0.5 mL vitamin D, or 0.5 mL multivitamin) as the freezing point was not achieved by the osmometer. The effects of combining these supplements with the 22 and 30 cal/oz formulas are shown in Figure 3.

DISCUSSION

This was a bench-tested model based on the prevailing NICU feeding practices here at Nationwide Children's Hospital, Columbus, OH. These are the same bottles and formula combinations that are commonly used at the bedside. The salient findings from this study are: 1) Cereal thickening amounts and agents added to ready-to-feed liquid preterm formulas impact osmolality and can cross the limits of AAP safety thresholds. Specifically, the thickening agent increases osmolality, and oatmeal contributed to greater osmolality compared with rice on an equi-volume basis. These changes are further compounded by agent, amount, and caloric density combinations. For example, for each 0.5 tsp/oz of rice cereal added to 22 cal/oz formula the osmolality increases by 16.7 mOsm/kg, while each 0.5 tsp/oz of oatmeal cereal to 30 cal/oz formula increases the osmolality by 45.3 mOsm/kg (Table 2). 2) Commonly used vitamin and electrolyte supplements added to ready-to-feed preterm formula can remarkably increase osmolality (Figure 3).

Consequences of thickening for dysphagia or GER management

It is known that there is high variability in feed-thickening practices, and consequences of thickeners are numerous and may include NEC, hypernatremia, malabsorption of nutrients, constipation, dehydration, delayed gastrointestinal transit, fatigue from nipple extraction, difficulty extracting liquid, decreased oral intake, or prolonged transition of oral feeding in the presence of oropharyngeal dysphagia[1,6,19,22–31,34–38]. Additionally, each 1 tsp/oz of rice cereal or oatmeal adds 5 kcal/oz, and this increased energy density alters metabolism can lead to excessive body fat deposits[19,39].

Thickeners are frequently used to treat dysphagia with the assumption that thickening decreases the flow rate, thus increasing oropharyngeal transit time to improve airway protection and oromotor control[40]. However, milk extraction is usually a problem due to the non-homogeneous mixtures or due to the nipple hole diameter which may further contribute to dysphagia. Although thickening liquids may reduce the risk of penetration-aspiration, it can increase the amount of post-swallow pharyngeal residue, which can contribute to delayed pharyngo-esophageal transit[38]. There is also the possibility of aspiration of thickened feeds which can have significant pulmonary consequences. The inherent reason for dysphagia cannot be addressed fully by adding thickener, and the risks may outweigh any potential benefits. Thickeners are also commonly used to treat GERD as they have been shown to decrease the frequency of regurgitation[41]. Another study has shown that thickened feeds reduced the height of the refluxate, but not acid GER[42]. However, current recommendations from the NASPGHAN on GER guidelines state that the overall quality of evidence for using thickened feeds to treat GERD in infants and children was low to very low[43]. They also state that visible regurgitation is improved but the impact on symptoms is not clear[43].

Despite limited evidence, thickening continues to be a common practice in NICUs and other clinical settings[22]. Thus, there is a need for developing innovative treatment strategies other than thickened feeds for complex NICU infants with dysphagia and/or GERD.

Gastrointestinal effects, potential dysmotility mechanisms and hyperosmolality

Hyperosmolar feeds can contribute to feeding intolerance in multiple ways. Increased caloric content delays gastric emptying which is mediated by osmoreceptors in the duodenum[1,44]. Similar effects were noted on small bowel motility[45]. In some studies hypertonic solutions (630 mOsm/kg) have been shown to produce pain when infused into the adult esophagus[46]. Unlike small intestine, the gastric secretions do not alter the osmolality of the ingested material, and its contents can remain hypertonic for a while[47]. Emesis and prolonged GI transit are common reflex mechanisms of feeding intolerance and hyperosmolarity of feeds is a triggering factor[20] by activating the gastric mucosal afferents and osmoreceptors[48]. On a different note, gastrointestinal stasis can cause malabsorption, bacterial overgrowth, and diarrhea, thus modifying the structure of intestinal villi and crypts; thus setting up a situation for acute or chronic inflammation with mucosal injury[49]. The effects of osmolality from modified feeds and or the alteration of physico-chemical and or spatio-temporal characteristics of gastric contents can be a contributing factor in the genesis of troublesome symptoms[50]. Thus the presence of troublesome symptoms leads to further escalation of diagnostic assessments and or therapies and therefore costs.

In the presence of persistent troublesome symptoms, we simply propose clinical examination during an oral feeding session and recording a feeding diary over a 5-day period to gather overall feeding symptoms and capabilities. Attention is needed to document the contents, frequency, timing, nipple use, posture and feeding methods, all in relation to the symptoms and underlying disease. Such simple determinations may provide insights into feeding-difficulty triggering factors which can often have simple solutions based on pathophysiology and associations.

Limitations

We have attempted to model our study design as close as possible to the actual NICU feeding practices by using the same materials and formula combinations. However, multiple limitations to this study exist. One limitation to the study is that this experiment was a bench tested model and was not performed at the infant's bedside where the feeding session was actually occurring. Testing at bedside can have technical inaccuracies; hence we performed this study in the lab setting. Other factors that may impact the osmolality such as consistency in preparation, caregiver variability in regards to prescription, dwell time, thickener amounts, mixing, and how feeds and supplements are administered. Additionally, adding thickeners to human milk is a unique challenge due to breast milk composition and enzymatic (amylase) digestion[3]. We limited our study to 2 ready-to-feed preterm formulas from one brand with the lowest and highest caloric densities used for preterm infants in order to show the range of osmolality from 22 to 30 calorie formula. Further studies are needed to evaluate the effects of varying practices at the bedside.

Clinical implications while considering additives to infant feedings

In the NICU setting, there are numerous provider recommendations and parental/nursing practices when preparing feeds. However, we have shown the use of additives significantly increases osmolality, which may be counter-productive to other gastrointestinal mechanisms.

With thickening, practices vary widely among therapists and providers regarding consistency, thickening agent, and preparation[22]. When thickening is still a strong consideration for Dysphagia/GER management, the ready-to-feed thickened formulas may be a safer alternative as the mixture is more homogeneous and has been vigorously tested, and passes FDA regulations including osmolality thresholds. Other alternative treatment strategies may include modifications to nipple flow or feeding volume, pacing while feeding, or appropriate positioning of the infant during feeding.

With the administration of oral medications, there are also many nursing practice scenarios. With tube feeding: medications can be administered directly into the gavage tube prior to the feed, after the feed, mixed with part of the feed, or mixed in the entire feed. With oral feeding: medications may be given on their own, mixed with a small volume of the feed, or mixed in the entire feed. Regardless, if medications are given without feeds or mixed with a small volume of feed, the osmolality could be dangerously high. Although we did not test combinations of medications mixed with different volumes of breast milk or formula, all medications in isolation exceeded the osmometer freezing point limit of 2000 mOsm/kg. Therefore, we recommend mixing medications in the entire volume of feed, or dividing doses across multiple feeding sessions mixed with feeds to decrease the osmolality as much as possible.

Summary and Conclusions

The relationship between osmolality and modifications to the preterm formulas in relevance to the AAP safety threshold for osmolality are highlighted using a bench-tested experimental model. This is because the prescription of supplements, increasing caloric density and restricted fluid intakes are commonly adopted strategies for troublesome symptoms in preterm infants with bronchopulmonary dysplasia, gastroesophageal reflux and or dysphagia. Additives to the formulas significantly impact the product osmolality, some exceeding the safety threshold levels. These factors need closer scrutiny when feeding difficulties persist. Addition of thickeners for preterm infants is not advisable owing to possibility of contamination and inadequate sterility and shorter shelf life. Most importantly, the AAP has advocated against the use of thickening agents for high risk preterm infants under 44 weeks postmenstrual age[23]. We strongly advocate that only infant formulas produced under supervision according to the AAP recommendations should be used without adding thickening agents. Such an approach will not need changes to bottles and nipples, thus sterility and milk extraction rates are not compromised. On the other hand, if additives such as electrolytes and medications are to be administered, then, they could be given in divided doses so that osmolarity is not all concentrated in one aliquot. Thus, osmolality is distributed over multiple feed preparations. If in any given situation, thickeners and supplements are added, then providers and parents need to be aware of the risks and monitor the patient closely for signs and symptoms. Due to unintended consequences of hyperosmolality, this study supports the concept of achieving volume tolerance prior to further manipulation of additives to feeds.

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ABBREVIATIONS

AAP	American Academy of Pediatrics
PMA	Post-menstrual age
GER	Gastroesophageal reflux

NEC	Necrotizing enterocolitis
GERD	Gastroesophageal reflux disease

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CLINICAL RELEVANCY STATEMENT

The American Academy of Pediatrics (AAP) Committee on Nutrition cautions against infant feedings over 400 mOsm/liter [450 mOsm/kg] based on human milk norms and historical consensus observed at the time. Formula modifications (increasing caloric density, restricting fluid volume, thickening feeds, and/or prescribing supplements) are common strategies for preterm infants with bronchopulmonary dysplasia, gastroesophageal reflux, and/or dysphagia to improve growth and minimize troublesome symptoms. However, caution should be exercised as additives (thickening agents or supplements) to ready-to-feed preterm formula significantly impact product osmolality and may exceed the AAP limit. When making modifications to ready-to feed liquid preterm formulas, parents and providers should be aware of these risks and monitor the patient closely for signs and symptoms related to hyperosmolality.

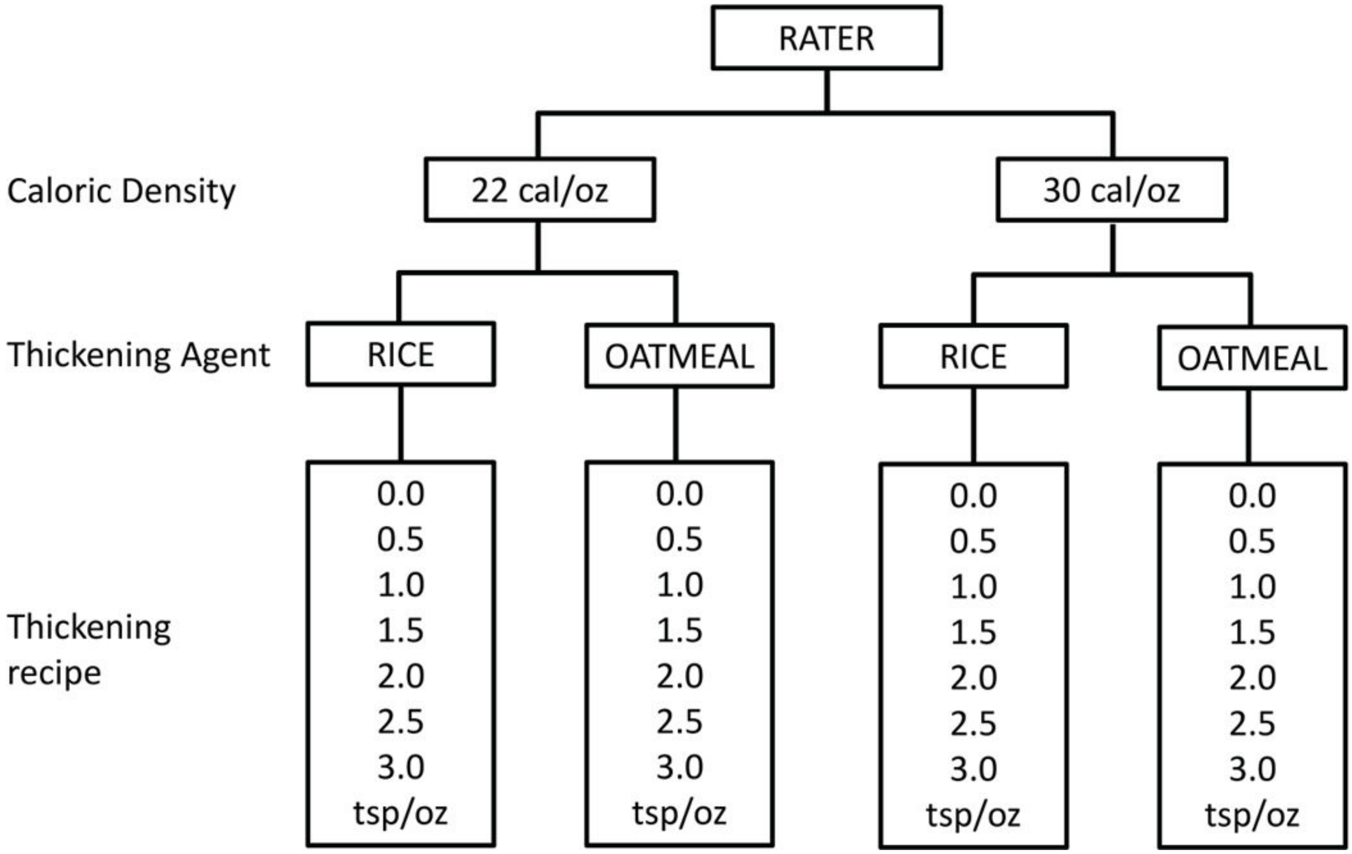

Figure 1. Study Design

Each rater (WH and KAH) tested 5 samples from 28 different formula combinations. Variations included preterm formulas with different caloric densities, cereal thickening agents, and thickening amounts.

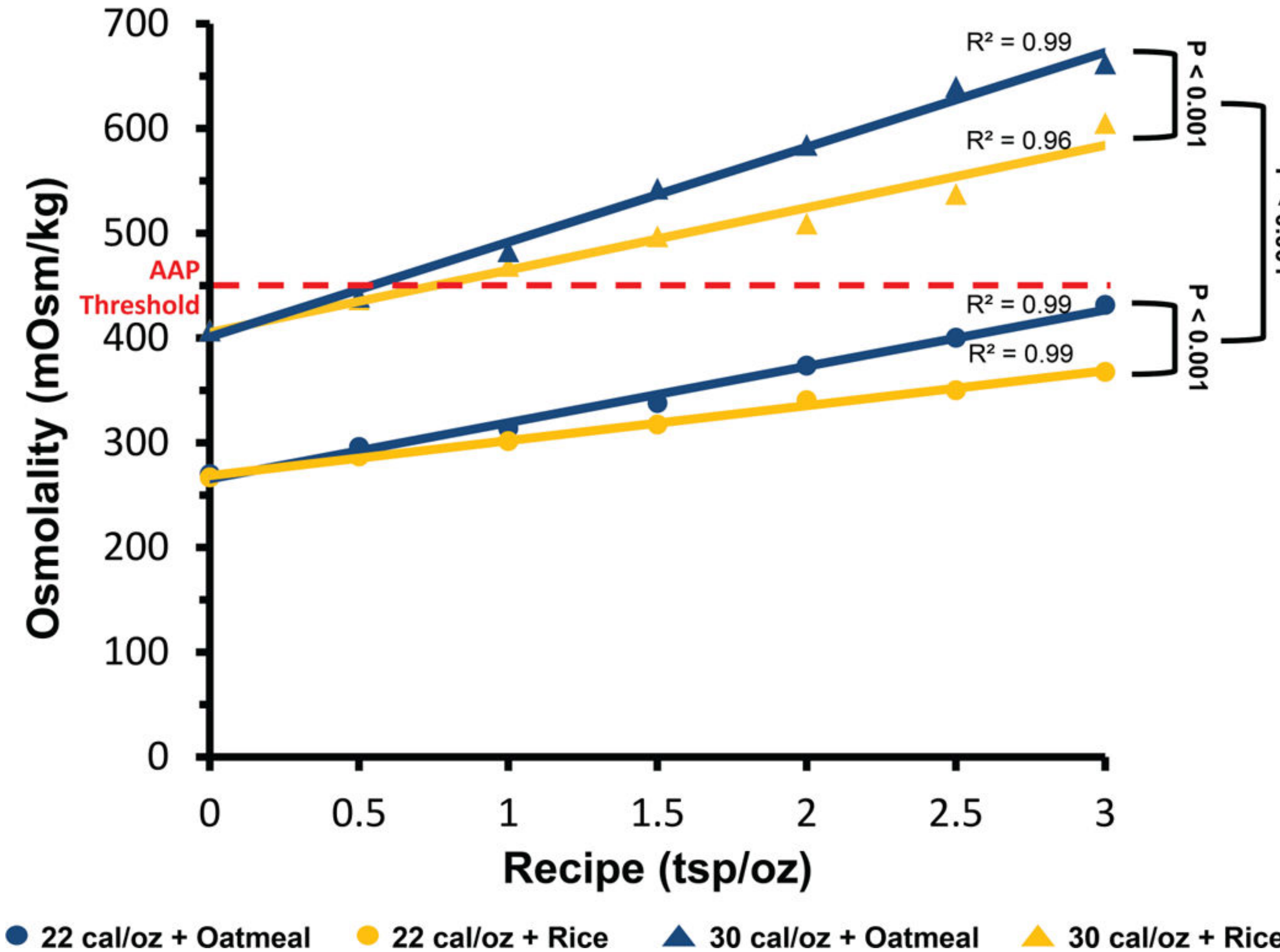

Figure 2. Effects of formula caloric density, thickening agent, and thickening amount on osmolality

AAP, American Academy of Pediatrics. Formula type- 30 cal/oz had significantly increased osmolality vs 22 cal/oz. Thickener type- The oatmeal thickener had increased osmolality vs the rice thickener. Thickener amount (recipe) - As the thickening agent recipe increases, the osmolality increases. Also note the 30 cal/oz formula crosses the AAP guidelines threshold for safe feeding.

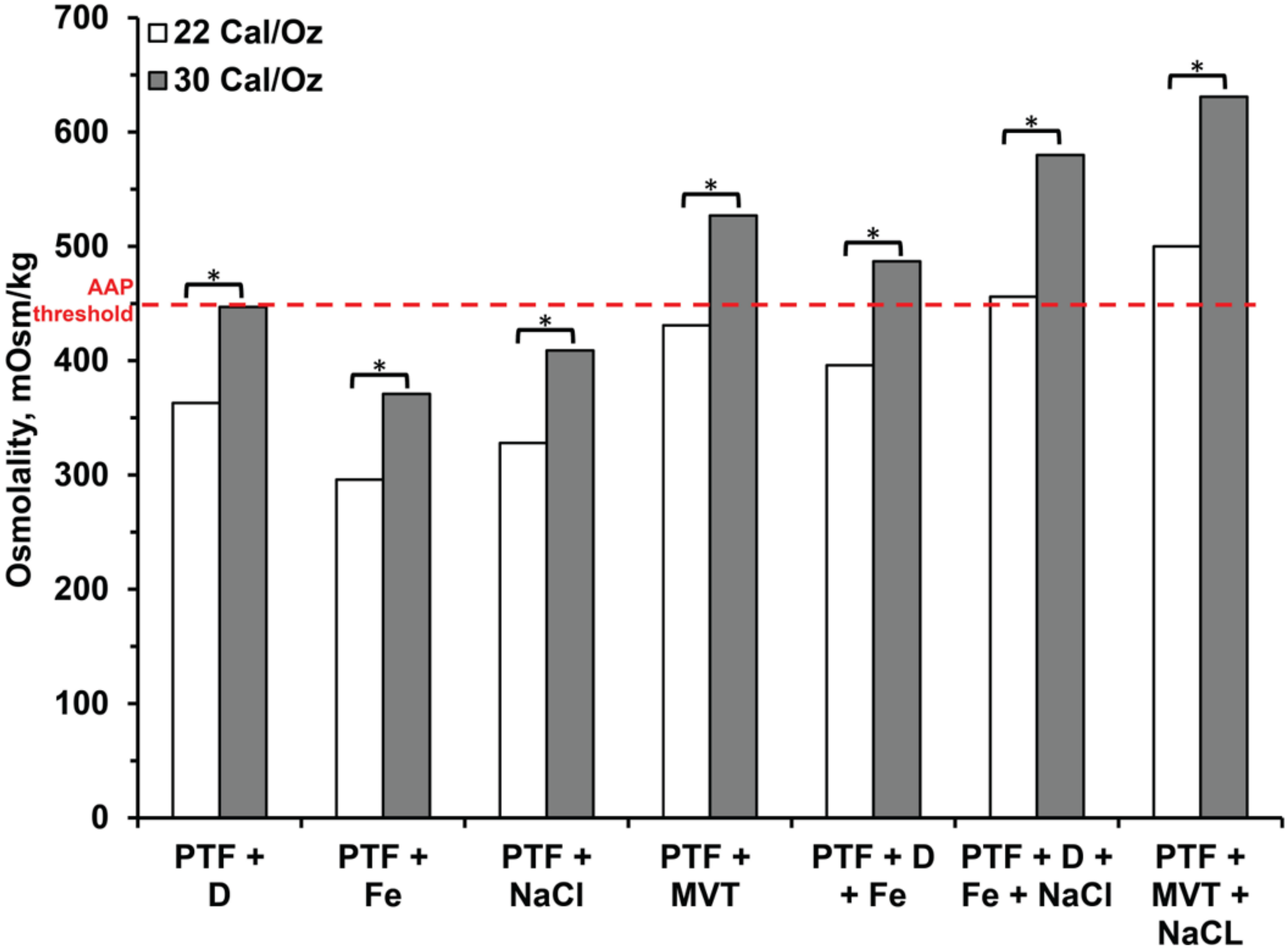

Figure 3. Effects of supplementation added to ready-to-feed preterm formula on osmolality

AAP, American Academy of Pediatrics; D, vitamin D; Fe, ferrous sulfate; MVT, multivitamin; NaCl, saline, PTF; ready-to-feed preterm formula. The red line represents the AAP threshold. Note the combinations of supplements that cross the AAP threshold. Also note the osmolality is significantly increased for all supplement combinations added to the 30 cal/oz density.

Table 1

Manufacturer Reported Osmolality of Common Fortifiers and Ready-to-feed Formulas*.

Formula Types	Caloric Density (Cal/fl oz)	Osmolality (mOsm/kg)
Preterm Human Milk (PHM)	20	290
PHM + Similac® Human Milk Fortifier Concentrated Liquid (1 pkt: 25 mL)	24	385
PHM + Similac® Human Milk Fortifier Hydrolyzed Protein Concentrated Liquid (1 pkt: 25 mL)	24	450
PHM + Enfamil® Human Milk Fortifier Acidified Liquid (1 vial : 25 mL)	24	326
Preterm Infant Formula		
Similac® Special Care® 20	20	235
Enfamil® Premature 20 Cal	20	260
Similac® Special Care® 24	24	280
Enfamil® Premature 24 Cal	24	320
Similac® Special Care® 24 High Protein	24	280
Enfamil® Premature 24 Cal High Protein	24	300
Similac® Special Care® 30	30	325
Enfamil® Premature 30 Cal	30	320
Preterm Infant Post-Discharge Formula		
Similac® Neosure®	22	250
Enfamil® EnfaCare®	22	230
Term Infant Formula		
Similac® Pro-Advance™	19	310
Enfamil® Newborn	20	300
Enfamil® Infant	20	300
Similac® Pro-Sensitive™	19	200
Enfamil® Gentlease®	20	220
Enfamil® Reguline™	20	260
Similac® for Spit-Up	19	180
Enfamil® A.R.™	20	240
Hypoallergenic Formula		
Similac® Alimentum®	20	370
Enfamil® Nutramigen®	20	320
Enfamil® Pregestimil®	20	290

*Data from Abbott Nutrition Laboratories (https://static.abbottnutrition.com/cms-prod/abbottnutrition-2016.com/img/simlac-productguide.pdf) and MeadJohnson Nutrition (https://www.meadjohnson.com/pediatrics/us-en/sites/hcp-usa/files/LB6-ProductGuide-REV-10-14-lo.pdf). PHM, Preterm Human Milk.

Table 2

Effect of Thickening Agent in 0.5 tsp/oz Increments (from 0 – 3 tsp/oz) on Ready-to-Feed Preterm Formula Osmolality (mOsm/kg)

Thickening Agent	**Slope ß ± SE**	**Slope p-value**
Any thickener	29.9 ± 2.3	<0.001
22 cal/oz + Rice *	16.7 ± 0.5	<0.001
22 cal/oz + Oatmeal	26.9 ± 1.5	<0.001
30 cal/oz + Rice	29.8 ± 2.3	<0.001
30 cal/oz + Oatmeal	45.3 ± 4.2	<0.001

* Interpretation example: In the 22 cal/oz ready-made preterm formula, the osmolality increases by 16.7 mOsm/kg for every 0.5 tsp/oz of rice cereal additive.