

# Feed thickeners in gastro-oesophageal reflux in infants

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## GASTRO-OESOPHAGEAL REFLUX

Gastro-oesophageal reflux (GOR) is the involuntary retrograde passage of gastric contents into the oesophagus with or without regurgitation. This is a common physiological, self-limiting condition in healthy infants with a prevalence peaking at 3–4 months of age, occurring more than once a day in 50% of healthy infants. As infants achieve upright posture with neurodevelopment maturation and acquire a more solid diet with age, symptoms usually improve by 6 months old with resolution by 12–14 months old.<sup>1</sup> Transient inappropriate relaxation of the lower oesophageal sphincter and delayed gastric emptying are common mechanisms leading to GOR. This is further exaggerated in preterm infants who have shorter and immature oesophagus with non-peristaltic motility.

## How is gastro-oesophageal reflux disease diagnosed?

With increasingly frequency and severity, GOR becomes pathological. Gastro-oesophageal reflux disease (GORD) is defined as 'reflux of gastric contents causing troublesome symptoms or complications or both' by the North American Society for Paediatric Gastroenterology, Hepatology and Nutrition and the European Society for Paediatric Gastroenterology, Hepatology and Nutrition.<sup>2</sup> Rather than distinct entities, GOR and GORD are commonly seen as a continuum and non-invasive distinction of GOR and GORD is difficult. The term 'troublesome symptoms' in infants is vague due to the non-specific and pervasive nature of GOR symptoms. The lack of gold-standard objective measures and reliance on symptom reporting by caregiver complicate the diagnostic process. Diagnosis is usually inferred when infants display frequent reflux episodes with clear association between symptoms and reflux without an alternate diagnosis.

## MANAGEMENT

The management aim of GORD should be to reduce symptoms and prevent complications

without side effects. Current consensus<sup>2</sup> recommends expectant management with parental education and reassurance for uncomplicated GOR. Giving small frequent feeds is commonly used but may be impractical and may even increase the number of reflux episodes due to a shorter post-prandial time.<sup>3</sup> Although placing infants in the prone or left lateral position improves GOR, this cannot be recommended in infants without cardiorespiratory monitoring due to risk of sudden infant death syndrome.<sup>3</sup> There is also insufficient evidence to support head-up positioning in reducing GOR.<sup>3</sup> Pharmacological management should be reserved for infants who fail to respond to conservative approaches.

## Feed thickeners

Feed thickeners are commonly used for managing infants with GOR despite the lack of strong supporting evidence.<sup>1</sup> It is postulated that feed thickener reduces GOR by increasing the viscosity or 'stickiness' of the liquid content, enabling the feed to be retained in the stomach. However, feed thickeners can increase the energy density and osmolality of the feed which may increase the frequency of relaxation of the lower oesophageal sphincter and delay gastric emptying, worsening GOR.

## EVIDENCE

Our recent Cochrane review<sup>4</sup> identified eight randomised clinical trials analysing the impact of feed thickener in 637 healthy term formula feeding infants up to 6 months of age with symptoms of GOR or abnormal oesophageal pH probe measurement. The trials compared feed thickened with various thickeners including carob bean gum, rice cereal, corn starch or alginate, with unthickened feed, over a 1–8 weeks period. The trials were of variable methodological quality. Despite blinding of caregivers and that thickened feed mainly thickens when coming



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into contact with gastric acid, caregivers may notice the higher viscosity of the thickened feed both before feeding and after vomiting. This inevitable risk of bias may overestimate the improvement in reported symptoms by caregivers.

### Regurgitation

The review<sup>4</sup> found moderate quality of evidence that feed thickeners reduced the number of regurgitations by nearly two episodes per day (mean difference (MD) -1.97, 95% CI -2.32 to -1.61, 6 studies 442 infants). This is consistent with findings from previous reviews. Infants given feed thickeners were also 2.5 times more likely to be asymptomatic from regurgitation (risk ratio 2.5, 95% CI 1.38 to 4.51, number needed to treat 5, 2 trials in 186 infants). However, this evidence is of low quality due to the small number of available trials and participants. The impact of feed thickeners on volume or severity of regurgitation was not analysed due to lack of standardisation in reporting.

### Non-regurgitation symptoms

The impact of feed thickeners on non-regurgitation symptoms was unclear with variable effects reported on failure to thrive, irritability and respiratory symptoms such as cough.

### Side effects

No significant side effects were identified by the review.<sup>4</sup> The effect of feed thickeners on diarrhoea was variable but trials were not powered to measure side effects and only reported short-term follow-up outcomes. Feed thickeners, especially non-standard thickeners added to feeds, may increase caloric density with high carbohydrate content. The long-term impact of providing infants with such high carbohydrate and low protein feed is unclear.

### Oesophageal pH monitoring

Oesophageal pH monitoring is an objective and sensitive measure of acid reflux with established normal ranges based on a pH cut-off value of 4. However, insensitivity to weak acid or non-acid reflux poses a problem in infants due to their milk diet which buffers gastric acid. Our review<sup>4</sup> found improvement in the reflux index (percentage of time pH <4) by 5% in infants with feed thickeners (MD -5.08, 95% CI -8.89 to -1.28, 2 trials 116 infants). This must be interpreted with caution due to the small number of trials analysed with previous reviews showing contradictory findings.

### Other investigations

Multiple intraluminal impedance (MII) measures the change in resistance caused by movement of substances along the oesophagus. Hence, the combination of MII and pH monitoring can quantify reflux regardless of pH. However, there is no established normal range for MII. These investigations may detect normal variation and cannot predict severity or prognosis of GOR. Invasive endoscopy with histology is mainly used to rule out other

conditions rather than diagnosing GOR.<sup>2</sup> No trials in the review<sup>4</sup> reported these outcomes.

## DISCUSSION

### Impact on clinical practice

Feed thickeners should be considered in healthy term formula feeding infants with troublesome GOR. The reduction of nearly two episodes of regurgitation per day may be of clinical significance to caregivers. Currently, there is insufficient evidence to recommend the use of one form of feed thickener over the other. However, it is prudent to consider using feed thickeners which have undergone clinical evaluation.

Although alginate is commonly used in breastfeeding and preterm infants,<sup>1</sup> the evidence behind this is lacking and its impact on breastfeeding and other side effects such as obesity or necrotising enterocolitis in preterm infants are unclear.

### Impact on research

Due to the self-limiting nature of GOR, adequately powered, randomised controlled trials with controls should be used to investigate the efficacy of feed thickener and the balance of side effects and benefits. Future studies in term infants should investigate the impact of different types of feed thickener on GOR. Standardised reporting of symptoms such as the validated 12-item Infant Gastro-oesophageal Reflux Questionnaire Revised<sup>5</sup> should be used. Impact of feed thickeners on breastfeeding should also be explored.

In preterm infants, randomised trials with strict safety monitoring should be used. The thickened feed should be designed to meet the nutritional demands of preterm infants and started when infants tolerate full enteral feeds. Clinically important outcomes such as regurgitation, growth and cardiorespiratory events should be assessed alongside objective measures such as combined pH and MII monitoring.

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