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Review Article

Thickened infant formula: What to know

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A B S T R A C T

Objectives: This study aimed to provide an overview of the characteristics of thickened formulas to aid health care providers manage infants with regurgitations.
Methods: The indications, properties, and efficacy of different thickening agents and thickened formulas on regurgitation and gastroesophageal reflux in infants were reviewed. PubMed and the Cochrane database were searched up to December 2016.
Results: Based on the literature review, thickened formulas reduce regurgitation, may improve reflux-associated symptoms, and increase weight gain. However, clinical efficacy is related to the characteristics of the formula and of the infant. Commercial thickened formulas are preferred over the supplementation of standard formulas with thickener because of the better viscosity, digestibility, and nutritional balance. Rice and corn starch, carob bean gum, and soy bean polysaccharides are available as thickening agents. Hydrolyzed formulas have recently shown promising additional benefit.
Conclusions: Thickened formulas reduce the frequency and severity of regurgitation and are indicated in formula-fed infants with persisting symptoms despite reassurance and appropriate feeding volume intake.

Introduction

Infantile regurgitation is a common, physiological, transient manifestation of gastroesophageal reflux (GER) that does not require treatment but only parental reassurance and dietary management [1–4]. Thickened formulas (TFs) are indicated in infants who are formula-fed and have persistent regurgitation and poor weight gain [1,3] or marked distress [4] instead of overprescribed acid inhibitors [5–7].

Different antiregurgitation formulas (AR-F) are available on the market [8] and frequently used [9]. However, the advantages and disadvantages with regard to cost as well as nutritional and gastrointestinal effects should be carefully balanced [10]. The aim of this narrative review was to provide an updated overview of the rationale for and characteristics of AR-F to aid health care providers manage infants with regurgitation.

Conflicts of interest: S.S. has participated as a consultant and/or speaker for Danone-Nutricia, Deca, IMS-Health, Menarini, Nestlè. F.S. has participated as a consultant and/or speaker for Menarini, Danone, Nutricia, HiPP GmbH, Nestlè, and BioGaia. A.S. has participated as a clinical investigator, and/or advisory board member, and/or consultant, and/or speaker for D.M.G., Valeas, Angelini, Miltè Menarini, Danone, Nestle'. M.A.B. has participated as a clinical investigator, and/or advisory board member, and/or consultant, and/or speaker for Astrazeneca, Norgine, Coloplast, Zeria, Sucampo, Shire, Mead Johnson, Danone, Abbott, Frieslandcampina, Novalac, and Sensus. Y.V. has participated as a clinical investigator, and/or advisory board member, and/or consultant, and/or speaker for Abbott Nutrition, Biogaia, Biocodex, Danone, Hero, Nestle Nutrition Institute, Nutricia, Mead Johnson, Merck, Orafti, Phacobel, Sari Husada, United Pharmaceuticals, Wyeth, and Yakult. The other authors did not report any conflicts of interest. All the referenced manufacturers and companies had no input or involvement in any aspect of this review or any other previous reviews carried out by the authors. There are no other interests to declare.

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Materials and methods

We searched PubMed up to December 2016 using the following keywords: "antiregurgitation" OR "thickened formula" OR "thickening agents" AND "regurgitation" OR "gastro (o) esophageal reflux" OR "GER" OR "GOR" and restricted the search to publications on humans and infants. Intervention trials, reviews, guidelines, meta-analyses, and reference lists of these studies were considered.

Results

Rationale for antiregurgitation formulas

Despite the spontaneous remission in most infants, voluminous and persistent regurgitation is a frequent reason for parental concern, formula changes, and feeding distress [9,11–15]. The rationale for AR-F is based on the addition of a thickening agent (e.g., cereal starch or carob/locust bean gum flours) to increases its viscosity [8,10,16].

Viscosity and digestibility of antiregurgitation formulas

In vitro models have demonstrated that carob seed flour is the thickening agent with the highest viscosity and particularly in predominant casein formula [17,18]. The digestibility of carbohydrates that are added to infant formula has long been a matter of concern [19–22]. To convert starch to glucose, six enzymes (two salivary and pancreatic alpha-amylases, sucrase-isomaltases, and maltase-glucoamylases) are involved [23]. Sucrase-isomaltases and maltase-glucoamylases are the key enzymes that digest starch in young infants before pancreatic alpha-amylase secretion matures [24].

The starch digestion rate is correlated to its chemical structure and determined by the different botanic sources, concentrations, food processing techniques, and the age of the infant [23,25]. The crystalline structures that are observed in x-ray diffractions classify starch granules into Type A (e.g., wheat, normal maize, and rice), B (e.g., potato and green banana), and C (e.g., beans and seeds) on the basis of high, low, or intermediate susceptibility to hydrolysis [23]. The increasing resistance to hydrolysis from waxy maize to tapioca, sorghum, ordinary corn, wheat, rice, potato, and high-amylose corn has been attributed to both the ratio of amylose and the surface pores that facilitate the access of enzymes [25]. However, cooking and gelatinization change the granular structure of the native starch and decrease the resistance to enzymatic attack and the differences between the varieties [22–24].

In infants, wheat, tapioca, corn, rice, or potato starch that is cooked for 10 min in water are all digested and efficiently (>98%) absorbed when the concentration is 1.6 g to 1.9 g/100 mL at 1 mo and 3.1 g to 3.5 g/100 mL at 3 mo of age. However, at 5 g to 6 g/100 mL, fermentative diarrhea has been reported in 2 of 5 infants who were tested [24]. An expert group from the European Society for Paediatric Gastroenterology Hepatology and Nutrition recommended that (precooked or gelatinized) starches be added to the infant formula up to 2 g/100 mL [26].

Locust bean gum is a different thickening agent that is obtained from the endosperm seed of the locust/carob tree (Ceratonia siliqua [L.] Taub) of the plant family of Leguminosae, which consists of high molecular weight polysaccharides (50 000–3 000 000 dalton) of which at least 75% are galactomannans. Locust bean gum is coded as INS/E 410 in accordance with food additive numbering and commonly used in various food items for thickening, stabilizing, emulsifying, or gelling properties. Locust bean gum is resistant to human digestive enzymes and excreted unchanged in the feces or fermented by the gut microbiota [27].

(Home) thickening compared with antiregurgitation formulas

Many parents use AR-F or add thickening agents to standard formula (SF) to reduce infants' regurgitation and/or vomiting, improve night sleep, and decrease failure to thrive [9]. Commercial AR-F has a controlled composition with thickening components less than 2 g/100 mL for starch and 1 g/100 mL for carob bean gum, and a caloric content that is similar to SF. Moreover, pretreated (e.g., gelatinized) starch presents a low viscosity that allows for an easy flow through a standard nipple and thickens only in the stomach when in contact with acid potential hydrogen (pH) [28]. In contrast, carob bean gum maintains a constant viscosity because it is not split by salivary amylase and not influenced by pH.

Home-brewed thickened SF are often prepared by parents because of the limited availability or higher (1.5–2 times) cost of AR-F but the effects of home-thickened feeding may differ from AR-F due to a heterogeneous composition. One study reported that a heaping tablespoon added a quantity of starch between 3.6 g and 4.6 g [29], which was well above the regulatory limit for starch (2 g/100 mL) in AR-F [26,30], increased the osmolarity of the formula, and provided an extra caloric intake of 20 calories per 100 mL. Moreover, overthickening of formula results in a higher viscosity that needs an increased sucking effort and/or a crosscut nipple to flow through [17,18,31–34]. Hence, parents should receive clear advice about thickening modalities in case of home-brewed TFs.

In a prospective, case-controlled study of 100 infants, regurgitation disappeared after 3 mo in a slightly higher percentage of infants (52% vs. 40%) who were fed AR-F versus a homemade, cornstarch TF [35].

Clinical effects of antiregurgitation formulas

Gastric emptying

A thickening agent (particularly a fiber) may delay gastric emptying and potentially worsen postprandial GER and symptoms but its effect depends on viscosity and concentration [36] as well as protein content. Antral cross-sectional areas that were measured by ultrasound were not significantly different in 47, 20, and 20 infants who frequently regurgitated and were fed a locust bean gum AR-F or SF (0.35 g/100 mL; 0.4 g/100 mL; and 0.6 g/100 mL, respectively). However, antral cross-sectional areas were greater in another trial that used a different formula (HL-450) in 39 infants [37–40].

In 63 of 81 infants who regurgitated, corn starch AR-F had a gastric emptying time as measured by technetium 99 m milk scintigraphy that was similar to SF [41] and faster than a 25% strengthened formula [42].

In 90 healthy infants, the gastric residual content 2 h after feeding was the smallest with whey-hydrolyzed formula (HF) and breast milk and progressively higher with acidified, whey-predominant, casein, follow-up formula and whole cow's milk [43]. In 28 infants with GER, scintigraphy showed that gastric emptying significantly increased after feeding infants the same volume and calories of a casein-predominant, soy, or whey-partial HF (pHF) [44].

In a crossover, randomized, controlled trial (RCT) that performed 13 C-octanoic acid breath tests in 20 healthy newborns, extensive HF (eHF) significantly accelerated the gastric emptying compared with pHF and intact proteins SF [45].

In a 2-wk, crossover, double-blind trial, 12 infants who frequently cried and regurgitated showed significantly reduced symptoms and gastric emptying time (as assessed by 13-C acetate