

## CURRENT TOPIC

## Can pH monitoring reliably detect gastro-oesophageal reflux in preterm infants?

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Gastro-oesophageal reflux (GOR) is the regurgitation of gastric contents into the oesophagus. It is alleged to be the cause of many clinical problems in premature infants, such as failure to thrive, apnoea, desaturation, bradycardia, and stridor.<sup>1,2</sup>

Twenty four hour oesophageal pH monitoring is currently regarded as the optimal method of diagnosing occult GOR in infants with respiratory events. European and North American working parties have produced guidelines for the methodology and interpretation of oesophageal pH studies in infants and children.<sup>3,4</sup> However, pH monitoring in preterm infants has shortcomings, which makes the diagnosis of GOR in this group more difficult and its clinical significance more uncertain than in older children. This review seeks to highlight these shortcomings and to discuss the future of pH monitoring in preterm infants.

### Normal values

The lack of published normal values for reflux variables in preterm infants makes interpretation of pH monitoring difficult. A reflux index (% of time pH < 4) of > 10% is widely accepted to be indicative of pathological GOR in infants, but this value is based on a study of term infants.<sup>5</sup> There are only a few small studies involving preterm infants, with variable results<sup>6–10</sup>; they are summarised in table 1. Inconsistencies in feeding methods, ventilation, and positioning are reflected in the varying reflux indices.

Defining upper limits of normal is further hampered by the reporting of mean values for reflux indices rather than ranges.<sup>6,7,9,10</sup> Vandeplass *et al*,<sup>5</sup> who studied the largest series of mature infants, showed that the reflux index is not normally distributed in this population.<sup>5</sup> Attempting to define the upper limit of normal in preterm infants using mean (SD) is unlikely

to be meaningful for this reason. It may be more appropriate to divide the population into centiles to define the upper limit of normal.

### Gastric acidity

The detection of GOR with a pH probe in the lower oesophagus depends on the acidity of the refluxate. The probe is passed through the nares or mouth to measure oesophageal pH continuously for 24 hours. It depends on the principle that refluxed gastric contents will cause a dip in oesophageal pH to < 4. The percentage of time that the oesophageal pH is < 4 (reflux index) is the principal parameter used when defining pathological GOR.

Preterm infants are capable of hydrogen ion secretion,<sup>11</sup> but frequent milk feeds can buffer gastric acid, making the gastric pH high.<sup>12–15</sup> If the gastric pH is > 4, episodes of GOR will not be picked up by conventional oesophageal pH monitoring.

Washington *et al*<sup>13</sup> looked at mature infants (mean age 4 months) who were on standard feeds for their age, and found that the gastric pH was < 4 for a mean of 42% of the time (range 1.7–98.8%). Mitchell *et al*<sup>14</sup> studied a mixed group of term and preterm infants who were milk fed, and found that the gastric pH was < 4 for a mean of only 24.5% of the time (range 0.6–69.1%). Our own work studying only preterm infants who were exclusively milk fed showed even greater buffering, with a median gastric pH of < 4 for 8.2% of the time (range 2.0–41.2%).<sup>15</sup> This may be because preterm infants are fed more frequently.

It is possible to measure gastric and oesophageal pH simultaneously with a dual channel pH probe. The analysis of the oesophageal pH recording is then restricted to periods when the gastric pH is < 4. Both Washington *et al*<sup>13</sup> and Mitchell *et al*<sup>14</sup> have shown that this approach would substantially

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Table 1 Summary of studies on normal values in preterm infants

Reference	No of preterm infants	Mean gestation (completed weeks)	Type of feeds	Ventilated	Nursing position	Reflux index (%)
Ewer <i>et al</i> <sup>6</sup>	19	32	Enteral (3–4 hourly)	No	Not stated	11.9*
Chang <i>et al</i> <sup>7</sup>	20	32	Enteral (3 hourly)	No	Supine	2.03 (2.31)
Pradeaux <i>et al</i> <sup>8</sup>	42	31	Parenteral	Yes	Supine	3.5 (3.3)
Newell <i>et al</i> <sup>9</sup>	35	28†	Mixed	Mixed	Prone or lateral	4.5 (1.0)
Ng and Quak <sup>10</sup>	21	30‡	Enteral (1–3 hourly)	No	Not stated	0.7 (1.1)

Reflux index values are mean (SD).

\*No SD or range given.

†Median.

‡Postconceptual age.

reduce the period of time when reflux might be detected. Some infants may only reflux immediately after a feed, during the time most likely to be excluded from the analysis, and in cases where the gastric pH is almost always > 4, both single and dual probe monitoring are useless. It is not known whether a gastric pH probe positioned across the lower oesophageal sphincter could affect the degree of reflux by impairing sphincter competence.

To overcome the problem of buffering, in some studies of older infants, apple juice<sup>16</sup> or dextrose solutions<sup>17</sup> has been substituted for milk feeds during oesophageal pH monitoring. These substitutes do not have the same buffering effect on gastric acid as milk, but their safety in preterm infants has not been confirmed.

For the same reason, some investigators may wish to use pH 5 in place of pH 4 as a cut off for determining reflux. However, this would not overcome buffering because infant milk has a pH of around 7 and there would still be long periods when the gastric pH would be too high to allow any refluxate to be picked up. The normal oesophageal pH is thought to be between 5.0 and 6.8,<sup>18</sup> which means that a cut off of greater than pH 5 could not be used either.

#### Respiratory events and bradycardia

Oesophageal pH monitoring is performed when a causal relation between GOR and xanthine resistant apnoea, bradycardia, or oxygen desaturations is suspected but is not clinically evident. However, it is unclear whether a measure of GOR such as the reflux index, which was developed to investigate oesophagitis, is an appropriate tool when investigating reflux associated bradycardia or respiratory events. It may only require a few fleeting episodes of reflux to cause apnoea, while the overall reflux index may be within normal limits. Multichannel monitoring, in which simultaneous recordings of oesophageal pH, pulse oximetry, and nasal airflow are made, may be more useful. A temporal relation, in which an episode of reflux directly precedes an episode of apnoea, could then be shown.

However, it is contentious whether a temporal relation between GOR and respiratory events exists. Just as many studies have failed to show such a relation in preterm infants<sup>19–21</sup> as have appeared to show one.<sup>22–23</sup>

Suggested mechanisms by which GOR may be temporally associated with apnoea include autonomic responses to acid in the oesophagus, autonomic responses to oesophageal distension,<sup>24</sup> airway obstruction caused by aspiration of gastric contents, and laryngeal closure in response to gastric contents on the larynx.<sup>25</sup>

Other theories imply a causal, but not necessarily temporal, relation. For example, reflux induced inflammation may be a factor in impairing the reopening of a closed upper airway because of surface mucosal forces,<sup>26</sup> or pain from oesophagitis may induce respiratory events. It may be that there is no causal relation at all and that GOR and respiratory events simply coexist secondary to immature central

control of the upper airway and the lower oesophageal sphincter. Another possibility is that a temporal relation exists but is masked by the relative alkalinity of the preterm infant's gastric contents caused by the buffering effect of milk.

#### Probe position

When a pH probe is being sited, Strobel's formulae are widely used to calculate oesophageal length.<sup>27</sup> There are two formulae: one to calculate length from the mouth, the other from the nares. The pH probe is positioned at 87% of the calculated value, and the aim is to site the tip in the lower third of the oesophagus. For infants of body length 65.4 cm or less (which corresponds to age 4–6 months), Strobel's formulae estimate a shorter length for nasally positioned catheters than for oral catheters. This clearly cannot be correct.

More recently, Omari *et al*<sup>28</sup> measured oesophageal length using manometry. They suggested that Strobel's calculations overestimate the distance from nares to the lower oesophageal sphincter in infants of body length less than 40 cm, which could result in the probe being positioned in the stomach. They published predictive graphs based on the line of best fit, correlating body length with oesophageal length, which appeared to show a pronounced change in the relation between these two variables in smaller patients. However, of the 156 infants in their study, it appears that only 15 measurements were made in infants < 40 cm. They published no data on oral placement of pH probes.

Oesophageal pH reports in infants should be viewed with caution if the probe was sited by nomogram alone. Until more data are available, the position of each probe should be checked by radiography.

#### Conclusion

Current techniques in oesophageal pH monitoring cannot reliably detect GOR in preterm infants. They are not helpful in establishing an association between apnoea, bradycardia, or oxygen desaturation and GOR. The role of normal values has to be reconsidered. Gastric pH varies greatly between infants, and the reflux index does not take this into account. The reflux index was developed to investigate oesophagitis and may not be relevant to bradycardias and respiratory events. Simultaneous monitoring of oesophageal pH, pulse oximetry, and nasal airflow may provide a superior method of diagnosis, which does not rely on normal values, but the relative alkalinity of gastric contents remains a significant difficulty. Oesophageal probes must be accurately positioned.

Until these problems can be resolved, we suggest that oesophageal pH monitoring should not be performed in preterm infants. A trial of anti-reflux treatment may be the best option in symptomatic infants.

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### Commentary

This paper provokes an interesting argument that is worthy of further discussion, but the assertive conclusion that lower oesophageal pH monitoring should not be performed in preterm infants is hard to justify given the available evidence.

Monitoring of lower oesophageal pH is regarded as the optimal method for the investigation of gastro-oesophageal reflux (GOR).<sup>1,2</sup> However, there is no doubt that the presence of milk in the stomach has a buffering effect on the gastric pH and that this effect needs to be considered in the interpretation of studies on lower oesophageal pH that measure only acid reflux. Although the inability to detect non-acid reflux is acknowledged by both European and North American working parties, the 24 hour reflux index is reproducible<sup>3</sup> and remains the most specific and sensitive predictor of infants with GOR.<sup>1,2</sup>

Reflux in infants is a physiological condition, and the definition of a "normal range", particularly in preterm infants, is therefore not a precise science. However, the longer the oesophagus is exposed to acid the more likely oesophagitis, and the consequent symptoms, are to develop. Pragmatic cut off levels for reflux indices are helpful, but should not be regarded as absolute markers of significant disease. In preterm infants, the cut off I would recommend is 5%.<sup>4,5</sup>

The authors cite two published studies<sup>6,7</sup> and their own unpublished data in support of their argument, although the infants in the published studies were a heterogeneous group of preterm, term, and more mature infants and most of the subjects studied were not preterm. In these studies, the period of gastric acidity (pH < 4) varied dramatically from "never" (0.6% of the time) to "always" (98.8% of the time), but the small study sizes in both may exaggerate these extremes. In a much larger study, Hegar *et al*<sup>8</sup> investigated 90 infants and failed to find a significant effect of gastric buffering on reflux index. In addition, the implied assumption that the oesophageal pH can only be acid when the gastric pH is acid is not supported by either study, as the reflux index actually falls in a number of subjects after correction for non-acid gastric pH. This indicates that gastric pH dispersion is not homogeneous, and this phenomenon has been previously described.<sup>9</sup>

The mean reflux index in the study of Mitchell *et al*<sup>7</sup> was low (2.6% after correction), which suggests that most of these infants did not have GOR. Other studies in symptomatic preterm infants have reported much higher mean values (> 10%), which suggests that, in these patients, the effect of gastric buffering was less pronounced.<sup>4,5,10</sup>

Despite this, GOR (reflux index  $\geq$  5%) would have been successfully diagnosed by monitoring lower oesophageal pH alone in 16/20 cases in the study of Mitchell *et al*<sup>7</sup> and 26/30 cases in that of Washington *et al*.<sup>6</sup> In addition, if a value of 4% were used as "suspicious" (as is our practice), then in only four out of 40 subjects would the diagnosis of GOR not have been considered (only one subject in the cohort of preterm infants). Thus the impact of buffering on establishing the diagnosis of GOR is much less than the authors suggest.

Given this, should monitoring of lower oesophageal pH no longer be used in preterm

infants? Are there alternative modes of investigation? Dual pH studies may help, but they have been used in limited studies in preterm infants and an additional tube passing through the lower oesophageal sphincter is likely to increase the tendency to reflux.<sup>11</sup>

Acid in the lower oesophagus is likely to be the major cause of symptoms relating to reflux; this is strongly implicated by the response to treatment that reduces acid secretion and delay in response to anti-reflux treatment,<sup>10</sup> which suggests healing of oesophagitis. The presence of acid in the mouth has been shown to be a reasonably reliable indicator of GOR,<sup>4</sup> and this simple non-invasive test is used as standard practice on our unit in symptomatic infants. This, in conjunction with early positioning treatment (prone and left lateral position only),<sup>5</sup> has resulted in fewer pH studies being performed, although this investigation is undertaken in persistent cases to define the severity of the acid reflux. As the authors state, placement of the oesophageal probe using the Strobel formula<sup>12</sup> has been shown to be inaccurate in preterm infants<sup>13</sup> and should not be used in these patients. The use of routine radiology to determine probe position is recommended.

The authors suggest blind therapeutic trial of anti-reflux treatment; this is not good practice in my opinion. As Mitchell *et al*<sup>1</sup> clearly showed, symptomatic infants do not always have GOR. Indeed, only four out of 20 symptomatic infants in their study had a reflux index > 5% even after correction for gastric buffering.

I suggest the following protocol for the investigation of suspected reflux in preterm infants: (a) exercise a high degree of clinical suspicion; (b) test oropharyngeal secretions for acid, and, if positive on two or more occasions, GOR should be suspected; (c) nurse infants in the prone or left lateral position only; (d) if symptoms persist or do not respond to simple treatment consider pH study.

The results of lower oesophageal pH study must then be considered in the clinical context against the best reference data available. I recommend a reflux index of  $\geq 5\%$  should be regarded as indicating GOR.

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