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Use of Thickeners Versus Hydrolysed Formulae in the Management of Gastro-oesophageal Reflux Disease in Infants: A Systematic Review

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Abstract *Background and objective:* Regurgitation symptoms in many GERD infants might affect their nutrition status. This review compares thickeners and hydrolysis formula with cow's milk in the evolution of regurgitation, weight and stool consistency changes in infants with GERD based on currently available evidence, as the benefits of using AR-F in infants with GERD is still contradictory. There is also evidence that hydrolysed formula plays a crucial role in regulating reflux. *Methods:* The search terms 'thickener formula/pre-thickener' OR 'cow's milk allergy/hydrolysis formula' AND 'gastro-oesophageal reflux disease (GERD)/regurgitations' were used to search the electronic databases of NUsearch, Google Scholar, ScienceDirect and PubMed for randomised controlled trials (RCTs) published between 2005 and 2020 for thickened formula and 2010-2020 for hydrolysed formula that involved infants (<13 months) of both sexes who were diagnosed or at risk of regurgitation. *Results:* Seven eligible RCTs met the inclusion criteria. Thickened whey protein formula significantly reduced daily regurgitations by up to 7.7 episodes, while the results were insignificant in thickened or normal extensive hydrolysed casein milk (-4.2 vs -3, respectively). However, rice thickener significantly reduced regurgitation and weight gain by 1.261 kg in two months. An insignificant difference in stool consistency was found in most trials (P >0.05), except for the thickened casein formula as 64% of participants had normal stool density (P= 0.45). *Conclusion:* This study identified that using either thickening formula or extensively hydrolysed formula significantly reduced the number of regurgitations per day (mean range: -1.2 to -7.1; P<0.05). It does, however, seem that hydrolysed whey formula thickened with hydrolysed rice can support weight gain in failure to thrive infants.

Keywords: *GERD, regurgitation, weight gain, stool density*

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1. Introduction

Gastroesophageal reflux (GER) is defined as the normal phenomenon of passing gastric contents from the stomach to the oesophagus [1]. However, if this reflex does not disappear after the first year and affects the intake of infants or causes health problems, it is classified as *gastroesophageal reflux disease (GERD)* [2]. GERD's reported prevalence in patients of all ages worldwide is increasing, but it is nevertheless far less common than GER [3]. Population-based studies suggest reflux disorders are not as common in Eastern Asia, where the prevalence is 8.5%, compared with Western Europe and North America (10% to 20%) [4,5]. Some patients are highly likely to have GERD, such as those with neurologic impairment, obesity, congenital oesophageal disease, cystic fibrosis and some genetic diseases, especially down syndrome [2]. This is because of the potential weakness of the oesophageal sphincter [6] or highly contracting abdominal muscles [7]. However, while infants with frequent episodes of emesis do not necessarily suffer from GERD, they may have an allergy to cow's milk or have been overfed [2]. Also, half of prematurely born infants have reported at least one regurgitation per day [2,8].

Symptoms in infants with GERD can include vomiting or regurgitation, feeding refusal, poor weight gain, dysphagia, painful swallowing and arching of the back during feeding [9]. GERD symptoms can also be extraoesophageal; for example, in the respiratory system resulting in coughing and wheezing [10] or in the mouth cavity resulting in dental erosion pharyngitis, sinusitis and recurrent otitis media. Extensive and prolonged regurgitation can lead to insufficient nutrient intake, failure to thrive and an increased risk of health problems such as esophagitis, peptic stricture, Barrett oesophagus and adenocarcinoma [11,12,13]. Therefore, it was vital to search for the most appropriate and non-invasive management tools to prevent the possibility of these health complications.

GERD management: Rosen *et al*. [2] argue that infants with apparent GERD symptoms can be treated with both pharmacological and non-pharmacological intervention. Non-pharmacological treatment involves a combination of modifying positions during and after feeding, feeding volume, frequency and type of milk [8]. In contrast, there is a lack of evidence for GERD drug treatment [8] as there is a lack of diagnostic tests [2,14]. Thus, non-pharmacological strategies are still the first-line therapy to manage GERD [15] as it is highly possible to reduce the use of unnecessary medications and save more money through utilising anti- regurgitation feeding (AR-F) [16].

The impact of milk on GERD infants: The fundamental mechanism in GERD feeding intervention is to thicken the meal to restrain stomach content emission after a feed [16]. Therefore, thickened formula has been the subject of research since the 1980s [17,18]. There is also another mechanism theory to reduce controlled emesis episodes, which is fasting the empty gastric period [19]. However, each technique has positive and negative sides. The AR-F is higher in calorie than the standard formula as one tablespoon of rice cereal per ounce increases the energy density by 170% [8]. Hydrolysed formula has similar calories to cow's milk formula, but the protein is degrading [20]. Although this is more suitable when infants present with failure to thrive [21], restricting feed volumes and persistence may be used to manage undesirable weight gain (ibid). AR-F might decrease the absorption of nutrients, such as fat and carbohydrates and the bioavailability of iron, calcium, copper and zinc is also reduced [21,22]. Some indigestible thickener agents, such as carob bean gum, can lead to diarrhoea and allergy, while rice-thickened feeds may increase coughing [21].

Generally, the evidence regarding the benefits of AR-F is still contradictory [23] but there is evidence that hydrolysed formula plays a crucial role in regulating reflux in allergy patients [24]. This review aims to compare the use of thickeners and hydrolysis formula with regular milk in the evolution of regurgitation, weight and stool consistency changes in infants with GERD based on currently available evidence. However, one of the most significant challenges is the significant difference in GERD classification with several regurgitations per day and the variety of reflux aetiology. Additionally, it was not easy to compare the variety of thickener agents with the concentration of the formula.

Rationale: According to the latest updates from the North American Society for Paediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) and the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) guidelines (2018), thickening the feed is the first-line approach to treat GERD in infants and young children but the evidence is weak [2]. However, the National Institute for Health and Care Excellence [25] recommend a hydrolysis formula if the patient regurgitates or vomits without knowing the cause or has been diagnosed with a cow's milk allergy.

Many reviews studied the effect of thickening/pre-thickening feeding in regurgitation [26,27]. Huang *et al*. (2002) did not find inference; therefore, their research did not meet the requirement. Kwok *et al*. [27] produced moderate evidence that feed thickeners must be considered in infants with GERD to reduce regurgitation by two episodes per day. However, they were unable to assess the superior AR-F for the preterm infant with gastric emission. More recently, Duncan *et al*. [28] evaluated a variety of thickener risks and benefits in paediatric patients with GERD. They concluded that AR-F has some side effects but with continuous follow-up, patients will tolerate the formula and symptoms will improve sufficiently. Regarding hydrolysed formula, only one systemic review has compared various types of protein and grades of hydrolysation in gastric emptying and regurgitation in children [24]. This review is different from other reviews in that it analysed and compared both thickening and hydrolysed protein to find out which one was more superior in treating regurgitation.

2. Research Methodology

Moher *et al*. [29] recommended using the PRISMA flow chart to point out evidence-based search guidelines in the permeated context of a systematic review meta-analysis. Therefore, the official PRISMA flow chart was used in this systematic review to enable reliable, focused and transparent reporting, interpretation and synthesis.

Review question: This review compares the evolution of regurgitation, weight and stool consistency changes when feeding thickener or hydrolysis formula to infants. The review uses currently available RCT studies as evidence.

Search strategy: Universal and exceptional systemic reviews were conducted on NUsearch, Google Scholar, PubMed and ScienceDirect using the search terms 'thickener formula/pre-thickener' OR 'cow's milk allergy/hydrolysis formula' AND 'gastroesophageal reflux disease (GERD)/regurgitations.' Publication dates were restricted to 2005-2020 for thickener formula and 2010-2020 for hydrolysed formula. The difference in years results from not having enough available research to conduct a fair comparison between the two formulas. The results were filtered using open access to English language articles. Furthermore, references in other studies were reviewed to identify any additional studies. The last search on thickener formula was published by January 2008 and April 2013 for hydrolysis formula.

Inclusion criteria and study selection: The primary criterion for searching the selected database was a randomised control trial involving infants of both sexes who were less than one year old. They mainly assessed the evolution of regurgitations as well as collecting weight and stool consistency changes within the study analyses. The publication dates and titles of studies were double-checked to ensure they met the research criteria. Subsequently, the abstract sections were screened against inclusion and exclusion criteria. Finally, the full-text versions of papers that met the inclusion criteria were reviewed. Appendix 1 shows the study's acceptance criteria in more detail.

Quality and evidence-level assessment: The Cochrane risk bias tool was used to evaluate the quality of eligible RCTs [30]. This tool assessed the eligible trials for sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome

assessment, incomplete outcome data, selective outcome reporting and other sources of bias. The evaluation was conducted twice for each study. The risk of bias graph envisaged the risk bias quality of the eligible trials into three levels: high, low and unclear risk of bias.

Data analysis and subgroup analysis: The studies were selected depending on the amount of extract data. The summary table used to collect the outcome data from the source was observed using therapeutic milk (thickened or hydrolysing formula) in infants with GERD or regurgitation. The evolution of daily regurgitations was measured. Secondary data gathered three possible outcomes: (1) the gathering weight evolution date; (2) the mean percentage of participants with formed to soft stools (reasonable constancy). Standard deviation (±SD) was difficult to conduct in the summary table, as most of the evolution dates were manually calculated. All trials were compared by ANCOVA test to the mean of the outcomes between the groups, then the result was compared with the confidence interval (95%).

3. Results

Search results: In the first stage of PRISMA, the result was eight-seven. The titles and publication dates were double-checked to ensure they met the initial eligibility criteria (n=36). Subsequently, the abstracts were screened to check if they were relevant to the research questions. A total of 16 available articles were identified and after careful review, four RCTs for thickening formula and three RCTs for hydrolysed formula were used. Figure 1 shows the excluded studies in the PRISMA flow diagram in various stages.

Quality assessment of eligible trials: Figure 2 shows the result of the Cochrane risk bias tool in the eight eligible studies. Four trials were classified as having a low risk of bias, while two were classified as having an unclear bias and one was classified high risk. The rationale underpinning the risk of the bias assessment process is reported in Appendix 2.

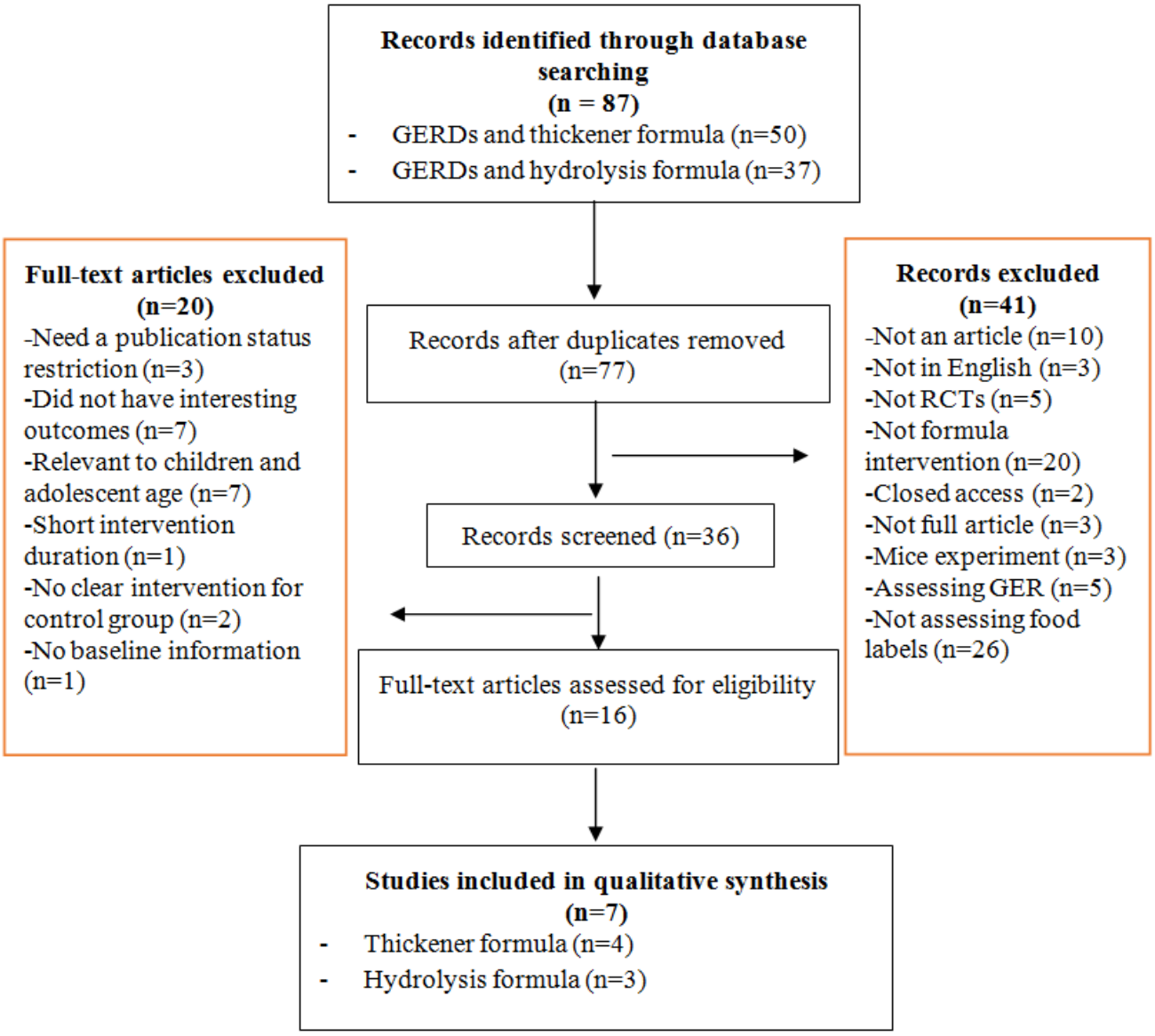

Figure 1. PRISMA flow diagram in the literature search process employed to identify articles that meet the inclusion criteria for this systematic review

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome data (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias	Interpretation risk of bias
(Ostrom *et al*., 2006) [31]	√	√	√	√	√	√	√	**Low**
(Chao and Vandenplas, 2007) [32]	-	X	X	X	√	√	√	**Unclear**
(Miyazawa *et al*., 2007) [33]	-	-	X	X	-	-	√	**High**
(Vandenplas *et al*., 2013) [34]	-	-	√	-	√	X	√	**Unclear**
(Vandenplas *et al*., 2014) [35]	√	√	√	√	√	X	√	**Low**
(Ummarino *et al*., 2015) [36]	-	√	X	X	√	√	√	**Low**
(Indrio *et al*., 2017) [37]	-	√	√	√	√	√	√	**Low**

Key: (√) low risk, (X) high risk, and (-) Unclear

Figure 2. The results of the studies included in the Cochrane risk bias tool

Included trials: Trials were conducted in America [31], Taiwan [32] and Japan [33]. Vandenplas *et al*. [35] conducted the only trial across countries (Belgium, Greece, Kuwait, Lebanon, and Slovenia). The remaining trials were carried out in France [34] and Italy [36,37].

Population characteristics: A total of 541 infants participated in the included RCTs and the sample sizes ranged from 20 to 115. The study duration was from two to eight weeks and the mean age of the participants was 2.6 months. Four RCTs had equal gender distribution except for Vandenplas *et al*. [34], who had significant variations concerning the number of boys and girls (70 and 45, respectively). Three trials did not present the gender ratio, but the differences were insignificant [31,32,37]. Additionally, the baseline weight for infants between groups had nonsignificant differences (P<0.05). More information about the study characteristics is provided in Table 1.

Five trials included a thickening formula that was given to full-term infants presenting with GERD symptoms or abnormal oesophageal pH examination (n = 397). Two studies involved patients diagnosed or at risk of cow's milk allergy who had excessive regurgitation (n = 144) [35,37]. It was unclear in two studies if premature infants were included [32,35], while two trials were ambiguous about whether breast-fed babies were included or excluded [31,33]. Generally, infants with complicated regurgitations (e.g., haematemesis, melena), other conditions associated with vomiting or previous treatment with therapeutic milk were excluded. In some trials, the small-for-gestational-age at birth, GERD patients with severe complications or those using antireflux medication were excluded. For more details, see Table 2.

Table 1. Summary of eligible studies characteristics

Reference	Mean age (months)	Sample size (n)	Gender M/F	Mean weight Int vs Con (kg) ± SD	Mean feeding ±SD Int vs Con -Volume (ml/d) - Frequency (n/d)
(Ostrom *et al*., 2006) [31]	0.63	135	N/A	N/A	- 743.96 ±18.72 vs 726.96 ±14.82 - 7.8 ±0.2 vs 7.8 ±0.2
(Chao and Vandenplas, 2007) [32]	4.3	63	N/A	6.14 ±0.87 vs 6.13 ±0.86	- 699.45 ±140.9 vs 6815 ±136.3 - 6.29 ±0.97 vs 6.31 ±0.99
(Miyazawa *et al*., 2007) [33]	1.1	20	8/12	N/A	N/A
(Vandenplas *et al*., 2013) [34]	2.5	115	70/45*	±1.08 vs 5.18 ±0.98	-819.5 ±1.015 vs 851.5 ±0.895 N/A
(Vandenplas *et al*., 2014) [35]	2.9	72	36/36	3.1 ±0.6 vs 3.2 ±0.4	N/A
(Ummarino *et al*., 2015) [36]	5	64	35/29	N/A	N/A
(Indrio *et al*., 2017) [37]	2	72	N/A	5.59 ±0.63 vs 6.28 ±0.39	N/A

n: number; M: male, F: female; kg: kilogram, SD: standard division; ml: millilitre, d: day
Int: Intervention group; Con: Control group
*Statistical significance difference in the participants at P<0.05
Note: All trials had a nonsignificant difference between groups in all baseline characteristics

Table 2. Study exclusion criteria in eight RCTs

Author (year)	Ostrom *et al.* (2006)	Chao and Vandenplas (2007)	Miyazawa *et al.* (2007)	Vandenplas *et al.* (2013)	Vandenplas *et al.* (2014)	Ummarino *et al.* (2015)	Indrio, *et al.* (2017)
Premature	√	-	√	√	-	√	√
Small-for-gestational-age at birth	√	-	√	√	-	-	-
Breast feeding	-	√	-	√	√	√	√
Already started the special milk before trial	-	-	-	-	√	√	√
Other conditions associated with vomiting	√	√	√	-	-	√	√
GERD patient with severe complications	-	-	√	√	-	√	-
Using pharmacological regurgitation suppression	-	-	√	-	-	√	√
Non-singleton birth	√	-	-	-	-	-	-

(√): Mention; (-): Did not mention.

Depending on the records from parents, the criteria of the frequency of regurgitation or vomiting symptoms were as follows.

- ≥ 3 episodes of regurgitation and/or vomiting per day: Chao and Vandenplas [32], Miyazawa *et al.* [33].
- ≥ 5 episodes per day and lasting for >1 week: Vandenplas *et al*. [34].
- ≥ 5 episodes of regurgitation and/or vomiting per day: Vandenplas *et al.* [35].
- ≥ 6 episodes per day: Ostrom *et al.* [31].
- Symptoms defined according to the Questionnaire on Paediatric Gastrointestinal Symptoms—Rome III Version [QPGS-RIII], with a positive symptom score (≥ 7) or without specifying a score in their including criteria: Indrio, *et al*., [37], Ummarino *et al.* [36].

3.1. Interventions and Comparison

Intervention: Table 3 summarises the interventions, which converged into three categories.

1) Thickening formula versus standard formula groups (n = 153 vs. 149)

- Six grams of soy-fibre agent per 100 ml in soymilk as a feed thickener, [31].
- Pre-prepared AR-F, regular milk mixed with rice-cereal by one scoop for every two scoops of powder formula, [32].
- Non-hydrolysed thickening formula with 0.35 g/100 mL locust bean gum agent [33].
- Non-hydrolysed thickening formula with rice starch 14.3 g/100 ml of milk (<6 months) and 14.2 g/100 mL (>6 months) plus keeping the patients in a supine position during sleep [36].

2) Thickening hydrolysate protein formula compared to AR-F (n=58 vs. 57)

- Thickened whey hydrolysate formula (HWF) with 0.66 grams starch per 100ml along with 1.15 g/100 ml of locust bean gum [34].

3) Thickening extensive hydrolysed protein formula vs. non-thickening extensive hydrolysed protein formula (n = 71 vs. 69):

- Thickening extensively casein-based hydrolysate formula (EHCF) with pectin fibres (1.2 g/100 ml) and 0.3 gram per 100ml of the starch agent [35].
- Thickening extensive hydrolysate protein milk with starch, but the amount or type of starch was not stated [37].

Control: Standard formula without feed thickeners was used as the control in trials that used extensive hydrolysates protein formula or soy fibre, rice cereals and carob bean gum as feed thickener. Two trials used a similar formula in the intervention group, but Vandenplas *et al.* [34] utilised a nonhydrolyzed form of the thickening formula, while Vandenplas *et al.* [35] did not apply any thickener agent in the EHCF.

Co-intervention: Some studied engaged in lifestyle modification where the infant was kept in a supine position while asleep, a straightforward postprandial position for 90 minutes and then fed small and frequent meal in all groups [36]. One study used lifestyle modification in the control group [32], while peri-positioning feedings in infants were at the parents' discretion [31].

3.2. Outcomes

Primary outcome: A total of 541 participants across seven RCTs measured the evolution of regurgitations caused by the particular thickening and/or extensively hydrolysed formula during experiments conducted over two to eight weeks. As Table 3 shows, six trials reported the mean episodes of regurgitations or vomiting per day [31,32,33,34,35,37] whereas the remaining trial reported the proportion of infants without regurgitation or vomiting at the end of the intervention [36].

Three of the RCTs studied the effect of thickening hydrolyse protein milk on the evolution of gastric emission (one unclear and two low risks of bias, n = 259). Vandenplas *et al.* [34] and Indrio *et al.* [37] found a

significant decrease in regurgitation in patients fed with thickened HWF with starch and locust bean gum or pectin fibre by -7.7 and -4.8 episodes per day, respectively. However, Vandenplas *et al.* [34] conducted a pleasing regurgitation reduction in the control group fed with standard formula supplemented with locust bean gum (7.7 vs. 7.1; P<0.013). The non-thickening standard formula used by Indrio *et al.* [37] showed a little significant improvement by 2.2 regurgitations per day. In the last study on hydrolysed protein feeding, Vandenplas *et al.* [35] found a nonsignificant difference between groups (P=0.24), whether the EHCF was thickened (with pectin fibre and starch) or not; infants were controlled by three to four gastric emissions per day.

Table 3. Summary of study design, results and conclusion

Reference	Intervention method - Sample size in group (n) - Milk type and formularisation		Duration (weeks)	Evolution of outcome - Mean regurgitations (daily number) - Mean weight change (g) - Normal stool consistency (formed & soft %)	Conclusion
	Intervention	Control			
(Ostrom *et al*., 2006) [31]	(89) Soymilk with soy fibre (6 g/100 ml)	(90) Standard milk without fibre	4	• -1.2 vs -1.9 (0.029) • 960 vs 990 (>0.005) • 96.6 vs 91(>0.05)	Feeding standard milk effectively managed regurgitation while providing balanced nutrition without altering caloric distribution, as occurs with adding rice cereal to formula.
(Chao and Vandenplas, 2007) [32]	(31) Cereal-thickening milk Preparation: 1 teaspoon of cereal per 2 spoons of regular milk powder Cereal containing: Extensively hydrolysed rice (>90%), corn-starch (<5%) and a small amount of other added starches not containing gluten	(32) Standard milk (Nestle NAN 1, Nestle Nan, Vevey, Switzerland) + Placed in a postprandial upright position (90 min after each meal) and a supine position while sleeping (within 30 degrees)	8	• -2.1 vs -1.31 (<0.001) • 1261.3 vs 1121.4 (<0.001) • N/A	Treatment of regurgitation with the cereal-thickened formula results in an increased caloric intake (>25%), related to increased gain in weight and length, in comparison with the regular formula and positioning therapy.
(Miyazawa *et al*., 2007) [33]	(10) Thickening milk with locust bean gum 0.35g/100ml	(10) Standard milk	2	• -2.3 vs -5.2 (0.00048) • No significant difference • N/A	Thickening milk decreased the number of regurgitation episodes without affecting gastric emptying delay in very young infants with recurrent vomiting.
(Vandenplas *et al.*, 2013) [34]	(58) HWF with locust bean gum 1.15g/100ml and 0.66 g/100ml of starch thickener agents	(57) Nonhydrolyzed protein with locust bean gum 1.05g/100ml	4	• -7.7 vs -7.1 (0.013) • 780 vs 790 (>0.001) • No significant difference	The efficacy of AR-F was demonstrated by the decreased number and volume of regurgitations. HWF with the thickener agent was statistically more effective than nonhydrolyzed protein. Note: Each group take the milk for two weeks then will shift to the other milk for two weeks also.
(Vandenplas *et al.*, 2014) [35]	(34) EHCF thickened with pectin fibres (1.2 g/100 ml) and starch (0.3 g/100 ml)	(34) Non-thickened EHCF	4	• -4.2 vs -3 (0.24) • 0.3 vs 0.4 (0.53) ** • 26.5 vs 8.6 (0.45)	Both formulas reduced cow's milk protein allergy symptoms.
(Ummarino *et al*., 2015) [36]	GA (24): Magnesium alginate aluminium-free formulation plus simethicone was given 2.5 mL 3 times/d (<5 kg) or 5 ml 3 times/d (>5 kg), to be given 10 minutes after feeding. GB (23): Thickening milk with rice starch 14.3 g/100 ml of milk (<6 months) and 14.2g/100 mL (>6 months)	(17) Only lifestyle changes	8	• 75 vs 43.5 vs 11.8% (P< 0.05) * • N/A • N/A	Magnesium alginate plus simethicone seems to be more efficacious on GERD symptom scores than thickened formula and reassurance with lifestyle changes alone. Note: The instruction of lifestyle changes was applied for all groups: 1) Small frequency feedings; 2) Keeping in the supine position during sleep.
(Indrio, *et al*., 2017) [37]	(37) Extensive HWF thickened with starch and supplemented with Lactobacillus reuteri	(35) Standard milk	4	• -4.8 vs -2.2 (<0.0001) • 690 vs 650 (<0.05) • N/A	Starch-thickened extensive HWF is more effective than standard milk in decreasing the frequency of regurgitation and can be of benefit to infants with functional regurgitation.

EHCF: Casein extensive hydrolysates formula, HWF: Hydrolysates whey formula, AR-F: Anti-regurgitation formula, N/A: The information not available: n: number; g: gram; ml: millilitre; d: day.
Int: Intervention group; Con: Control group.
*Percentage of non-regurgitation participants.
**Weight improved z-score.
ANCOVA: The P-value between the group.

On the other hand, four trials examined the effect of different thickener agents in the evolution of regurgitations in infants with a high GERD risk (one high, one unclear and two low risks of bias, n = 282). In two trials, the standard formula decreased regurgitation comparable to the soy-fibre agent (6 grams per 100 mL; P=0.029) and light locust bean gum (0.35 grams per 100 mL; P= 0.00048) thickening formula [31,33]. The other two studies discovered a significant decrease in daily regurgitation mean episodes if the evaluation position was compounded with thickened formula regardless of the type of the thickener agent used [32,36]. Furthermore, Ummarino *et al.* [36] discovered that 43.5% of participants recovered from regurgitations within eight weeks.

3.3. Secondary Outcomes

1) Weight evolution

Six trials explored weight changes (n= 477) during the regurgitation nutrition intervention journey.

Four of trials (two unclear and two low-risk bias trials) observed a nonsignificant difference in weight change between the group that had added thickening in the standard formula or EHCF [32,33,34,35]. The remaining studies found that by adding a starch agent to thicken the milk, even hydrolysed or nonhydrolyzed formula can significantly increase weight (P <0.05) [32,37]. However, Chao and Vandenplas [32] had the highest significant weight gain in the six eligible trials at almost 140 grams per 8 weeks, by adding hydrolysed rice cereal to regular milk at a ratio of 1:2 scoops. More details about the results can be found in Table 3.

2) Stool consistency

Three RCTs with a total of 322 participants studied the changes in stool consistency [31,34,35]. Ostrom *et al.* [31] and Vandenplas *et al.* [34] observed a nonsignificant alteration between the two groups, by adding six grams of soy-fibre into soymilk or adding 0.66 grams of starch into 100mL of HWF (low and unclear risk of bias trials, respectively; P<0.05). Ostrom *et al.* [31], also discovered a nonsignificant improvement in stool density within the soymilk and regular milk groups (96.6 vs. 91%, respectively; P<0.05). Conversely, a low-risk bias trial monitored a significant increase in participants with formed or soft stools when fed with EHCF (26.5 vs. 8.6 %; P= 0.45) thickened mainly with pectin fibre (1.2 g/100mL) and only 0.3g/100mL of starch [35].

4. Discussion

4.1. Evidence Summary

In 2018, NASPGHAN and ESPGHAN released clinical practice guidelines for paediatric gastroesophageal reflux. It noted that all nonpharmacological intervention in infants with GERD was weak, except for the position modification strategy [2]. With paradoxical opinions on the benefits of AR-F in recent times [23,26,28], they concluded that thickening formula, as empirical treatment for infants and young children, was dependent on the type and consistency of the thickener as well as the follow-up adherence with the dietitian [28].

While our findings regarding hydrolysed protein formula concern the work of Meyer *et al.* [24], it has a role in regulating reflux in patients allergic to cow's milk but not in other pathophysiology [24]. However, on reviewing Meyer *et al.* [24], it was observed that 100% whey protein formula emptied the stomach faster than the whole casein formula. Therefore, examining the effectiveness of thickened hydrolysed formula compared with therapeutic singular formula in infants with GERD had three outcomes, regurgitation evolution, weight and changes in stool consistency.

4.2. Summary of Main Results

Interestingly, the evolution of regurgitation episodes significantly decreased within groups, regardless of the type of intervention. This result may be explained by the fact that the tips on lifestyle modification might control regurgitation but only for a limited amount of time. This finding was also reported by Gonzalez Ayerbe *et al.* [1]. Lifestyle modification can be evaluated by a patient's peri-time feeding (around 60 minutes) and being fed with small and frequent meals [2]. However, lifestyle modification combined with suitable therapeutic milk may advance the improvement of shrinking reflux. As observed in work by Ummarino *et al.* [36], the non-pharmacological intervention group had three to seven times regurgitation-free participants than the modified lifestyle group.

Two studies found decreased regurgitation with standard formula versus thickened formula [31,33]. However, the study by Miyazawa *et al.* [33] did have a significantly small sample size and short duration, which could have affected the result; furthermore, the concentration of thickener (locust bean gum 0.35 g/ml) was less than that of Vandenplas *et al.* 34(2013), who used a higher dose (1.5 g/ml).

In contrast, two trials compared daily GERD reflux between the group fed rice-cereal thickened milk (intervention group) and the group fed with standard formula and modification of their body position [32,36]. Regardless of how the cereal was added (prepared or ready to use), regurgitation was significantly depressed compared to conventional milk.

Of the other formula intervention type in this review, only three studies, with a total of 259 infants, that examined hydrolysed protein formula on thickened vs. non-thickened hydrolysed protein milk or regular milk were suitable for inclusion. Vandenplas *et al.* [35] concluded that thickened EHCF slightly lowered regurgitation episodes than non-thickened feeds. This was supported by Indrio *et al.* [37], who found that thickened hydrolysed protein formula trial decreased the frequency of regurgitation, so it could assess functional regurgitation in infants. The study by Vandenplas *et al.* [34] provided the most significant clusters of infants with GERD but the ANOVA test showed that the evolution of regurgitation results was not statistically difference between thickened HWF and the non-thickened version. This data must be interpreted with caution because patients crossed-over the

formula after two weeks of feeding. This method of intervention possibly led to bias as infants needed at least two weeks to tolerate the new formula [2]. Conceptually, this superior regurgitation pattern with HWF or EHCF can demonstrate faster gastric emptying properties [38,39]. Therefore, results seem to indicate that hydrolysed protein formula suppresses reflux better if it was thickened.

The second question in this research was if the infants' difference in weight was caused by whether the hydrolysed protein formula was thickened or not? One interesting finding is that the HWF used by Vandenplas *et al.* [34] and Indrio *et al.* [37] increased the weight gain more than the EHCF used by Vandenplas *et al.* [35]. The main discrepancy could be attributed to the palpability of the formula. This finding supports evidence from previous observations by Miraglia *et al.* [40], which found better palatability of HWF than EHCF ($p < 0.05$). Surprisingly, the weight gain was significantly higher in thickened HWF than conventional milk ($P<0.05$). This discrepancy could be attributed to the higher HWF being better absorbed than whole protein in conventional milk. This result seems to be consistent with other research that found that breast milk rich with whey protein was faster in gastric emptying and absorption than regular formula [24].

With the various types of thickener and concentration, bodyweight results were varied. The most prominent finding to emerge from the analysis was that thickening regular milk with hydrolysed rice-cereal showed a significant increase in weight, provided that it was added in high concentration (one scoop for every two scoops of the regular formula) and for a long duration, more than four weeks [32]. This outcome is contrary to that of Hegar *et al.* [41], who found that weight gain was significantly higher when using bean gum rather than rice cereal with healthy infants. This brings us back to the importance of the concentration of thickener applied in respect to weight gain; Hegar *et al.* [41] used only 5 grams of cereal thickener in 100 mL of the standard formula, which was less than the amount used by Chao and Vandenplas [32].

The type of thickener is a factor that may impact weight change. Starch agent adds more calories depending on the amount used [42]. Therefore, Chao and Vandenplas [32] and Indrio *et al.* [37] had a significant increase in weight compared with the similar non-thickening formula. The other insoluble fibre agents, such as locust bean gum and pectin fibre, did not significantly enhance weight gain, regardless if it was used in standard or hydrolysed protein formula [33,34,35]. The result may be explained by the fact that starch-thickener agents can be digested and absorbed in gastrointestinal full-term infants, but insoluble fibre cannot [43]. This result agrees with the findings of Salvatore *et al.* [16], which supported that enhanced calories do not exist in locust bean gum as it is not absorbed.

Apart from normalised stool consistency, one study reported a significant change in the EHCF group [35] because EHCF is known to cause soft, liquid stools [44]. The other two studies reported no significant differences in side effects between the control, feed thickener and large thickened hydrolysed casein groups. However, the studies were mainly short term, with follow-up periods of up to four weeks. Hence, small but real differences in adverse effects may not be found without a large-scale RCT or observational study. Besides, some reports excluded infants who had side effects from the analysis.

4.3. Potential Limitations in the Review Process

The methodological quality of the included studies was varied (Figure 2). The included studies depended on parental records of regurgitation symptoms. Despite attempts to blind the parents from the formula type, it was likely that parents might have noted the higher viscosity of the thickened formula and the odour of the hydrolysed protein milk compared to the previous regular milk. It is essential to bear in mind that it could potentially lead to overestimation bias in their responses. However, this weakness of blinding may be unavoidable in such studies. Also, the findings of this review may not apply to infants with some neurological impairment or other medical causes of regurgitation symptoms. Further limitations of this systematic review, which reduces its ability to draw firm conclusions, are that most studies had small sample sizes, varying thickening composition (i.e., varying type, concentration and osmolality), type of hydrolysis, different patient groups (GERD versus cow's milk allergy with regurgitating) and the variety of comparable groups (standard formula, similar intervention milk but without thickener agent or similar intervention milk but non-hydrolysed protein milk).

5. Conclusion

This systematic review aimed to compare the impact of thickening versus thickening hydrolysis protein formula on the reduction of regurgitation, improved weight gain and change in stool consistency. This study has identified that both thickening formula and extensively hydrolysed formula significantly reduced the number of regurgitations per day (mean range: -1.2 to -7.1; $P<0.05$). It does, however, seem that thickened HWF better suppresses gastric reflux in comparison with whole thickened nonhydrolyzed protein formula and regular milk. However, this may be affected by the study duration and underlying diagnosis. It was challenging to find the impact of thickened hydrolysis protein formula on regurgitation due to the varying study designs and the thickener agent type and concentration. In general, it seems that adding a high concentration of starch to HWF is suitable for some GERD patients, particularly those suffering from failure to thrive. Only a small number of RCT studies have identified the changes in stool consistency and, therefore, limited conclusions can be drawn from this number of studies.

This research has thrown up many questions in need of further investigation. One of the questions is related to weight gain using starchy whey milk: because of the improvement in the hydrolysed test's pliability, what encourages drinking more milk? Or does the weight gain result from only calories that came from starch? Future research is needed to assess this explanation. Additionally, large randomised controlled trials that included premature infants could provide more definitive evidence.

References

[1] Gonzalez Ayerbe, J. I., Hauser, B., Salvatore, S. and Vandenplas, Y. (2019). 'Diagnosis and management of gastroesophageal reflux disease in infants and children: From guidelines to clinical practice', *Pediatric Gastroenterology, Hepatology & Nutrition*, vol. 22, no. 2, p. 107.

[2] Rosen, R., Vandenplas, Y., Singendonk, M., Cabana, M., DiLorenzo, C., Gottrand, F., Gupta, S., Langendam, M., Staiano, A., Thapar, N., Tipnis, N. and Tabbers, M. (2018). 'Pediatric gastroesophageal reflux clinical practice guidelines: Joint recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN)', *Journal of Pediatric Gastroenterology and Nutrition*, vol. 66, no. 3, p. 516-554.

[3] Sherman, P. and Hassall, E. (2009). 'A global, evidence-based consensus on the definition of gastroesophageal reflux disease (Gerd) in the pediatric population', *Paediatrics & Child Health*, vol. 14, no. A, p. 26.

[4] Jung H. K. (2011). 'Epidemiology of gastroesophageal reflux disease in Asia: A systematic review', *Journal Neurogastroenterol Motility*, vol. 17, no. 1, p. 14-27.

[5] Dent, J., El-Serag, H. B., Wallander, M. A., Johansson, S. (2005). 'Epidemiology of gastro-oesophageal reflux disease: A systematic review', *Gut*, vol. 54, no. 5, p. 710-717.

[6] Anand, I., Pentiuk, S., Garza, J., Su, W., Fei, L. and Kaul, A. (2020). 'GER characteristics after fundoplication in children with aerodigestive disorders', *Journal of Pediatric Surgery*, vol. 55, no. 3, p. 456-460.

[7] Fernandez, S., Aspirot, A., Kerzner, B., Friedlander, J., Di Lorenzo, C. (2010). 'Do some adolescents with rumination syndrome have "supragastric vomiting"?', *Journal of Pediatric Gastroenterol Nutrition*, vol. 50, no. 1, p. 103-105.

[8] Lightdale, J. R. and Gremse, D. A. (2013). 'Gastroesophageal reflux: Management guidance for the paediatrician', *Pediatrics*, vol. 131, no. 16, p. 84-95.

[9] Orenstein, S. and McGowan, J. (2008). 'Efficacy of Conservative Therapy as Taught in the Primary Care Setting for Symptoms Suggesting Infant Gastroesophageal Reflux', *The Journal of Pediatrics*, vol. 152, no. 3, p .310-314.

[10] Vandenplas, Y., Belli, D., Benhamou, P., Cadranel, S., Cezard, J., Cucchiara, S., Dupont, C., Faure, C., Gottrand, F., Hassall, E., Heymans, H., Kneepkens, C. and Sandhu, B. (1997). 'A critical appraisal of current management practices for infant regurgitation - recommendations of a working party', *European Journal of Pediatrics*, vol. 156, no. 5, p. 343-357.

[11] Chak, A., Faulx, A., Eng, C., Grady, W., Kinnard, M., Ochs-Balcom, H. and Falk, G. (2006). 'Gastroesophageal reflux symptoms in patients with adenocarcinoma of the oesophagus or cardia', *Cancer*, vol. 107, no. 9, p. 2160-2166.

[12] Mohammed, I., Cherkas, L. F., Riley, S. A., Spector, T. D. and Trudgill, N. J. (2003). 'Genetic influences in gastro-oesophageal reflux disease: A twin study', *Gut*, vol. 52, no. 8, p. 1085-1089.

[13] Cameron, A. J., Lagergren, J., Henriksson, C., Nyren, O., Locke, G. R., Pedersen, N. L. (2002). 'Gastroesophageal reflux disease in monozygotic and dizygotic twins', *Gastroenterology*, vol. 122, no. 1, p. 55-59.

[14] Van der Pol, R., Smits, M., van Wijk, M., Omari, T., Tabbers, M. and Benninga, M. (2011). 'Efficacy of Proton-Pump Inhibitors in Children With Gastroesophageal Reflux Disease: A Systematic Review', *PEDIATRICS*, vol. 127, no. 5, p. 925-935.

[15] Corvaglia, L., Mariani, E., Aceti, A., Galletti, S. and Faldella, G. (2013). 'Extensively hydrolyzed protein formula reduces acid gastroesophageal reflux in symptomatic preterm infants', *Early Human Development*, vol. 89, no. 7, p. 453-455.

[16] Salvatore, S., Savino, F., Singendonk, M., Tabbers, M., Benninga, M., Staiano, A. and Vandenplas, Y. (2018). 'Thickened infant formula: What to know', *Nutrition*, vol. 49, no. 1, p. 51-56.

[17] Orenstein, S. R., Magill, H. L. and Brooks, P. (1987). 'Thickening of infant feedings for therapy of gastroesophageal reflux', *Journal Paediatrics*, vol. 110, no. 2, p. 181-6.

[18] Vandenplas, Y. and Sacre, L. (1987). 'Milk-thickening agents as a treatment for gastroesophageal reflux', *Clinical Pediatric (Phila)*, vol. 26, no. 1, p. 66-8.

[19] Estevão-Costa, J., Campos, M., Dias, J. A., Trindade, E., Medina, A. M., Carvalho, J. L. (2001). 'Delayed gastric emptying and gastroesophageal reflux: A pathophysiologic relationship', *Journal of Pediatric Gastroenterol Nutrition*, vol. 32, no. 4, p. 471-4.

[20] Traves, D. (2019). Understanding infant formula. *Paediatrics and Child Health.*

[21] Horvath, A., Dziechciarz, P. and Szajewska, H. (2008). 'The effect of thickened-feed interventions on gastroesophageal reflux in infants: Systematic review and meta-analysis of randomized, controlled trials', *Pediatrics*, vol. 122, no. 6, p. 1268-1277.

[22] González-Bermúdez, C., Frontela-Saseta, C., López-Nicolás, R., Ros-Berruezo, G. and Martínez-Graciá, C. (2014). 'Effect of adding different thickening agents on the viscosity properties and in vitro mineral availability of infant formula', *Food Chemistry*, vol. 159, no. 1, p. 5-11.

[23] Owens, C., Labuschagne, I. and Lombard, M. (2012). 'Infant formula for gastro-oesophageal reflux disease', *South African Family Practice*, vol. 54, no. 2, p. 106-110.

[24] Meyer, R., Foong, R., Thapar, N., Kritas, S. and Shah, N. (2015). 'Systematic review of the impact of feed protein type and degree of hydrolysis on gastric emptying in children', *BMC Gastroenterology*, vol. 15.

[25] National Institute for Health and Care Excellence (2015). Gastro-oesophageal reflux disease in children and young people: Diagnosis and management [Online]. Available at https://www.nice.org.uk/guidance/ng1 (Accessed 27 April 2020).

[26] Kwok, T., Ojha, S. and Dorling, J. (2017). 'Feed thickener for infants up to six months of age with gastro-oesophageal reflux', *Cochrane Database of Systematic Reviews*.

[27] Huang, R., Forbes, D. and Davies, M. (2002). 'Feed thickener for newborn infants with gastroesophageal reflux', *Cochrane Database of Systematic Reviews*.

[28] Duncan, D., Larson, K. and Rosen, R. (2019). 'Clinical Aspects of Thickeners for Pediatric Gastroesophageal Reflux and Oropharyngeal Dysphagia', *Current Gastroenterology Reports*, vol. 21, no. 7, p. 30.

[29] Moher, D., Shamseer, L., Clarke, M., Ghersi, D., Liberati, A., Petticrew, M., Shekelle, P., Stewart, L. and PRISMA-P Group (2015). 'Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement', Systematic Review, vol. 4, no. 1, pp.1-9.

[30] Higgins, J., Altman, D., Gotzsche, P., Juni, P., Moher, D., Oxman, A., Savovic, J., Schulz, K., Weeks, L. and Sterne, J. (2011). 'The Cochrane Collaboration's tool for assessing risk of bias in randomised trials', *British Medical Journal*.

[31] Ostrom, K., Jacobs, J., Merritt, R. and Murray, R. (2006). 'Decreased regurgitation with a soy formula containing added soy fibre', *Clinical Pediatrics*, vol. 45, no. 1, p. 29-36.

[32] Chao, H. and Vandenplas, Y. (2007). 'Effect of cereal-thickened formula and upright positioning on regurgitation, gastric emptying, and weight gain in infants with regurgitation', *Nutrition*, vol. 23, no. 1, p. 23-28.

[33] Miyazawa, R., Tomomasa, T., Kaneko, H., Arakawa, H. and Morikawa, A. (2007). 'Effect of formula thickened with reduced concentration of locust bean gum on gastroesophageal reflux', *Acta Paediatrician*, vol. 96, no. 6, p. 910-914.

[34] Vandenplas, Y., Leluyer, B., Cazaubiel, M., Housez, B. and Bocquet, A. (2013). 'Double-blind comparative trial with 2 antiregurgitation formulae', *Journal of Pediatric Gastroenterology and Nutrition*, vol. 57, no. 3, p. 389-393.

[35] Vandenplas, Y. and De Greef, E. (2014). 'Extensive protein hydrolysate formula effectively reduces regurgitation in infants with positive and negative challenge tests for cow's milk allergy', *Acta Paediatrician*, vol. 103, no. 6, p. 243-250.

[36] Ummarino, D., Miele, E., Martinelli, M., Scarpato, E., Crocetto, F., Sciorio, E. and Staiano, A. (2015). 'Effect of magnesium alginate plus simethicone on gastroesophageal reflux in infants: A randomized, open trial', *Digestive and Liver Disease*, vol. 46, no. 1, p. 81.

[37] Indrio, F., Riezzo, G., Giordano, P., Ficarella, M., Miolla, M., Martini, S., Corvaglia, L. and Francavilla, R. (2017). 'Effect of a partially hydrolysed whey infant formula supplemented with starch and Lactobacillus reuteri DSM 17938 on regurgitation and Gastric Motility', *Nutrients*, vol. 9, no. 11, p. 1181.

[38] Staelens, S., Van Den Driessche, M., Barclay, D., Carrié-Faessler, A., Haschke, F., Verbeke, K., Vandebroek, H., Allegaert, K., Van Overmeire, B., Van Damme, M. and Veereman-Wauters, G. (2008). 'Gastric emptying in healthy new-borns fed an intact protein formula, a partially and an extensively hydrolysed formula', *Clinical Nutrition*, vol. 27, no. 2, p. 264-268.

[39] Caugant, I., Petit, H., Charbonneau, R., Saovie, L., Toullec, R., Thirouin, S. and Yvon, M. (1992). 'In vivo and in vitro gastric emptying of protein fractions of milk replacers containing whey proteins', *Journal of Dairy Science*, vol. 75, no. 3, p. 847-856.

[40] Miraglia Del Giudice, M., D'Auria, E., Peroni, D., Palazzo, S., Radaelli, G., Comberiati, P., Galdo, F., Maiello, N. and Riva, E. (2015). 'Flavour, relative palatability and components of cow's milk hydrolysed formulas and amino acid-based formula', Italian Journal of Pediatrics, vol. 41, no. 42.

[41] Hegar, B., Rantos, R., Firmansyah, A., De Schepper, J. and Vandenplas, Y. (2008). 'Natural evolution of infantile regurgitation versus the efficacy of thickened formula', *Journal of Pediatric Gastroenterology and Nutrition*, vol. 47, no. 1, p. 26-30.

[42] Greer, F. (2018). 'Use of starch and modified starches in infant feeding', *Journal of Pediatric Gastroenterology and Nutrition*, vol. 66, no. 1, p. 30-34.

[43] Qi, X., Al-Ghazzewi, F. and Tester, R. (2018). 'Dietry fibre, gastric emptying and carbohydrate digestion: A mini-review', Starch – Stärke.

[44] Niggemann, B., von Berg, A., Bollrath, C., Berdel, D., Schauer, U., Rieger, C., Haschke-Becher, E. and Wahn, U. (2008). 'Safety and efficacy of a new extensively hydrolysed formula for infants with cow's milk protein allergy', *Pediatric Allergy and Immunology*, vol. 19, no. 4, p. 348-354.

Appendix 1.

Table A1. Summary of inclusion and exclusion criteria employed and the rationale supporting decision-making

	Inclusion criteria	*Exclusion criteria*
Publication date	Thickening formula 2005-2020 Hydrolysis protein formula 2010-2020	<2015 <2010
Language	English	Non-English
Journal publication	-Peer-reviewed -Full-text version availability	-Non-peer reviewed -No access to full-text version -Only an abstract study
Study design	- Randomised controlled trials	-Reviews -Observation trials -Crossover or quasi-RCTs -Case-control, observational & cohort -Pilot trials
Location	-Both developed, developing and under-developed countries	-None
Study population	-Human -Paediatric (age: >1 year) -Both genders -Diagnosed with gastroesophageal reflux disease (GERD) -Has prolonged regurgitation that affects their health →Ideally, a clear description of diagnostic criteria →Clear description of treatment	-Animal and laboratory-based -Child (<1-16 years) and Adults ≥17 years old -Normal gastroesophageal reflux (GER)
Intervention	-Combination of thickening formula and hydrolysed protein formula or use of one as nutrition intervention → Include any soluble or insoluble fibres → Whey or casein-based formula → Prepared or ready-to-use thickener formula - With or without lifestyle modification	-Any other milk types -Pharmacology or surgery is part of the intervention
Control group	-Regular formula -Similar hydrolysates protein formula but non-thickened -Similar thickening formula but non-hydrolysed protein -Position correction	-Breastfeeding -No control groups -No clear description of the intervention followed by the control group
Primary outcome	-Regurgitation evolution →Values were converted to the difference (based on the formula: difference mean regurgitations daily number = mean baseline number -mean endpoint number) enabling comparison of outcomes	-Length changing -Gastric emptying rate -Crying rate -Esophagitis -Eczema/atopic dermatitis -Cost-effectiveness -No displaying baseline information -Anthropometric measurements →Head circumference
Secondary outcomes	-Anthropometric measurements → Weight changes -Assessment of stool consistency change →Preferably also using pre and post-intervention tests	
Study duration	≥2-weeks → As the regurgitations can decrease within 7 days. Studies had to evaluate outcomes at a time interval of at least 2 weeks post-intervention to assess the tolerance of the new milk [2])	<2-weeks

Appendix 2.

Table A2. The rationale underpinning the risk of the bias assessment process

Random generation	-Two trials used a computer-based random allocation system, two of which reported the exact system used [31,35]. -Four trials reported that an allocation sequence was generated to randomise participants in the study intervention groups, providing no further details on the exact process employed [32,34,36,37]. - Miyazawa *et al*. [33] randomised giving alternate feeds of the intervention and control feeding.
Allocation concealment	- Indrio *et al*. [37], Ummarino *et al.* [36], Vandenplas *et al*. [35] and Ostrom *et al*. [31] performed computer-mediated allocation concealment providing no further details on the precise process followed. - Chao and Vandenplas [32] used an opaque envelope for concealing the random allocation sequence of participants, while the authors reported no details on the process followed for maintaining the envelope's security throughout the study. -Two trials did not report executing an allocation concealment mechanism [33,34].
Blinding	-Chao and Vandenplas [32] and Miyazawa *et al.* [33] conducted a non-blinded randomised trial. - Indrio *et al*. [37], Vandenplas *et al.* [34] and Ostrom *et al.* [31] reported that researchers were blinded to the random sequence generation and allocation concealment process but did not report whether blinding was maintained throughout the trial. - Vandenplas *et al.* [35] reported that both participants and researchers were blinded to the group allocation sequence throughout the trial. -Ummarino *et al.* [36] conducted open-label trials and, therefore, neither the participants nor the researchers were blinded to the randomisation process and outcome measurements.
Incomplete outcome data	-Five trials reported retention rates >74.9% ranging between 75% to 100% [31,32,34,35,36,37]. - Miyazawa *et al*. [33] did not conduct retention rates. -Four trials adequately reported the rationale underpinning withdrawals throughout the study [31,32,36,37]. -Three trials conducted an intention-to-treat (ITT) analysis to account for participant dropout and missing data [31,34,35]. -Participants were equally distributed in the intervention and control groups of three trials [31,32,34]. - Ostrom *et al*. [31] conducted a withdrawal analysis and found no statistically powered differences among remaining and dropout participants. - Ummarino *et al*. [36] reported a withdrawal in one part of the study.
Selective reporting	-Four trials reported no statistically significant differences in participant baseline characteristics between study groups [31,32,36,37]. -Vandenplas *et al*. [34] reported that the gender distribution of the participants was unequal. -Vandenplas *et al*. [35] did not report statistically powered differences among baseline participant characteristics. -Six trials reported baseline and outcomes of data assessed, except for one trial, which reported the final output [33].
Other bias	-All trials adjusted for confounding outcomes in their statistical analyses, mainly accounting for participant demographics and baseline values.