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The surgical treatment of gastro-esophageal reflux in neonates and infants

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Gastro-esophageal reflux (GER) is a physiological process characterized by the involuntary passage of gastric contents into the lower esophagus not induced by noxious stimuli. It represents a common condition in preterm infants and may occur in healthy neonates. The phenomenon is only considered as GER *disease* when it causes the patient to be symptomatic or results in pathological complications. Fundoplication is recommended in symptomatic neonates and infants with GER that does not respond to medical treatment. The presence of respiratory symptoms related to GER is the primary indication for fundoplication in this selected population. The Nissen fundoplication is the antireflux procedure of choice and the experience concerning other procedures, including laparoscopic techniques, is limited in this age group. The best results are achieved in newborn infants with isolated GER, as the recurrence rate of GER in infants with associated anomalies is high. Further studies are necessary to evaluate the benefit of laparoscopic fundoplication in this age group.

Gastro-esophageal reflux (GER) is a physiological process characterized by the involuntary passage of gastric contents into the lower esophagus not induced by noxious stimuli. The phenomenon is only considered as GER *disease* when it causes the patient to be symptomatic or results in pathological complications. GER represents a common condition in preterm infants and may occur in healthy neonates. In the former, the incidence of GER can be as high as 85%[1] with male to female preponderance of 1.6.[2] In the majority of cases GER resolves spontaneously, with its prevalence decreasing to 18% in childhood.[3] The incidence of GER is highest in neurologically impaired children (70%), who comprise 44 to 67% of children undergoing antireflux surgery.[4-6]

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The newborn infant with GER typically presents with vomiting or feeding intolerance, aggravated at night during the supine position. If GER is left untreated, failure to thrive from calorie deprivation may ensue. Reflux of gastric contents into the airways may result in coughing and choking, and chronic aspiration may cause the infant to present with complications of GER, including laryngospasm with apnoic and bradycardia spells (particularly during sleep), stridor or pneumonia.

Antireflux surgery is required in the neonatal period and during early infancy in the presence of severe GER-related symptoms that persist despite medical treatment. Although several reports have documented the effectiveness of fundoplication in older children and adolescents,[7-10] few studies have evaluated the results of fundoplication in infancy and the benefits of surgery in this population are not clearly defined. This article will focus on the surgical treatment of GER in neonates and infants. We have reviewed the liter-

ature on the topic and appraised the results of surgery for GER in these age groups.

Pathophysiology

A number of physiological and anatomical factors normally contribute to prevent chronic reflux of gastric contents into the lower esophagus. The combination of esophageal motility and gravity facilitates esophageal clearance of refluxed material as well as of saliva, which is rich in bicarbonate that coats the esophagus. These esophageal clearance mechanisms are usually developed by 31 weeks gestation.[11] Other physiological barriers to GER include antral contractions facilitating gastric emptying, and the production of mucous, prostaglandin and epithelial growth factors, which help to prevent damage to the esophageal mucosa.

Anatomically, the length of the intraabdominal esophagus, the phreno-esophageal ligaments, the gastric mucosal "rosette," and the esophageal hiatus, which is a sling formed by the crura of the diaphragm causing a pinchcock effect, all contribute to a higher-pressure zone in the lower esophagus. This high-pressure zone forms the lower esophageal sphincter (LES), a physiological rather than a true anatomical sphincter. Pressures at this gastro-esophageal junction (10-30 mmHg) are greater than gastric luminal pressure (5 mmHg), thereby preventing retrograde passage of gastric contents. In addition, the acute angle of His (made by the esophagus and the axis of the stomach) and the above physiological factors cumulatively contribute to limit the volume and frequency of gastric contents refluxing into the lower esophagus. Much of these anatomical features however are poorly developed in the first weeks of an infant's life, predisposing it to the higher risk of GER within this period. For instance the angle of His is obtuse in newborns and only decreases as the infant grows while the length of intraabdominal esophagus is shorter, only 1 cm at birth, compared with 3 cm by 3 months of age. Other abnormalities that predispose to GER include disruption of the gastro-esophageal junction (with resulting hiatus hernia), weakness or incompetence of the LES, and poor clearance of acid from the esophagus.[12]

A mean intraabdominal pressure of less than 10 mmHg is necessary for the LES to remain competent. GER is made more likely in groups with raised intraabdominal pressure, eg, following repair of omphalocele (43%),[13] congenital diaphragmatic hernia[14] and chronic respiratory infections.

Previous studies indicated that GER is a temporary condition and that symptoms resolve spontaneously without medical intervention.[15-17] Indeed, physiological antireflux mechanisms, such as increasing length of the intraabdominal esophagus and maturation of the LES, occur in the first few months after birth.[18] However, some neonates and infants develop serious symptoms related to GER.

These symptoms are more frequent in patients with neurological disorders[8-10,19-23] and following repair of esophageal atresia and/or tracheo-esophageal fistula.[19,21,24-27] Neurologically impaired patients have the highest incidence of GER (65-70%).[28] This is due to a combination of poor esophageal and gastric motility (due to vagal nerve dysfunction), chronic supine positioning, abdominal spasticity, diaphragmatic flaccidity, scoliosis, retching and increased use of gastrostomy for feeding. GER occurs in 30 to 80% of children treated for esophageal atresia, the incidence being related to the length of the atresia gap. The GER is attributed partly to poor esophageal motility in these patients and partly to a shortened esophagus. The shortened esophagus, from the original anomaly and compounded by the surgical repair, results in upward displacement of the gastro-esophageal junction.

Insertion of gastrostomy tubes has been reported to be associated with the development of or worsening of preexisting GER. The gastrostomy, which fixes the stomach to the anterior abdominal wall, potentially opens the angle of His[29] and lowers the LES pressure[30] thereby predisposing to GER.

Diagnosis

Investigations used for diagnosis of GER in newborn infants include 24-hour pH monitoring, upper gastro-intestinal contrast studies and esophagoscopy. Gastric isotope scintiscan and esophageal manometry are rarely used in neonates. The 24-hour pH monitoring is currently the most sensitive and specific test available for diagnosing GER. Monitoring is performed for 24 continuous hours, during which time the patient is only fed breast-milk, formula or apple juice. The latter is preferable as the alkaline content of milk feeds may neutralize the gastric acid reflux and thereby potentially produce a false negative result. Acid reflux is defined by pH < 4.0 in the lower esophagus. Esophageal exposure to gastric acid is assessed in terms of the cumulative time during which the esophageal pH is below 4.0, expressed as the percentage of the total 24 hours. A positive test for GER is indicated by a pH below 4.0 for more than 5% of the duration of the study. Upper gastro-intestinal contrast studies may diagnose active episodes of GER. However, they are more useful for detecting anatomical abnormalities, eg, hiatus hernia, stricture, esophageal motility, and may rule out the presence of malrotation of the bowel or gastric outlet obstruction as a cause of vomiting. Esophagoscopy allows visualization of the gastro-esophageal mucosa. However, only 40% of GER will demonstrate unequivocal esophagitis. Endoscopy is therefore a poor tool for diagnosis of GER, and is more useful in the assessment of complications of reflux, eg, esophagitis, stricture and in obtaining biopsies (eg, *Helicobacter pylori* infections, development of Barrett's esophagus). The presence of lipid laden alveolar macrophages in tracheal aspirates/broncho-alveolar lavage may indicate aspiration secondary to GER. However, its sensitivity and specificity for detecting GER is as low as 38% and 59%, respectively,[31]

and elevated levels of lipid laden macrophages are found in a number of pulmonary disease without any evidence of aspiration.[32]

Medical treatment

The two main aims of treatment are to prevent the respiratory complications of GER and improve the nutritional status of the child from resumption of normal feeding.

Conservative measures for GER in infants frequently advocated include the avoidance of medications that reduce LES tone (caffeine, theophylline, anticholinergics), dietary modifications (changing the feed pattern with use of frequent, small volume feeds) and positioning maneuvers. However, many of these have no proven efficacy. Thickening of formula feeds (eg, with carob bean gum, or rice flour) may reduce frank emesis but does not reduce GER measurably compared with placebos.[33-36] Furthermore, there is no quality data to support that more frequent but smaller volume feeding reduce GER.[37] With respect to positioning maneuvers, positioning at a 60-degree head elevation position increases GER compared with the prone position.[38] However, the association of the prone position with Sudden Infant Death Syndrome has brought controversy with this maneuver. No significant difference has been found between the flat and head-elevation prone positions.[39]

Pharmacotherapy forms the main first-line treatment modality of GER. A wide spectrum of agents is now available, aimed at decreasing acid secretion (H_2-bloking agents or proton pump inhibitors) and to increase gastric emptying.

Indications for surgery

For symptomatic neonates and infants with GER that does not respond to medical treatment, fundoplication is recommended to prevent further morbidity. The indications for antireflux surgery vary largely in reported series. Table 1 summarizes the symptoms and indications for surgery in published studies on neonates and infants with GER. Recurrent aspiration pneumonia is the primary and widely accepted indication for fundoplication in this selected population. Other common indications include:

a) The presence of apnoic episodes, bradycardia and apparent life-threatening events (ALTEs). The association between GER and apnea is controversial.[40-42] However, recent reports have documented that GER is significantly associated with apnoic episodes.[43,44]

b) The presence of bronchopulmonary dysplasia (BPD). The association between GER and chronic lung disease is also debated.[45-47] A significant relationship between pulmonary disease and the severity of GER has been reported.[45]

Table 1 Review of the literature: symptoms and indications for fundoplication in selected series of neonates and infants with gastro-esophageal reflux

		Symptoms and indications (%)					
Study	Number of patients (age group)	Apnea and/or bradycardia and/or ALTEs	Aspiration and/or pneumonia	BPD and/or RDS	Failure to thrive	Severe emesis	Stricture or esophagitis
Randolph, 1983[50]	72 (≤1 yr)	11	33	-	49	-	7
St Cyr et al, 1986[23]	45 (≤6 mo)	17	44	16	20	2	-
Hrabovsky and Mullett, 1986[75]	17 (prem infants)	29	35	82	-	6	-
Giuffre et al, 1987[74]	9 (prem infants)	-	100	100	100	-	-
St Cyr et al, 1989[81]	51 (≤2 yr)	18	55	27	-	-	-
Justo and Gray, 1991[77]	11 (prem infants)	27	82	54	-	-	-
Kazerooni et al, 1994[20]	160 (<2 yr)	30	53	-	68	58	8
Krishnamoorthy et al, 1994[73]	39 (LBW infants)	64	31	31		23*	-
Thompson et al, 1996[55]	25 (<1 yr)	-	8	-	92	-	-
Rowe et al, 1995[78]	21 (prem infants)	58	19	-	14	-	-
Zamir et al, 1997[58]	11 (<2 yr)	9	82	-	36	27	-
Kubiak et al, 1999[82]	66 (<4 mo)	24	29	-	52	39	11
Fonkalsrud et al, 1999[85]	110 (<3 mo)	52	13	44	37	56	-
Somme et al, 2002[57]	53 (<1 yr)	21	-	-	96	-	-
Barnes et al, 2003[76]	10 (8 prem infants, 2 term infants)	100	100	60	100	100	-

Abbreviations: ALTEs, apparent life threatening events; BPD, bronchopolmunary dysplasia; LBW, low birth weight; prem, premature; RDS, respiratory distress syndrome.

*23% of the patients had failure to thrive or severe emesis.

Sindel and coworkers[46] postulated that aspiration may be sufficient to aggravate lung disease. However, St Cyr and coworkers[23] observed that it is difficult to assess the effectiveness of antireflux surgery in infants with BPD since its pathogenesis may be related to prolonged mechanical ventilation as well as to GER. In addition, Akinola and coworkers[48] reported that there is no clear correlation between the degree of GER and the presence of severe lung disease in preterm infants.

c) Severe emesis and failure to thrive. These conditions are frequent indications for antireflux surgery in children with neurological impairment. In these cases a gastrostomy is regularly performed together with the fundoplication. Recently, Puntis and coworkers[49] reported that in children with neurological impairment, in the absence of symptoms suggestive for GER, fundoplication is unlikely to be necessary after the insertion of a percutaneus endoscopic gastrostomy.

d) The presence of a documented esophagitis or esophageal stricture. Although esophagitis is rare in neonates and infants,[50] Shub and coworkers[51] reported that histologically documented esophagitis is frequent in infants with symptomatic GER even in the absence of gross endoscopic findings and inflammation increases after 6 months of age. However, complications of esophagitis including anemia or esophageal stricture are more common in older children.

Antireflux surgery in infants may be also required for treatment of GER following repair of esophageal atresia or GER associated with anatomical defects such as congenital diaphragmatic hernia.

Surgical techniques

Open techniques

Table 2 reports the types of fundoplications performed in reported series of neonates and infants with GER. The Nissen fundoplication is the most common antireflux procedure performed in neonates and infants. The procedure aims to establish a high-pressure zone in the distal esophagus. The hiatus is repaired by approximating the crura of the diaphragm, the angle of His is accentuated, and a flutter valve is created at the esophago-gastric junction. Adequate mobilization of the fundus and the great curvature of the stomach then allows division of the short gastric vessels. A point of the gastric fundus is passed posteriorly to the esophagus and a 360° floppy wrap is performed with non-absorbable sutures. Alternatively, the short gastric vessels may not be divided (modified Rossetti technique). The Thal fundoplication is an alternative technique used in these young patients. The procedure combines a partial 270° wrap with a crural repair. Data comparing results of Thal fundoplication with that of Nissen fundoplication in neonates and infants are inadequate. The experience with other antireflux procedures (Toupet, Nissen-Rossetti or Lortat-Jacob fundoplication) is limited in these patients.

Laparoscopic techniques

Most recently, laparoscopic fundoplication has been described in neonates and infants.[52-58] Experience in adult population[59-70] suggests that laparoscopic and open fundoplication are equally effective in alleviating gastro-esophageal acid reflux. Nevertheless, proficiency and technical aspects for laparoscopic fundoplication unique to neonates in infants are required. The available operative field is smaller and there is the need to use small instruments and to handle them with particular care to avoid visceral injuries. In particular, the liver is often very large in these patients, making intraoperative retraction and adequate visualization of the operative field far more difficult. The pneumoperitoneum should be maintained at low pressure (usually 7-8 mmHg) to avoid difficulty in ventilation and consequent hypercapnia. Compared with older children and adults, newborn infants absorb a higher proportion of the exogenous CO_2 used for pneumoperitoneum and this may cause metabolic acidosis.[71] Extreme care is required during dissection in the presence of hiatus hernia although the presence of minimal fat and loose connective tissue make the dissection planes clearer. While the level of proficiency with laparoscopy required in neonates and infants remains unclear. Dagash and coworkers[72] performed a systematic review of the evidence in the literature to quantify the learning curve in laparoscopic surgery. Proficiency was reported after 28 (20-60) fundoplications. The operating time was reduced from 178 (109-248) minutes at initial experience to 92 (55-203) minutes at late experience. Conversion rates fell from 26.7% (9.8-56) to 7.1% (0-21) and complications from 15% (12-20) to 4% (0-7.4). Meehan and Georgeson[53] observed that proficiency in the laparoscopic Nissen fundoplication in infants and children can be obtained within the first 25 cases with a rapid decrease of operative time and complications rates in the early learning phase.

Results and outcome

Table 2 reports the incidence of GER-associated disease and the results of fundoplication in neonates and infants. Regardless of the technique, the success rate after fundoplication in neonates and infants ranges between 67% and 100% and the incidence of redo fundoplication ranges between 7% and 26%. Although experience with antireflux surgery in neonates is limited, fundoplication seems to be effective in controlling symptoms related to GER in these patients. Has been documented that fundoplication is effective in decreasing oxygen requirements in infants with GER-related respiratory symptoms[73] and that in premature infants with BPD, the pulmonary status significantly improves after fundoplication.[74-76] Furthermore, Justo and Gray[77] reported that

Table 2 Review of the literature: patient's characteristics, gastro-esophageal reflux associated diseases and results of fundoplication in selected series of neonates and infants with gastro-esophageal reflux

Study	Number of patients (age group)	Age at fundoplication	Weight at fundoplication (kg)	Associated diseases [EA/TEF] (%)	NI (%)	Type of fundoplication (%)	Symptoms improved (%)	Redo-fundoplication (%)
Randolph, 1983[50]	72 (≤1 yr)	6 mo	-	-[4]	-	100 Nissen	88	7
St Cyr et al, 1986[23]	45 (≤6 mo)	2.4 mo	3.09	78 [11]*	*	100 Nissen	92†	20
Hrabovsky and Mullett, 1986[75]	17 (prem infants)	4 mo	-	-	-	100 Nissen	94	-
Giuffre et al, 1987[74]	9 (prem infants)	31.7 wk	-	-	-	100 Nissen	100§	-
St Cyr et al, 1989[81]	51 (≤2 yr)	3.92 mo	3.71	73	21	100 Nissen	91†	-
Justo and Gray, 1991[77]	11 (prem infants)	3 mo	2.6	-	-	82 Nissen 18 Thal	82	9
Kazerooni et al, 1994[20]	160 (<2 yr)	9 mo	-	54 [13]	47	79 Nissen 21 Thal	88‡	16‡
Krishnamoorthy et al, 1994[73]	39 (LBW infants)	17.5 wk	3.51	23	-	100 Nissen	95	-
Thompson et al, 1996[55]	25 (<1 yr)	6 mo	5.1	20	92	100 LAP Nissen	100¶	-
Rowe et al, 1995[78]	21 (prem infants)	9.1 wk	2.1	76 [5]*	*	100 Nissen	91	5
Zamir et al, 1997[58]	11 (<2 yr)	3 mo to 19 mo	7.2	91	36	100 LAP Nissen	82	-
Kubiak et al, 1999[82]	66 (<4 mo)	9 wk	3.5	85 [30]*	*	86 Nissen 14 Thal	68 67	26 11
Fonkalsrud et al, 1999[85]	110 (<3 mo)	1.8 mo	3.6	41	32	94.5 Nissen 5.5 Thal	79	6
Esposito et al, 2001[56]	36 (<13 mo)	7 mo	4.7	41.6 [14]	27.7	47.2 LAP Toupet 22.2 LAP Nissen 27.7 LAP Nissen-Rossetti 2.9 LAP Lortat-Jacob	89	11
Somme et al, 2002[57]	53 (<1 yr)	2 wk to 11.8 mo	1.8 to 8.3	-	89	73.6 LAP Nissen-Rossetti 26.4 Nissen-Rossetti	97 86	-
Bames et al, 2003[76]	10 (8 prem infants, 2 term infants)	11.5 wk	3.25	50 [10]	-	100 Nissen	100	-

Abbreviations: EA/TEF, esophageal atresia and/or tracheo-esophageal fistula; LAP, laparoscopic; LBW, low birth weight; NI, neurological impairment; prem, premature.

*Patients had associated diseases including neurological abnormalities.

†92% and 91% of the surviving infants (36 and 43, respectively).

‡Of 96 patients with follow-up more than 2 years. Infants with EA/TEF had a higher recurrence rate of symptoms.

§100% of the surviving infants. Two patients died at post-operative day 14 and 52, respectively.

¶Of 19 patients alive at 1 year mean follow-up.

fundoplication is effective in management of intractable apnea while Rowe and coworkers[78] reported a resolution of GER-related symptoms in 91% of small infants after fundoplication. Various studies have demonstrated that results of fundoplication are negatively influenced by the presence of associated anomalies, both in older children[8,9,21,27,79-81] and infants.[82] Kubiak and coworkers[82] demonstrated that fundoplication in infants is associated with a high failure rate in those patients with associated anomalies, mainly in those with repaired esophageal atresia. Moreover, in this series the incidence of redo-fundoplication due to recurrence of GER was high (24%) indicating that the presence of associated anomalies is a negative prognostic factor in infancy. Other authors[26,27,83,84] have also reported a high incidence of failure rate (15-38%) after fundoplication following esophageal atresia repair. Wheatley and coworkers[27] reported a 33% recurrence of GER in 21 patients who underwent a Nissen fundoplication after repair of esophageal atresia. Similarly, Kazerooni and coworkers[20] reported that infants with esophageal atresia experienced a slightly higher incidence of recurrent reflux compared with the rest of the patient population. Experience with antireflux procedures other than Nissen fundoplication is very limited in neonates and infants (Table 2) although the data available[20,77,82,85] seems to confirm that Thal fundoplication is as effective as Nissen fundoplication. Following this operation patients should be able to burp and vomit if necessary and should have less dysphagia or "gas bloat" which may otherwise be present after the Nissen fundoplication.[86] However, it is not clear whether the recurrence rate of GER after Thal fundoplication is higher than after Nissen. Furthermore, the small numbers of patient and the selection criteria for the two operations may have introduced selection bias and therefore prospective randomized trials are necessary to compare the two procedures objectively. Laparoscopic fundoplication has recently been introduced in the management of GER in early infancy. Although the number of patients treated with this technique is small, it appears to be feasible in neonates and infants and the surgical outcome appears to be comparable to that of open fundoplication.[52-58] These series reported a reduction of intraoperative and postoperative complications, length of hospital stay and a more rapid resumption of feeds, which in turn may reflect in overall cost reduction. In particular, laparoscopic fundoplication may reduce postoperative pulmonary complications in small children who require antireflux surgery for lung disease. However, at present long term follow-up data are not available to compare the incidence of late failure rate with the open technique. Future randomized trials are necessary to confirm these preliminary results.

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