Outcome of Nissen fundoplication and placement of a gastrostomy in children

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Contents

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2. Summary

This thesis presents outcome after Nissen fundoplication and gastrostomy placement in children treated at the pediatric surgical departments at Oslo University Hospital. Long-term results with main focus on parental satisfaction with the postoperative outcome were obtained by retrospective chart reviews and telephone interviews with the parents. In a prospective, randomized trial we compared short term outcome after open and laparoscopic Nissen fundoplication. Lastly, we have studied gastric emptying in children with gastroesophageal reflux.

Caring for a child with severe gastroesophageal reflux or feeding problems can be strenuous and time-consuming. In most cases, the daily care is provided by the parents. Few studies have addressed the parental perspective when assessing outcome of surgical treatment of severe gastroesophageal reflux and feeding problems. We telephone interviewed parents of children who had undergone Nissen fundoplication, with and without gastrostomy, and percutaneous endoscopic gastrostomy, and asked them to evaluate results. For these interviews, only parents of children alive at follow-up were contacted. We were able to reach more than 90% of parents whose child had undergone Nissen fundoplication (75/80) or percutaneous endoscopic gastrostomy (85/92).

Parental satisfaction after percutaneous endoscopic gastrostomy was high, and 94% of parents reported that the percutaneous endoscopic gastrostomy had a positive influence on their child's situation median 5.6 years (range 1-10 years) after surgery. 96% of parents reported that the percutaneous endoscopic gastrostomy had decreased the main problem, defined as inability to be sufficiently enterally fed. Preoperatively, 82% of children had a nasogastric tube. Symptoms suggestive of GER (vomiting/retching) were present in 77% preoperatively. Excluding the 13 % of children operated with antireflux surgery after PEG placement, vomiting was significantly reduced postoperatively. The change in frequency of vomiting was not significantly different between those who had a pathological pH index before PEG and those who had a normal pH monitoring. Stoma related complications were frequent and was reported by 73% of the parents/caregivers at follow-up. Complications occurring the first 30 days after PEG insertion were seen in 12% of the children (15/121), and included pneumonia (n = 2), stoma-related infection (n = 10) and tube dislodgement (n = 3). Despite these complications, 98% of the parents would have chosen PEG insertion again.

Parental satisfaction of outcome after surgery was also high in children undergoing a Nissen fundoplication as treatment for gastroesophageal reflux. Median 6.0 years (range 2.5-12) after surgery, 92% of children with a primary fundoplication had improved overall condition according to the parents. In 86% of the children, vomiting and retching occurred never or less frequently. Respiratory symptoms were improved in 59%. Furthermore, 68% of children had better quality of sleep as evaluated by the parents. Complete satisfaction with the result was reported by 83% of the parents whose child had a primary fundoplication. Of the 10% of children who had undergone a second fundoplication before follow-up interview, all had benefited from the redo procedure according to the parents.

In the retrospective chart reviews of Study II, we registered 10 (11%) major complications following 93 primary fundoplications during the first 30 postoperative days. These complications included rupture of the wound (n = 1), wound infection (n = 2), pneumothorax (n = 2), sepsis (n = 3), splenectomy (n = 1), and ascites needing drainage (n = 1). Four children died the first 30 days of causes related to their underlying disease. The majority of fundoplications in this study were performed with laparotomy.

It has been demonstrated that laparoscopic surgery has fewer complications, reduces analgesia demand, and shortens length of hospital stay compared to laparotomy in adults. Consequently, laparoscopic surgery has become the preferred technique for many surgical procedures, also in children. However, there have been few high quality studies comparing conventional open surgery and laparoscopic surgery in children. Therefore, we designed a randomized trial to compare open and laparoscopic Nissen fundoplication. We did not find that laparoscopic fundoplication was superior to open fundoplication with regard to the number or severity of early postoperative complications or hospital stay. Overall, 48 (54%) out of the 88 patients experienced one or more postoperative complications. The most frequent complications were airway complications (n = 22), feeding problems (n = 17), and gastrostomy infection (n = 7). Eight complications required surgical, endoscopic or radiological intervention because of food impaction (n = 3), port site hernia/wound rupture (n = 3), and redo gastrostomy (n = 2). There was no early mortality in this study. Both less severe complications and a

higher number of complications were identified in the prospective study than in the retrospective chart review. The difference in complication rate is not surprising since the retrospective chart review only allowed identification of complications clearly registered in the medical charts.

There are studies suggesting that children with gastroesophageal reflux have delayed gastric emptying, and that this may influence outcome after antireflux surgery. Few have compared gastric emptying in gastroesophageal reflux patients and in healthy children. In order to evaluate whether children with gastroesophageal reflux have delayed gastric emptying, we examined gastric emptying rate by scintigraphy in 51 patients with gastroesophageal reflux and in 24 healthy children. There was no significant difference in mean gastric emptying rate of milk in children with gastroesophageal reflux and healthy children. Only one patient (2%) had a gastric emptying rate that was outside the range of the healthy child with the slowest gastric emptying rate. In both groups, a wide range of gastric emptying rates was observed.

To conclude, the majority of parents thought that Nissen fundoplication and percutaneous endoscopic gastrostomy had benefited their child. Early complication rate and length of hospital stay were not significantly different in children randomized to open or laparoscopic fundoplication. Gastric emptying rate in children with gastroesophageal reflux was not significantly slower than gastric emptying in healthy children.

3. List of papers

This thesis is based on the following papers which in the text are referred to by their Roman numerals (I-IV)

I. Åvitsland TL, Kristensen C, Emblem R, Veenstra M, Mala T, Bjørnland K. Percutaneous endoscopic gastrostomy in children: A safe technique with major symptom relief and high parental satisfaction. J Pediatr Gastroenterol Nutr 2006;43(5):624-628

II. Kristensen C, Åvitsland T, Emblem R, Refsum S, Bjørnland K. Satisfactory long-term results after Nissen fundoplication. Acta Paediatrica 2007; 96(5):702-705

III. Knatten CK, Fyhn TJ, Edwin B, Schistad O, Emblem R, Bjørnland K. 30-days outcome in children randomized to open and laparoscopic Nissen fundoplication. J Ped Surg 2012;47(11):1990-6

IV. Knatten CK, Åvitsland TL, Medhus AW, Fjeld JG, Pripp AH, Emblem R, Bjørnland K. Gastric emptying in healthy children and in children with gastroesophageal reflux. (In press: J Ped Surg).

4. Abbreviations

DGE Delayed gastric emptying

ESPGHAN European Society for Pediatric Gastroenterology, Hepatology, and Nutrition

GER Gastroesophageal reflux

GERD Gastroesophageal reflux disease

LNF Laparoscopic Nissen fundoplication

NASPGHAN North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition

ONF Open Nissen fundoplication

PEG Percutaneous endoscopic gastrostomy

$T_{1/2}$ Half time of gastric emptying

UGI Upper gastrointestinal contrast study

5. Definitions

Gastroesophageal reflux (GER): Passage of gastric contents into the esophagus with or without regurgitation and vomiting

Gastroesophageal reflux disease (GERD): When reflux of gastric contents causes troublesome symptoms and/or complications

Heartburn: A burning sensation in the retrosternal area

Regurgitation: Passage of refluxed gastric contents into the pharynx or mouth

Reflux index: Percentage of the total measured time with pH below 4.

Vomiting: Expulsion of refluxed gastric contents from the mouth

6. Gastroesophageal reflux

6.1 Pathophysiology

Gastroesophageal reflux (GER) is defined as gastric contents that passes into the esophagus with or without regurgitation and vomiting (1). GER occurs when the protective barrier mechanisms of the esophagus are ineffective in preventing retrograde movement of gastric contents. The most important antireflux mechanism is the lower esophageal sphincter and the crural diaphragm (2). Other barriers contributing to reduce or prevent GER are the angle of His and the intra-abdominal part of the esophagus (2–4) (Figure 1). In addition, protective mechanisms such as peristaltic movements, esophageal mucosal resistance, and saliva secretion aid in preventing damage to the esophagus from food or refluxed material (5). When these mechanisms are ineffective or insufficient, GER may occur (3,6).

Transient lower esophageal sphincter relaxations, a relaxation of the lower esophageal sphincter and diaphragmatic crura is the most important mechanism of GER (2). When this occurs, the pressure of the lower esophagus sphincter drops, and gastric contents may refluxate into the esophagus. It has been demonstrated that transient lower esophageal relaxations are triggered by several factors, including cholecystokinin secretion stimulated by food entering the duodenum, body posture, and gastric distension (7). Studies investigating gastric motility find abnormal pooling of ingested liquids in the stomach in patients with reflux esophagitis (8), as well as disturbed gastrointestinal motility patterns on esophageal manometry and electrogastrography (9). Furthermore, it has been demonstrated that delayed gastric emptying (DGE) may accentuate GER by prolonging transient lower esophageal sphincter relaxations and by increasing the volume of the refluxate (10). In spite of extensive research, the underlying mechanisms of GER is not fully understood, but is seems that GER is a multifactorial condition (1,7,11–15) (Figure 2).

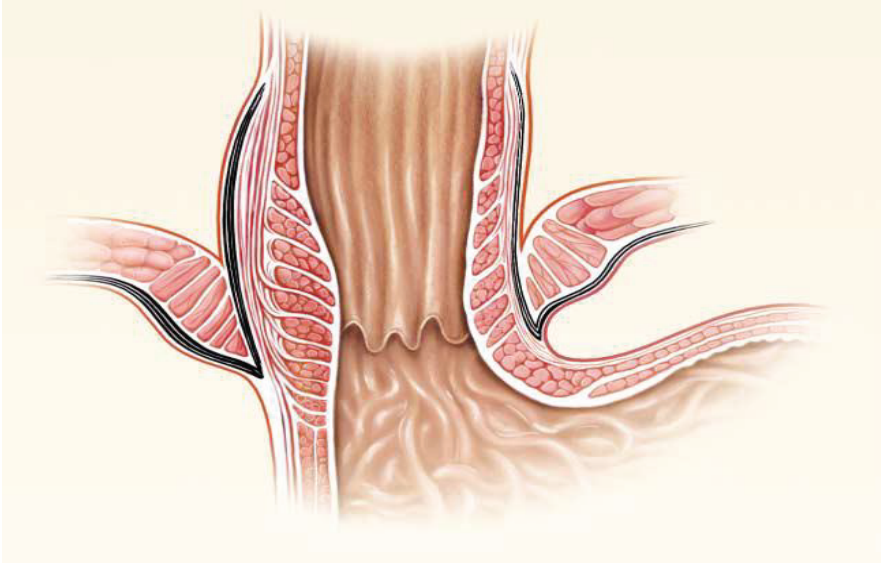

Figure 1. Anatomy of the Esophagogastric Junction.

The lower esophageal sphincter and the crural diaphragm constitute the intrinsic and extrinsic sphincters, respectively. The two sphincters are anatomically superimposed and are anchored to each other by the phrenoesophageal ligament. (Reproduced from "The esophagogastric junction" by Mittal RK et al, The New England Journal of Medicine, volume 336, page 924-32, 1997, with permission from Copyright Massachusetts Medical Society.)

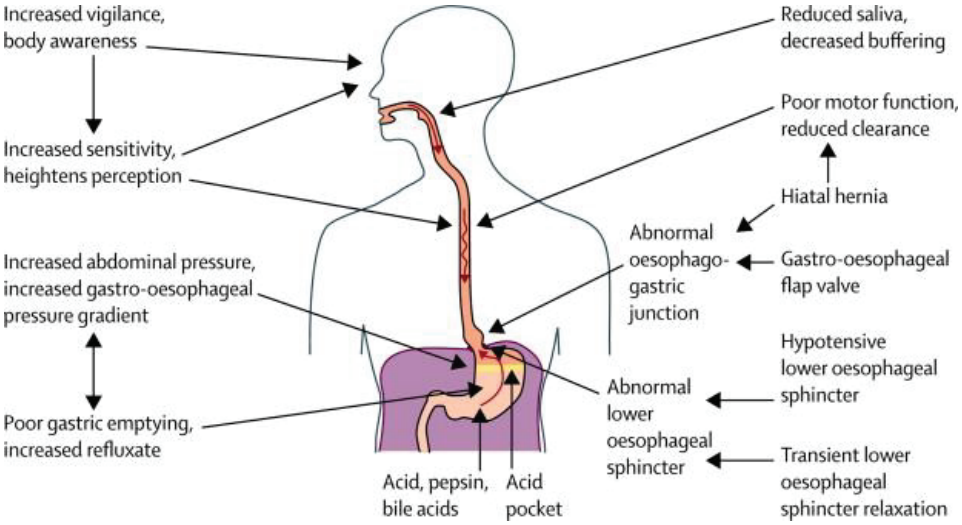

Figure 2. Pathophysiology of gastroesophageal reflux disease

Dysfunction of the antireflux barrier, increased esophageal sensitivity, poor motor function of the esophageal body, and gastric factors (such as raised intragastric pressure and the acid pocket) all play a part. (Reprinted from The Lancet, 381, Bredenoord, AJ et al, "Gastro-oesophageal reflux disease", 1933-42, 2013, with permission from Elsevier.)

6.2 Symptoms and complications

GER in infants is often observed by parents as spitting or regurgitation. Fuzzing, crying, irritability, pulmonary symptoms, abnormal sucking and swallowing, decreased food intake, food aversion, and poor weight gain are other symptoms that may be caused by GER (3,16,17). In older children regurgitation, vomiting, retrosternal pain, abdominal pain, and epigastric pain can be symptoms of GER (16,18,19). In both infants and older children GER has also been associated to symptoms such as sinusitis, dental erosions, apparent life-threatening events, asthma, pneumonia and bronchiectasis (11,16,18,20). Generally, many symptoms of GER are non-specific and overlap with those of other conditions (1), such as feeding problems and food allergies (21–24).

When GER causes troublesome symptoms and/or complications, it is defined as gastroesophageal reflux disease (GERD) (11). Complications of GER in children may include esophagitis, esophageal strictures, failure to thrive, feeding problems, and respiratory symptoms (16,17,20,25,26).

Esophagitis and other esophageal complications

GER may damage and cause inflammation of the esophageal mucosa, resulting in reflux esophagitis (4). In patients with severe, chronic GER the repetitive damage of the esophagus may lead to erosion, ulceration, and esophageal strictures (4,17). In some patients chronic acid exposure and inflammation may also lead to metaplasia of the esophagus, recognised as the premalignant condition Barrett`s esophagus that may progress further to esophageal adenocarcinoma (4,17,27).

Feeding problems

Symptoms and complications of GER such as esophagitis, esophageal strictures, vomiting, regurgitation, and airway infections may cause or aggravate feeding problems by causing dysphagia, food aversion, expulsion of ingested food, and infection related increased caloric need related to infections. Thus, there are many plausible explanations why GER may cause or contribute to feeding problems in children. However, although many children with GER have some feeding problems, severe feeding problems necessitating tube feeding is usually a complex problem (28). For instance, neurologically impaired children have an increased risk of developing severe, chronic GER which may affect feeding, but they are also at risk of developing severe feeding problems because of their underlying condition which may affect the child`s medical condition, motility of the gastrointestinal tract, and sensory and motor coordination of the oral cavity (28–30). In neurologically normal children with severe feeding problems requiring insertion of a gastrostomy, the two most common diagnosis are congenital heart conditions and cancer (28,30). Children with GER that are otherwise healthy, rarely have such severe feeding problems that tube feeding is required, although GER may cause or contribute to some feeding problems in these children.

Respiratory symptoms

Respiratory complications associated to GER include conditions such as chronic cough, asthma, pneumonia, and apparent life-threatening events (1,18,31). Aspiration of gastric contents may cause recurrent pneumonias (32). In addition, acid reflux in the esophagus may induce bronchial constriction leading to respiratory symptoms (1). However, the literature generally report limited benefits of surgical and pharmacological antireflux treatment on respiratory symptoms (31–33). Nevertheless, the current treatment guidelines on GER from NASPGHAN and ESPGHAN recognises that some patients

may benefit from treatment, and recommend that antireflux treatment should be considered in children with concomitant respiratory symptoms and GER (1).

6.3 Risk factors

There are some conditions that increase the risk of GER and GERD. These include neurological impairment and anatomical foregut abnormalities such as esophageal atresia and malrotation (1,11,27). Furthermore, conditions that increase the intraabdominal pressure, such as obstructive lung disease, seizures, and obesity are associated with an elevated risk of GER (27). There are also studies showing an association between DGE and GER (12–14). In addition, a positive family history of GER has been observed to increase the risk of GER (15). Some of the disorders associated with GER are also associated to feeding disorders (28).

6.4 Prevalence

The overall prevalence of GER in French children between 0-17 years was recently estimated to be 10.3%. The highest frequency was found in infants aged 0-23 months, where physiological GER was diagnosed in 24.4% (20). Two studies from USA also found a high occurrence of GER in infants, reporting that more than half of children aged 0-3 months regurgitate daily (34,35). The peak incidence occurs around the age of four months (15,34,35). After this age, regurgitation gradually decreases and often resolves spontaneously by 12-24 months of age (15,20,25,36). The resolution of GER during infancy is likely caused by the significant physical development that occurs, including elongation of the esophagus and the lower esophageal sphincter, larger volume of the stomach, maturation of gastrointestinal motility, changes in sleep pattern, and more time in the upright position. However, GER does not always resolve spontaneously during infancy. According to the French study, GER was present in 7.2% of children between 2-11 years and 10.7% of adolescents aged 12-17 years (20). The risk of developing persistent and symptomatic GER is highest in children having one or more risk factors (1).

The prevalence of GERD, defined as children having symptoms of GER impairing their daily lives, was assessed in the French cross-sectional study. The overall prevalence of

GERD in the pediatric population was estimated to be 6.2%; 12.6% among infant aged 0-23 months, 4.1% among those aged 2-11 years, and 7.6% among those aged 12-17 years (20). In selected cohorts, such as institutionalized intellectually disabled individuals, a much higher prevalence of GERD is reported (27). No cross-sectional study has been performed in Norway, and the overall prevalence of GER and GERD in infants and children in Norway is therefore unknown.

6.5 Diagnosing gastroesophageal reflux

A number of diagnostic modalities can be applied to verify GER and identify complications of GER. Which test to use depends on the information sought, and it is important to be aware of each test's limitations (1). Diagnostic tests are usually combined with medical history and physical examination to exclude conditions that may have similar symptoms as GER and to identify complications of GER (1,23,24).

pH monitoring

24-hour esophageal pH monitoring has long been the recommended test in investigating patients with suspected GER (1,37). It allows detection of acid reflux and quantification of esophageal acid exposure. The test may be useful in correlating symptoms to acid reflux episodes and to evaluate the effect of medical antireflux therapy. Test parameters such as reflux index (percentage of total measured time with pH below 4.0), number, and duration of reflux episodes are recorded by the pH probe. DeMeester and Boix-Ochoa score are calculated from these parameters to make results from a pH study easier comparable between patients. However, the reflux index is the most sensitive and reproducible marker (38).

A standardized protocol for the methodology and the interpretation of esophageal pH monitoring was published in 1992 by the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) (37). Current guidelines from the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPHGN) and ESPGHAN suggest that a reflux index >7% is considered abnormal, a reflux index <3% as normal, and a reflux index between 3% and 7% as indeterminate (1). Other cut-offs for pathological reflux index may be recommended by other guidelines, but the majority of these guidelines are based on older trials using glass electrodes, which record a lower mean pH than the antimony electrodes commonly used today (39).

Assessing GER with pH monitoring has several limitations. The pH probe does not detect esophagitis, anatomical abnormalities, or nonacidic reflux. Furthermore, symptom severity does not correlate well with the severity of pathologic acidic reflux (1,40). In addition, there are potential technical errors, the reproducibility is suboptimal, and some patients change diet and behaviour because of discomfort from the pH probe (27,38,40). These factors may affect the test result, and the investigation should be considered repeated or extended if the result does not correlate with the patient's clinical history (41).

Combined pH monitoring and multichannel intraluminal impedance

A 24-hour multichannel impedance with esophageal pH monitoring has been suggested as the new standard test for detecting GER in children (42,43). Multichannel impedance monitoring allows detection of bolus movements of liquid, fluid or gas bolus in the esophagus by recording changes in the electric resistance/impedance between electrodes placed along the probe (44). The multichannel impedance is usually combined with pH monitoring to allow a more complete characterization of GER. The pH probe registers the acidity of the bolus identified by the multichannel impedance electrodes, and the refluxed bolus is usually described as acidic (pH < 4), weakly acidic (pH 4-7) or nonacidic (pH > 7) (43). Combined pH monitoring and impedance is useful to quantify and detect reflux, particularly in the postprandial period or at other times when gastric contents are nonacidic (1,43). With combined pH monitoring and multichannel impedance a higher number of patients with GER and a better correlation between symptoms and GER can be detected than with conventional pH monitoring (42,44,45).

Data analysis is more time-consuming compared to pH monitoring only, and there is variable reproducibility and potential technical errors (44,46). So far, there is no data from combined pH monitoring and impedance from healthy children, and normal ranges are defined from studies in adults (42,43). Patient discomfort is similar to that of a pH monitoring.

Upper gastrointestinal contrast study

An upper gastrointestinal contrast study (UGI) involves swallowing of contrast and subsequent X-rays. It is useful to rule out or identify anatomical abnormalities in the upper gastrointestinal tract such as esophageal strictures, hiatal hernia, and malrotation

(47,48). Other conditions such as GER, esophagitis, Barrett's esophagus, and dysmotility in the esophagus can be evaluated with higher sensitivity and specificity using pH-monitoring, endoscopy, or manometry (45,49,50). Because of the UGI's low sensitivity and specificity in detecting GER, it cannot be recommended as the sole examination for diagnosing GER (1,47,48). It is a well-tolerated investigation due to short duration and minimal discomfort, but has the disadvantage of radiation exposure.

Endoscopy

Endoscopy offers direct visualization of the esophageal mucosa and stomach. Macroscopic lesions such as erosions, ulcerations, strictures, and changes consistent with Barrett`s esophagus can be detected directly (1). Microscopic lesions, including esophagitis, are diagnosed by taking multiple biopsies. Esophageal lesions are not common in children with GER, and their absence does not rule out GER (1). Endoscopy can be useful to rule out conditions that may mimic GERD, such as coeliac disease, eosinophilic esophagitis, and intestinal malabsorption (51). Endoscopy is an invasive procedure, and sedation or general anesthesia is required in children.

Scintigraphy

Gastrointestinal scintigraphy allows detection of acidic and non-acidic reflux to the esophagus and lungs, and assessment of gastric emptying rate. However, reflux demonstrated by scintigraphy has poor correlation to pH monitoring, and test results are limited by the lack of age specific norms and standardized procedure (52). It also involves radiation exposure (53). At present, NASPGHAN and ESPGHAN does not recommend nuclear scintigraphy as a routine diagnostic tool for GER (1).

6.6 Treatment of gastroesophageal reflux

Parental education, reassurance and anticipatory guidance are generally recommended for infants with GER symptoms that are not severe and where spontaneous resolution can be expected. In infants and children with GERD, treatment should be started to avoid complications if the diagnostic and clinical findings are consistent with GER (17). Conservative treatment using non-pharmacological and pharmacological treatment is the main approach. If this fails to relieve symptoms, one may consider surgical treatment.

Conservative treatment

Non-pharmacological treatment such as dietary modifications and positioning therapy are often recommended and used in infants and children with GER (20,34). However, there is little scientific evidence to support the effectiveness of these methods in reducing GER (54,55).

Dietary modifications commonly applied in infants include formula change, thickening agents and small frequent meals (20,34). Changing formula to one without cow's milk proteins may improve GER symptoms in some children (23). Thickened food does not reduce acid reflux index, but reduces the number of observed regurgitations (1,54). However, the effect of thickened food is moderate and side effects such as weight gain, coughing, and reduction or termination of breast feeding have been reported (34,54,56). Reducing the volume or frequency of feeds may relieve problems with regurgitation, but may have adverse effects on weight gain (1,15). Food that provokes symptoms should be avoided, but there is no clear evidence to support dietary changes in children/adolescents.

The effect of positioning therapy on GER has been assessed in a few studies. It seems that placing the child in the horizontal prone position or the left lateral position significantly reduce the number of reflux episodes compared to placing the child in the supine, the right lateral position, or in an infant seat inclined at 60° (55,57,58). However, in children less than 1 year the prone and lateral position are not recommended as sleep position, because these positions increase the risk of sudden infant death syndrome (59). Elevating the head of the bead when the child is in the supine position is often recommended to reduce GER (20). However, the data to support this advice is limited (55,58).

Pharmacological treatment is often used in addition to non-pharmacological treatment to achieve better symptomatic relief and prevent complications. Medical treatment for children includes altering the viscosity of feeds by alginates (Gaviscone), reduce gastric acid (antacids, histamine H_2- antagonists and proton pump inhibitors), and change the gut motility by prokinetics (metoclopramide, domperidone, cisapride, erythromycin, bethanechol) (60). Acid suppression by proton pump inhibitors are the mainstay of treatment in children and may be combined with alginate in infants to further reduce symptoms (60,61). In the majority of patients acid suppression therapy is effective

(61,62). However, acid suppressants do not reduce the total number of reflux episodes, and nonacidic reflux may also give troublesome symptoms (63). Particularly children with neurological impairment and repaired esophageal atresia, are prone to insufficient therapeutic response (62). There is limited evidence for the effectiveness of prokinetics in children with GER, and available data do not support the use of these drugs (60,64).

Surgical treatment

Different surgical procedures can be performed if conservative treatment fails to resolve GERD, such as gastrostomy feeding, jejunal tube feeding, and fundoplication (65–69). In children with GER and severe feeding problems it is debated which surgical treatment is most feasible as first line treatment (70–72). Currently, gastrostomy placement without fundoplication is commonly used as the primary approach in these patients (73–75). If GER remains a problem after gastrostomy placement, fundoplication should be considered (76).

Gastrostomy

A gastrostomy may be indicated if the child requires exclusive or supplemental nasogastric tube feeding for more than 1-3 months (77). A gastrostomy may simplify food administration, reduce feeding times and improve nutritional status. It has been established as a safe device for enteral feeding, and the gastrostomy can also be used for gastric decompression and administration of medications (77).

There are different methods for inserting a gastrostomy tube (78). Percutaneous endoscopic gastrostomy (PEG) insertion is widely used and has few technical contraindications (77). The PEG tube is often replaced by a button after 3-4 months when a gastrocutaneous fistula has been established. In the recent years, some centers have advocated a shift towards laparoscopic-assisted gastrostomy techniques, either as laparoscopic-assisted PEG insertion or other laparoscopic techniques for gastrostomy placement (79–81). Laparoscopic-assisted gastrostomy techniques provide direct visualization of the abdominal organs, and may thereby reduce the risk of organ injury associated with the blind component of the PEG technique. According to a Swedish literature review from 2010 comparing laparoscopic-assisted gastrostomy techniques and PEG insertion in a total of 4331 children, the frequency of severe gastrointestinal complications was 0% and 1,27%, respectively, and significantly higher in the PEG group (82). Other complications of gastrostomy placement include those related to

anaesthesia and procedure related complications such as granuloma, wound infection, leaks, clogging, breaking and detachment of the tube (30). However, it is not known whether some of these complications occur more frequently after PEG than after laparoscopic-assisted gastrostomy techniques, as no randomized trial has been performed in children. Furthermore, the data on complication rates after PEG and laparoscopic-assisted gastrostomy techniques are generally of low quality as only a few prospective trials have been published (79,83).

The effect of a gastrostomy on GER is debated. Some studies find increased GER after PEG placement, whilst others find no difference (84). One explanation of the controversial results it that the placement technique influences postoperative GER. One study reported that more patients receiving an open gastrostomy developed GER postoperatively than those receiving a PEG (76). Another study found that placing the gastrostomy in the antrum was unfavourable as it seemed to increase GER postoperatively (85). However, few studies have verified GER pre- and postoperatively by objective measurements such as pH monitoring, and the quality of the studies assessing the effect of a gastrostomy on GER are generally low (84). Consequently, the issue remains controversial.

Jejunostomy

Small bowel feeding may be preferred over gastric feeding in patients with severe GER and a high risk of aspiration. Jejunal tube placement has been suggested as a less invasive alternative to fundoplication in patients prone to severe complications of general anaesthesia or in those where previous antireflux surgery has failed (78,86,87).

Jejunal feeding access can be obtained by placing a gastrojejunal tube through the gastrocutaneous fistula or by surgically establishing a jejunostomy. Nasogastrojejunal or gastrojejunal tubes can be inserted radiologically or endoscopically. Although postpyloric feeding decreases the risk of aspiration and GER, the risk is not eliminated (86), and the risk of aspiration pneumonia with gastrojejunal feeding tube is comparable to that of fundoplication (32). Jejunal feeding requires 12-24 hours of feeding each day to avoid malabsorption (88,89). A main disadvantage of gastrojejunal tubes and some jejunal tubes is the need of hospitalisation for change of tube (22).

Fundoplication

Fundoplication should be considered in children who have significant symptoms of GER despite optimal conservative treatment (1). A fundoplication may relieve regurgitation, reduce esophageal stricture formation, improve weight gain, reduce the risk of aspiration pneumonia and other airway symptoms, and reduce the need for pharmacological antireflux therapy (90–92).

Fundoplication can be performed with various surgical techniques; Nissen, Thal, and Toupet fundoplication (66). These procedures are all based on folding the cranial part of the fundus around the esophagus. The goal of the operation is to restore normal antireflux barriers and thereby reduce GER related symptoms. The methods mainly differ by how much of the fundus that is wrapped around the esophagus. Narrowing the hiatus may be part of the procedure, and together with the wrap this constructs a higher pressure in the lower esophagus. Nissen fundoplication is the most commonly performed fundoplication procedure, and it can be done either by open or laparoscopic technique (93–95) (Figure 3).

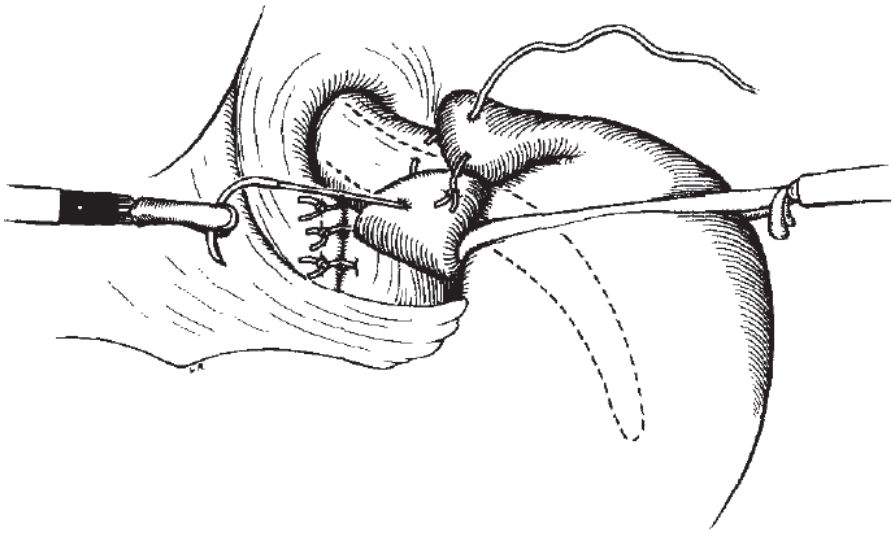

Figure 3. Nissen fundoplication. The fundus is wrapped 360° around the esophagus. (Reprinted from "Laparoscopic Nissen fundoplication in childhood" by Lobe TE et al, Journal of Pediatric Surgery, volume 28, page 358-361, 1993, with Permission from Elsevier.)

Complications after fundoplication include early postoperative complications related to general anesthesia and surgery, and complications related to the fundoplication. Early postoperative complications after fundoplication include pneumonia/atelectasis occurring in 4-17% (94,96–99), urinary tract infection in 3-7% (97,99), wound infection in 2-5% (94,96,97), sepsis in 3-6% (97,100), postprandial hypoglycaemia in 24% (101), wound dehiscence in 1-2% (97,99,100), dysphagia in 0-33% (90,94) and surgery-related mortality in 0-6% (90,94,99,100,102). Complications that may occur later include dumping syndrome in 1-4% (94,100), retching in 27-32% (96,103), small bowel adhesions in 5-28% (99,100,104), herniation of the wrap 4-30% (26,100,105), and recurrence of GER in 5-25% of patients (91,94,96,99,100,106–109). Patient comorbidity affects early and late outcome, and it is generally accepted that children with esophageal atresia and neurological impairment have the highest complication rate and poorest outcome (100,110–112). The wide range of reported complication rate likely depends on the study design and the patient selection (113).

In studies relating gastric emptying rate to outcome after fundoplication, the presence of DGE has been associated to recurrence of GER after fundoplication (114,115). Consequently, some surgeons do a pyloromyotomy concomitantly with the fundoplication if DGE has been demonstrated (114,116). A pyloromyotomy may have unwanted side effects such as dumping and diarrhoea (117), and the benefit of adding a pyloromyotomy has been questioned (118,119). Since there are no clear recommendations on which patients that should have a pyloromyotomy concomitantly with a fundoplication, further studies on the occurrence of DGE in GER patients and whether DGE affects outcome after surgery should be performed before children are selected for a drainage procedure.

6.7 Laparoscopy

In the recent decades laparoscopic surgery has become the preferred technique for a variety of surgical procedures in children (120). Laparoscopic surgery was first described in 1901 by the German urologist Georg Kelling (121). Technical and medical challenges restricted the use of laparoscopy in general surgery for nearly a century, but with evolution of technology, laparoscopic surgery could be performed more safely and

efficiently. A rapid development of the laparoscopic technique and increased enthusiasm were seen from the late 1980`s in adult surgery. Less postoperative pain, faster convalescence, reduced length of hospital stay, and better cosmetic results are some of the advantages achieved by laparoscopy compared to the open approach (122,123).

The assumed benefits of laparoscopy and the development of laparoscopic surgical instruments suited for children have increased the popularity of the technique, leading to a rapid shift towards laparoscopic surgery during the last two decades (124,125). A wide range of laparoscopic procedures are now being performed in pediatric surgery, but the increased use has not been followed by an equally large increase in the scientific evidence of the advantages of laparoscopy compared to laparotomy (124). A recent review assessing the number of randomized trials comparing laparoscopic and open surgery in children, identified only six trials on appendectomy, three trials on pyloromyotomy, three trials on inguinal hernia repair, one trial on pyeloplasty, two trials on orchidopexy, four trials on varicocelectomy, and one trial on fundoplication. Interestingly, no randomized trials of the Kasai`s procedure, pediatric malignancies, surgical treatment of Hirschsprung`s disease or intrathoracal procedures could be found (120). Although some of the randomized trials in children demonstrated advantages of the laparoscopic technique compared to the conventional open approach regarding postoperative pain, length of hospital stay, complication rate and improved cosmetics, this was not a uniform finding (120,124). Therefore, assuming superiority of laparoscopy in children by transferring results from adults to pediatric patients may be doubtful. Children are not “small adults” and may respond differently to a surgical trauma than adults (126).

Laparoscopic versus open Nissen fundoplication

The first pediatric laparoscopic Nissen fundoplication (LNF) was performed in 1993 (93). Since then, an increasing proportion of fundoplications in children is being performed laparoscopically, and the majority of pediatric surgeons consider LNF as a better method than open Nissen fundoplication (ONF) (97,127–130). Laparoscopy may have lowered the threshold for surgical treatment of GER in children since many physicians and parents consider keyhole surgery less traumatic than open surgery (131). Despite the preference of laparoscopy to laparotomy, and that it is two decades since

LNF was introduced, there is still only one randomized trial that have examined if LNF is superior to ONF in children (96). The majority of publications comparing LNF and ONF are retrospective or prospective cohort studies, concludes that LNF is superior to ONF with regard to length of hospital stay, costs, analgesia demand and complication rate (90,97).

Short-term results

Non-randomized studies comparing analgesia demand after LNF and ONF generally conclude that LNF patients require significantly less analgesia postoperatively than ONF patients (130,132,133). There are also reports favouring LNF when assessing short-term complication rate (106,109,134,135). In line with this, a meta-analysis from 2011 comparing LNF and ONF in children concluded that 30-day morbidity was significantly lower after LNF than ONF (129). Shorter length of hospital stay after LNF compared to ONF has been reported by several trials (97,109,130,132,133,135). In contrast to these non-randomized studies and the meta-analysis, the two only randomized trials comparing LNF and ONF in children did not find any difference in complication rate or length of hospital stay between LNF and ONF (96,136). One of these studies also assessed analgesia requirements, and found no difference between LNF and ONF groups (96).

Long-term results

Adhesions after abdominal surgery may cause small bowel obstruction. The incidence of this complication after LNF and ONF was compared in a retrospective study including 232 patients. Adhesional bowel obstruction occurred in 4.8% of patients, with no significant difference between the groups (104).

In the randomized trial from Great Ormond Street Hospital for Sick Children comparing LNF and ONF in children, a similar redo and recurrence rate among the groups was reported (96). However, recurrence of GER was a secondary outcome measure in this study, and the small number of patients renders the study with low power to detect differences in outcome. Recurrence of GER after LNF and ONF has also been reported in some non-randomized trials in children. A recent meta-analysis included three of these studies which included a total number of 99 children, and concluded that there was no difference in recurrence rate at 12 months after LNF and ONF (129). In contrast, a meta-analysis in adults including only randomized trials and a total number of 1036

patients, reported a 79% higher reoperation rate caused by treatment failure after LNF compared to ONF (122). Moreover, two recent publications in children reported high recurrence rate after LNF compared to previous experience with ONF (26,105).

6.8 Evaluating outcome after surgery

Traditionally, studies evaluating outcome after surgery have reported morbidity and mortality related to the surgical procedure as assessed by the surgeon or by other professional health care workers. These outcome measures are usually referred to as clinical outcome or measures of disease process (137). The focus in such studies has mainly been to assess severity and frequency of various postoperative complications, comparison of surgical techniques, whether the surgical procedure improved the condition as judged by the surgeon, and whether a successful outcome can be predicted by specific patient demographics, choice of surgical technique, or other clinical variables (75,76,81,94,109,138).

Until recently, there were few surgical studies assessing the patient's perspective of outcome. Outcome judged by the patients themselves may differ from judgement by professionals (137,139). Therefore, there has been increased attention towards obtaining the patient's view on treatment efficiency and outcome in the recent years (140). This is generally denoted as "patient reported outcome", which refers to various types of self-reports by the patient. Patient reported outcome measures can be classified as disease-specific measures, generic measures, and measures of patient satisfaction (137). Questionnaires are frequently used in research assessing patient reported outcome, and the questionnaires may contain questions assessing one or more constructs such as organ specific symptoms, functioning, quality of life, and health-related quality of life. The questionnaires are often filled out by the patients themselves or completed by interviews. In patients who are neurologically impaired, too young to understand the questions or for other reasons are unable report outcome, one may use substitutes to obtain patient reported outcome data such as asking parents or care-givers about how they assess symptoms or perceive outcome (108). A number of questionnaires on health related quality of life assessment for adults with gastrointestinal disease or GERD have been developed (141). There are also a number of studies assessing pre- and postoperative quality of life in adults undergoing fundoplication (142). In children,

structured assessments of patient reported outcome after fundoplication using validated instruments have so far been scarce (142).

The choice of primary outcome measure may affect which treatment is considered the best option. The study design is also important when assessing treatment efficiency, particularly when comparing outcome between different patient groups or interventions. The majority of studies evaluating outcome after surgery have been retrospective or prospective cohort studies. Randomized controlled trials are generally scarce in the surgical literature. Less than 4% of the published studies in the time period from 1966 to 2000 in the five leading surgical journals (Annuals of Surgery, Archives of Surgery, British Journal of Surgery, World Journal of Surgery, and Surgery) are randomized controlled trials, and more than half of the published randomized trials in surgical patients from 1991-2000 compare medical therapies and not different surgical procedures (143). As randomized trials are considered the highest level of evidence in the concept of evidence-based medicine, it has been argued for many years that more randomized trials are needed in surgery in order to decide whether one treatment is superior to another. In addition, the adherence to guidelines such as the CONSORT guidelines (Consolidated Standards of Reporting Trials) developed to improve the quality of reporting studies in the medical literature is generally low (144). In many fields of adult surgery, various scales and classifications have been developed to standardize how pain, postoperative complications, and disease-related symptoms are measured and reported (113,142,145). In the field of pediatric surgery there have been developed many pain scales (146), but there is still a need to validate or develop scales and classifications on complications and other outcomes to ensure that these are reported more heterogeneously (135,147). Taken together, these issues regarding study design and how results are reported may influence how outcome of surgery is perceived.

7. Hypotheses

1. Gastrostomy improves feeding problems and the child's overall condition

2. Nissen fundoplication improves GER symptoms and the child's overall condition

2. Hospital stay is shorter and complication rate is lower after LNF than after ONF

3. Children with GER have DGE compared to healthy children

8. Aims

1. To study short and long-term outcome of gastrostomy placement and fundoplication with particular emphasis on parents' assessment of postoperative outcome

2. To study complications and early outcome in patients randomized to LNF or ONF

3. To study whether children with GER had slower gastric emptying than healthy children

9. Materials and methods

Study I

Subjects

Children receiving a PEG from January 1994 to December 2002 at Rikshospitalet were considered for inclusion. Of 125 eligible children, 121 were included. The remaining 4 patients were excluded because of insufficient data (n = 1) or because of Nissen fundoplication concomitantly with PEG insertion (n = 3). Of the 121 included children, 29 died in the period between PEG insertion and phone interviews. Only families of the 92 children that were alive in 2004 were approached for phone interviews. Eighty-five caretakers (92%) were successfully contacted and agreed to participate in the follow-up study.

Method

Retrospective chart reviews recording patient demographics, preoperative investigations, indications, and complications related to the PEG procedure were performed. In addition, a semi-structured phone interview with the child's caretakers was done. Outcome measures were parental satisfaction, child's well-being, effect of the gastrostomy on feeding, vomiting/retching, GER, and stoma-related complications. The number of patients having a subsequent Nissen fundoplication was recorded.

Statistics

No power calculation was performed as the main aim was to describe the patient population and register long-term results as evaluated by the parents. Due to skewed data, age was given in median [range] and compared among subgroups by Mann Whitney U-test. Influence of PEG on changes in vomiting/retching and feeding habits was tested using McNemar test. Analysis was performed with SPSS software (SPSS 12 for Windows; SPSS, Inc, Chicago, IL). A value of $P \leq .05$ was considered statistically significant.

Study II

Subjects

The study population comprised patients operated with a primary Nissen fundoplication between 1990 and 2001 at Rikshospitalet. Of the 101 children operated, eight were excluded from the study because of missing or faulty records. Hence, 93 patients were included for the medical chart registration. Only parents of the 80 children alive in 2004 were contacted for phone-interview, of which 75 (94%) were successfully contacted and agreed to participate in the follow-up study.

Method

Retrospective chart review recording patient demographics, indications and complications related to the Nissen fundoplication, and a semi-structured phone interview with the child's caretakers were performed. Outcome measures included parental satisfaction after the Nissen fundoplication and their evaluation of the child's overall well-being. In addition, frequency of vomiting/retching, changes in sleep pattern, respiratory symptoms, and whether the child had undergone a redo fundoplication was recorded.

Statistics

No power calculation was performed as the main aim of the study was to describe the patient population and register long-term results after Nissen fundoplication as evaluated by the parents. Due to skewed data, age was given in median [range]. Age in children with and without neurological impairment was compared by Mann Whitney U-test. Analysis was performed with SPSS software (SPSS 12 for Windows; SPSS, Inc, Chicago, IL). A value of $P \leq 0.05$ was considered statistically significant

Study III

Subjects

All patients accepted for a primary Nissen fundoplication from January 2003 to December 2009 at Rikshospitalet, and from January 2007 to December 2009 at Ullevål, were considered for inclusion. During this period, a total of 107 patients were eligible.

Patients were excluded from the study for the following reasons: Age over 15 years at referral (n = 2), parents that did not speak Norwegian (n = 1), multiple previous laparotomies (n = 4), comorbidity assessed to be incompatible with laparoscopy (n = 4), need of urgent operation and no time for randomization (n = 2), and unwillingness to participate (n = 6). Thus, 88 children entered the study, 75 patients from Rikshospitalet and 13 from Ullevål.

Method

The study was designed as a prospective randomized trial. Included patients had a preoperative pH-monitoring and an UGI. Included patients were randomized to either ONF or LNF in non-stratified blocks of 10. Patients and parents were informed about operative method prior to surgery. LNF and ONF were done according to strict surgical and anesthesiological guidelines, and procedures were performed identically except from the approach of laparoscopy or laparotomy. Only trained laparoscopic surgeons having performed at least 30 LNF performed the laparoscopic procedures. ONF was done by trainees under supervision of a consultant or by consultants.
Patient demographics such as gender, neurological status, scoliosis, presence of a preoperative gastrostomy tube, and symptoms of GER were recorded. Postoperative complications were graded according to the Clavien-Dindo classification (145). All outcome measures were secondary end-points and included operating time (from skin incision to wound closure), complications during surgery, complications occurring the first 30 postoperative days, and length of hospital stay.

Statistics

Gender, neurological status, the presence of preoperative gastrostomy tube, scoliosis, and postoperative complication were categorical variables and analyzed with Pearsons Chi-square or Fishers exact-test as appropriate. Duration of surgery had a normal distribution and was expressed as mean ± [SD]. The student`s t-test was used to compare duration between LNF and ONF. Age, duration of surgery in patients having a gastrostomy concomitantly with fundoplication, and length of hospital stay in the LNF and ONF group were not normally distributed and thus expressed as median [range] and compared by Mann-Whitney U test. All analyses were performed with PASW Statistics version 18 (IBM SPSS, Armonk, NY). A P value $< .05$ was considered statistically significant.

The primary outcome of the study was recurrence of GER. A secondary power analysis was performed to determine the number of patients required to detect differences in the complication rate. The power was set at .80 and the significance level at .05. With the sample size of 88 patients, the minimum difference in complication rate that we would have been able to detect is 30%, corresponding to approximately 24 patients with complications in one group, and 15 in the other group.

Study IV

Subjects

Patients in this study were children accepted for Nissen fundoplication from 2003 to 2009 or gastrostomy insertion from 2003 to 2006 at Rikshospitalet. Predefined exclusion criteria were previous antireflux surgery, major abdominal surgery within the last six months prior to referral, and parents that did not speak Norwegian. Inclusion criteria were symptoms of GER and GER diagnosed by a 24-hour ambulatory pH monitoring. A total of 102 GER patients (gastrostomy n = 25, Nissen fundoplication n = 77) were eligible for the study according to these criteria. Half of these patients (n = 51) were excluded for the following reasons; parents reporting any form of cow's milk intolerance or allergy, unable to lie still, or parents refusing participation.

Twenty-five healthy children with no symptoms suggestive of GER including heartburn, regurgitation, vomiting, and feeding difficulties, were recruited among children of the hospital staff as a control group. One healthy child was excluded because it did not cooperate during the scintigraphy.

Method

Gastric emptying was examined in 51 GER patients and 24 healthy children using scintigraphy and a test meal of cow's milk. Patients and controls ≥ 4 years were given 200 ml of full cream cow`s milk (277 kJ, 3.2 g protein, 4.6 g carbohydrates, and 3.9 g fat /100 ml) to finish, while younger children were asked to drink at least 100 ml. Patients having a gastrostomy or a nasogastric tube were fed through the tube using the same criteria. According to these criteria, all children were given the highest volume up

to 100 or 200 ml they were willing to drink, or, in those having a feeding tube, able to tolerate without vomiting.

After intake of the test meal, the children were immediately placed in the supine position under the gamma camera. Serial scintigrams in ventral and dorsal position over the abdomen were acquired at 90 second intervals for 90 minutes. From these data, half time ($T_{1/2}$) of gastric emptying was calculated. Age, gender, neurological status, presence of a feeding tube, and symptoms of GER were prospectively recorded in all patients and controls regardless of the volume received.

Statistics

Categorical variables of neurological status and feeding tube were analyzed with Fisher`s exact test or Pearson Chi-Square. Age and reflux index were not normally distributed and therefore compared by Mann-Whitney U test. Gastric emptying rates in GER patients and healthy children, and in subgroups of GER patients, were compared using a two-tailed Student t test. Multivariable regression analysis was performed to determine difference in mean $T_{1/2}$ between patients and controls adjusted for any confounding effect by age, neurological status, and volume received. Analyses were performed with PASW Statistics version 18 (IBM SPSS, Armonk, NY). A p-value $< .05$ was considered statistically significant.

10. Ethics

For all four studies the protocols were reviewed and approved by the Regional Ethical Committee. Before phone interviews were conducted in study I and II, a letter was sent to parents/guardians to inform about the study. In study III and IV, written informed consent was obtained from all parents/guardians before inclusion. The randomized trial recruiting patients to study III and IV was registered in ClinicalTrials.gov with identifier NCT015511342.

11. Summary of main results

Paper I: *Percutaneous endoscopic gastrostomy in children: A safe technique with major symptom relief and high parental satisfaction*

Parental satisfaction after PEG was high, and 94% of parents reported that the PEG had a positive influence on their child's situation median 5.6 years (range 1-10 years) after surgery.

Preoperatively, 82% of children had a nasogastric tube. Symptoms suggestive of GER (vomiting/retching) were present in 77% preoperatively. Excluding the 13 % of children operated with antireflux surgery after PEG placement, vomiting was significantly reduced postoperatively. The change in vomiting frequency was not significantly different between those who had a pathological pH index before PEG and those who had a normal pH monitoring. Stoma related complications were common and reported by 73% of the parents at follow-up. Most of these were easily treated and handled by the parents without requiring hospital admissions. In the retrospective chart review, complications occurring the first 30 days after PEG insertion were registered in 12% of the children (15/121), and included pneumonia (n = 2), stoma-related infection (n = 10) and tube dislodgement (n = 3). All infections were treated either with local or systemic antibiotics. The dislocated tubes were all replaced without the need for a second surgical procedure. Despite the complications, 98% of the parents would have chosen PEG insertion again.

Paper II: *Satisfactory long-term results after Nissen fundoplication*

Overall, 83% of parents of children operated with a Nissen fundoplication were completely satisfied with postoperative outcome median 6.0 years (2.5-12 years) after surgery, and 92% reported better well-being of the child at follow-up. When dividing patients into subgroups, improved overall condition was reported by 96% of parents with a neurologically normal child, 94% of those with a neurologically impaired, and 78% of those with a child with repaired esophageal atresia. Pulmonary symptoms were reduced in 59% of patients, and the quality of sleep improved in 68%. At follow-up,

10% of the patients had been operated with a redo Nissen fundoplication. All patients undergoing redo fundoplication were either neurologically impaired or had repaired esophageal atresia. According to the parents, all children had benefited from the redo procedure.

Of the 93 children included in the chart-review, we registered 10 major postoperative complications (11%): Wound infection, sepsis, pneumothorax, rupture of the wound, splenectomy, and ascites needing drainage. Four children died within the first 30 postoperative days of causes related to their underlying disease. Another nine patients died during follow-up. In one of these nine children the cause of death was related to the fundoplication, as it had a splenectomy at the same time as the fundoplication and died of sepsis caused by *pneumococcus*. The cause of death was unknown in the other eight children.

Paper III: *30-days outcome in children randomized to open and laparoscopic Nissen fundoplication*

Operating time was significantly longer for LNF (mean 150 minutes ± 34) than for ONF (mean 89 minutes ± 25) ($p = .001$). There were 65 early postoperative complications occurring in 48/88 patients. Thus, some patients had more than one postoperative complication. There was no significant difference in number or severity of postoperative complications between the ONF and LNF groups. The most commonly identified complications were airway related symptoms, feeding problems and gastrostomy infections. Length of hospital stay at Ullevål or Rikshospitalet was significantly shorter after LNF than ONF (LNF: median 4.5 [range 2-21] versus ONF: median 6.0 [range 2-9]) ($p = .04$) However, there was no difference in total length of hospital stay (LNF: median 7.0 [range 3-57] versus ONF: median 7.5 [range 2-20]) when combining days at Rikshospitalet/Ullevål and local hospital ($p = .74$). Twenty-three patients were readmitted to hospital after discharge, and the most frequent cause was feeding problems. Renewed hospitalization was required in 11 of the 23 readmitted patients. There was no difference between the LNF and ONF groups with regard to the number of patients readmitted, requiring a second hospital stay, or complication type reported at readmission.

Paper IV: *Gastric emptying in children with gastroesophageal reflux and in healthy children*

There was no significant difference of the gastric emptying rate in the 51 GER patients as compared to the 24 healthy children ($T_{1/2}$ patients: mean 49 minutes [SD 20.1] versus $T_{1/2}$ controls: mean 46 minutes [SD 14.2], p = .51). Patients with severe GER had gastric emptying rates similar to those with mild GER, and neurologically impaired GER patients did not have slower gastric emptying than those without neurological impairment. In the multiple regression model the difference in $T_{1/2}$ between patients and controls increased from 3.1 minutes (95% C.I: -6.2 to 12.4) to 7.7 minutes (95% C.I: -3.8 to 19.3) when adjusting for confounding effects of age, neurological status and volume received. However, this difference in $T_{1/2}$ was not statistically significant (p =.18). A wide range of gastric emptying rates was observed in both GER patients (range 16-121) and controls (range 29-94). Only one (2%) of the patients had a longer $T_{1/2}$ (121 minutes) than the control child with the slowest gastric emptying ($T_{1/2}$ = 94 minutes). Interestingly, the gastric emptying rate was within normal ranges 6 months after fundoplication in this particular patient ($T_{1/2}$ = 61 minutes). The group of excluded patients was not significantly different from those included in the study with respect to age (p = .06) and number of neurologically impaired patients (p = .52).

12. Discussion

12.1 Parental assessment of effects of gastrostomy insertion

The majority of parents in Study I reported that the child's situation had improved after PEG and that they would have chosen gastrostomy again. There are many effects of a gastrostomy that likely contributed to the parental assessment that the PEG insertion was of great help for themselves and their child. Most children in Study I had a nasogastric tube preoperatively. A nasogastric tube may increase facial defensiveness and oral aversion (148). Furthermore, parents may consider the nasogastric tube as a visible sign of disability (149). A gastrostomy is less visible and generally better accepted, and some parents expressed relief that they "got rid of the nasogastric tube" during follow-up interviews for Study I. Parents also reported that vomiting was significantly reduced postoperatively. Vomiting may cause loss of ingested food, and parents may worry that the child will aspirate or choke. We have recently reported that feeding problems are associated to increased maternal distress, and that gastrostomy insertion reduces maternal psychological distress and maternal concerns for the child's feeding problems (150). Caregivers of children with feeding problems spend several hours a day on feeding, and reduced feeding time is associated with more quality time with the child and reduced parental stress (22). The tension during meals when parents struggle to make their child eat may have been reduced after PEG insertion, as well as parental concerns about the child's nutritional status (151). In Study I we found that nearly half of the children had improved the degree of oral intake after PEG insertion, and one-quarter of the patients had permanently removed the gastrostomy tube at follow-up. Oral feeding is considered an important social activity by many parents, and therefore improved oral intake after gastrostomy insertion is likely considered as a positive outcome (149). We believe that all these factors contributed to the high parental satisfaction rate and their conclusion that the gastrostomy had improved the overall well-being of the child. The high parental satisfaction suggest that PEG insertion is a good treatment option in children with severe feeding problems (152).

In the chart-review, we registered a 12% complication rate during the first 30 days after PEG insertion. A recent literature review report similar frequency and severity of early complications after PEG insertion in other trials (30). Most children had experienced

one or more skin problems related to the gastrostomy such as stomal infection, hypergranulation, leakage and redness around the tube, but most of these problems were easily treated and handled by the parents. However, some parents reported that they had experienced lack of knowledge among health care providers (mainly general practitioners and local hospital) about how to treat the skin problems. This is an important feedback that needs to be addressed, as long-term complications of PEG and gastrostomy tubes are common, particularly stoma related complications (77). Nonetheless, the overall positive impact of having a gastrostomy for enteral feeding access was considered to outweigh the negative sides by the large majority of parents, and 98% would have chosen gastrostomy again.

12.2 Gastrostomy and gastroesophageal reflux

Vomiting in children is an unspecific symptom, but may be indicative of GER. We found that three-quarter of the patients accepted for PEG insertion had frequent vomiting/retching preoperatively. After PEG insertion, most children had improved with regard to these symptoms.

The reduction of vomiting/retching after PEG insertion may be caused by several factors. Preoperatively, 82% had a nasogastric tube. It is well known that a nasogastric tube may increase GER by acting as a stent through the lower esophagus sphincter (153). Therefore, just removing the tube may reduce GER and thereby relieve GER symptoms. A generally improved medical condition may also have contributed to the reduction in vomiting/retching.

After PEG insertion, 13% of patients included in the follow-up had undergone antireflux surgery. The number of patients undergoing fundoplication after PEG insertion corresponds well to that of other studies (71,74,75,154). It is difficult to predict how insertion of a PEG will influence GER symptoms (73) and which patients that ultimately will need a fundoplication (71,75,154). A prospective study measuring reflux index before and after PEG-placement found that a PEG did not provoke GER (85), and a systematic review from 2012 came to a similar conclusion (84). Fundoplication is a major procedure and the rate of major complications is considerably higher than after placement of a PEG. A fundoplication can relatively easily be performed as a second procedure should the child develop severe GER after PEG insertion (73–75). Therefore, our policy is to give the child a gastrostomy first unless

the child suffers from massive GERD or have complications of GER such as esophageal stricture.

12.3 Parental assessment of results after Nissen fundoplication

In study II, we found that the majority of parents reported reduced vomiting, reduced pulmonary symptoms, improved quality of sleep, and better well-being of the child after Nissen fundoplication. Moreover, most parents were completely satisfied with the postoperative results. Interestingly, parents of neurologically impaired children reported equally good results as parents of neurologically normal children.

The high parental satisfaction and improved situation of the child after Nissen fundoplication in Study II may have several reasons. Daily vomiting may be a major concern for parents. One mother participating in the phone-interviews in Study II had a designated hand bag that the child could vomit in when they went outside the house, and she described that the uncontrolled vomiting and the associated smell was a significant social stigma. Other parents reported that they never slept a whole night preoperatively because the child had sleeping problems due to discomfort from GER, and if the child vomited they needed to get up to change the child's bed and clothes (Study II, unpublished data).

The association between asthma and GER, and other respiratory symptoms and GER, remains debated (18,31). In some of the children in Study II, medical records suggested that frequent pulmonary infections could be due to aspiration of gastric contents. We found that approximately half of the children had less severe and/or less frequent respiratory infections as evaluated by parents postoperatively. A recent trial found that 91% of children with steroid-dependent asthma reported subjective improvement after fundoplication, and 80% could be weaned off oral steroids (155). Another study reported that more than 80% of neurologically impaired children with predominantly respiratory symptoms before surgery, were symptom free at 3 and 15 months after fundoplication (111). However, other studies found no improvement in respiratory symptoms after fundoplication (156,157). No improvement of hospital admissions for pneumonia, respiratory distress/apnea, and failure to thrive was found before and after Nissen fundoplication in a study including 342 children (157). These findings were supported by another trial including 3721 neurologically impaired children, which reported that the number of hospital admissions for pneumonia and asthma either

remained constant or increased after fundoplication (156). However, in this latter study hospital admissions decreased for aspiration pneumonia, GERD and mechanical ventilation. The decrease in reflux related admissions after fundoplication was dependent on the child's age at surgery, and was greatest in children who had surgery before the age of 1 year. In our study, the reduced number and severity of respiratory infections may be related to increased age in the children, improved medical condition, or improved nutritional status after fundoplication, and not necessarily caused by disappearance of GER.

Fundoplication may improve growth and weight gain in children with major feeding problems related to or aggravated by GER (142). The weight gain after fundoplication may be attributed to reduced food spilling by inefficient oral intake caused by retching/vomiting, less food aversion, and/or concomitant gastrostomy insertion. The children that got a gastrostomy concomitantly with the fundoplication probably experienced gastrostomy-related benefits as discussed in paragraph 12.1, adding to the positive influence of outcome after fundoplication.

We believe that all the above mentioned factors contributed to the overall improved well-being of the child that was reported by 94% of parents who had children alive when follow-up was conducted in Study II. In general, trials interviewing caregivers report good results after Nissen fundoplication (22,91,108,142). In our study, one of the parents stated that "The whole family got a new life after the Nissen fundoplication", another that "Our child is much more contempt and happy now" (Study II, unpublished data), illustrating the significant subjective improvement that some parents experienced after fundoplication. Changes in quality of life induced by fundoplication was assessed in a prospective study, finding improved growth, symptom score, feeding parameters and quality of life in parents and child measured by the Gastrointestinal Quality-of-Life Index (GIQLI) (142).

During phone-interviews of parents in Study II, it was revealed that some parents had unrealistic expectations about postoperative outcome. These expectations included among others cessation of all feeding problems, no more vomiting or retching, and complete relief of respiratory infections and symptoms after surgery. Unmet expectations are a powerful predictor for patient dissatisfaction (158,159). This may explain some of the tendency towards discrepancy between number of parents reporting

improved well-being of the child (94%) and the number of parents that were completely satisfied with the postoperative result (83%) in Study II.

Some parents reported during phone-interviews that they did not fully comprehend the preoperative information about common complication and consequences following Nissen fundoplication (Study II). For instance, a few reported that they did not understand the practical implication that their child might not be able to vomit postoperatively. Parents of neurologically normal children reaching adulthood worried that their child might intoxicate themselves with excessive amounts of alcohol and not be able to vomit. Other parents reported that they constantly worried that the fundoplication had failed if the child had retched during gastroenteritis. Furthermore, severe retching lasting several hours and a prolonged duration of gastroenteritis worried parents who had not been informed about this preoperatively. We also learned that some children in Study II needed weeks or even months after discharge from hospital before they had recovered and were "themselves again" and the positive effects of surgery were revealed. Some of the neurologically impaired children needed months before they tolerated the same feeding volume as preoperatively without retching. However, most parents reported improvement over time, which was recently demonstrated in another study reporting increased feeding volume and reduced duration of feeding time six months postoperatively compared to the preoperative status (142).

Many of the parents in Study II and III reported that their child had had symptoms of dysphagia, frequently combined with inability to belch and more flatulence postoperatively (unpublished data). In Study III, we found that three children required endoscopic treatment of food impaction during the first 30 postoperative days and 17 children had postoperative feeding problems. Data on dysphagia in children after fundoplication is generally scarce in the literature, possibly because these data can be difficult to obtain since many of the patients are non-verbal due to neurological impairment and/or young age. Still, a recent meta-analysis reported that postoperative dysphagia is a rather common symptom after fundoplication, occurring in 0-33% of children (90). According to the same study, dysphagia usually resolves spontaneously after a few months (90), although dysphagia requiring dilatation has been reported (160). Thus, parents should be informed preoperatively that postoperative feeding problems and dysphagia is common in the first months after fundoplication. In addition,

informing parents to encourage the child to chew food thoroughly, drink fluids between each bite, and avoid certain types of food such as sausages, hamburgers and hard fruits, may reduce readmissions caused by dysphagia and food impaction. Moreover, pureeing the food the first weeks after surgery may relieve feeding problems caused by dysphagia according to some parents, and the discomfort associated with inability to belch/more flatulence was often reduced by avoiding large meals, fizzy drinks, cabbage, and onions.

We found that Nissen fundoplication was associated with a relatively high complication rate, but comparable to that reported by others with a similar patient group (94,96,99,112). In both study II and III we registered complications requiring surgical or endoscopic treatment. In study II, there were also four early mortalities. Both complications requiring surgical treatment and complications resulting in mortality have been reported previously (94,160). The children that died within the first 30 days after surgery in Study II all had severe underlying comorbidities, and were operated because they had experienced severe life-threatening episodes of aspirations. In retrospect, accepting these children for fundoplication might be questioned. Accepting children with severe comorbidities to a procedure that may have fatal outcome is ethically challenging, although the fundoplication was performed to prevent further life-threatening aspiration episodes in these patients.

It is generally accepted that patients with severe underlying comorbidities are most likely to experience severe early postoperative complications and recurrence of GER (98,112). However, when assessing result in those still alive at follow-up, we and other studies found a surprisingly high parental satisfaction rate in these patients (91,108,142). Therefore, if conservative management fails, we think parents of children with GERD should be informed that fundoplication might be an option and that these children should be referred to a pediatric surgical department for an evaluation. However, parents must be informed that severe complications may occur, requiring surgical intervention and/or resulting in surgery-related death. Taken together, we emphasize that thorough preoperative information about short- and long-term outcome is important and must be given to ensure realistic expectations and satisfaction with the result.

12.4 Laparoscopic versus open Nissen fundoplication

The results of our randomized trial comparing LNF and ONF contradict the general assumption that laparoscopy gives a shorter hospital stay and fewer complications than the open technique (129). We found that frequency and severity of early postoperative complications and total length of hospital stay were similar after LNF and ONF.

In both LNF and ONF groups, more than half of the patients experienced one or more early postoperative complications. Neither severity nor frequency of early complications differed between LNF and ONF groups. Non-randomized trials frequently have selection bias towards patients with more severe comorbidities in ONF groups, which may explain why many trials report higher complication rates in ONF than LNF groups (135).

Patients in the LNF group were discharged earlier to their local hospital in our trial, but the total length of hospital stay was not significantly different between LNF and ONF groups. Our conclusion is supported by the blinded, randomized trial by McHoney et al (96). A recent meta-analysis comparing LNF and ONF concluded that duration of hospital stay is shorter with LNF than ONF (129). However, the duration of hospital stay is affected by many factors including surgical method, postoperative pain, complications, use of fast-track elements and discharge criteria, which was not standardized in our trial or among those included in the meta-analysis.

Although our findings did not support the general assumption that children undergoing LNF have less early complications or a shorter hospital stay than patients undergoing ONF, we did show that LNF is a safe alternative to ONF with regard to early outcome. Particularly, there was no difference in the number of patients with severe complications requiring endoscopic or surgical treatment, airway complications, or readmission rate.

12.5 Recurrence of gastroesophageal reflux after Nissen fundoplication

Reported recurrence rate after fundoplication varies significantly. Patients with recurrent GER may present with retching and/or vomiting after feeding and complications secondary to GER such as weight loss, pneumonia, and abdominal pain (26,161). Recurrence of GER is associated to neurological impairment, esophageal atresia, DGE, and young age at primary fundoplication, and thus patient selection likely

affects recurrence rate (111,114,138). We found that all patients undergoing redo fundoplication in Study II were either neurologically impaired or had repaired esophageal atresia. In total, 10% of patients had been operated with a redo fundoplication, which is an acceptable recurrence rate compared to other trials with similar patient population (94,112).

12.6 Delayed gastric emptying rate and gastroesophageal reflux

The association between GER and DGE has been debated for decades (115,162–164). Some studies find DGE in children with GER (12–14), whereas others find no association between gastric emptying rate and GER (164–170). In our study assessing gastric emptying of a caloric, liquid meal, we did not find that children with GER have significantly slower gastric emptying than healthy children. Even when we adjusted for confounding effects of age, neurological status, and ingested volume of the test meal, no statistical difference in $T_{1/2}$ was found between patients and controls. When considering the wide range of gastric emptying rates that was observed in both controls and GER patients, we do not think that the small, non-significant difference in $T_{1/2}$ (7.7 min) between the two groups has clinical significance. A wide range of gastric emptying rates has also been reported by others, both in patients with GER and in healthy children (164,166,168,171–174). Many studies comparing gastric emptying of cow`s milk (164,166,168) and other liquid meals in children with and without GER support our findings that children with GER do not have DGE (165,167,169,170). However, some studies evaluating gastric emptying of liquid meals in children conclude otherwise (12–14). We and many other studies examined gastric emptying of liquids, because children with GER referred for antireflux surgery often are unable to take a solid meal. However, a liquid meal has a lower sensitivity to detect gastric emptying pathology than a solid meal or a combined liquid and solid meal (175,176). A few studies have assessed gastric emptying of a solid or a combined liquid and solid meal in children with GER (163,165,173,174,177,178). Also in these studies, the conclusion regarding the association between DGE and GER are conflicting.

The conflicting results regarding DGE in GER patients may be due to methodological differences. Most studies trying to elucidate the role of DGE in GER, did not compare gastric emptying in healthy children and in GER patients, but examined children with GER symptoms and then compared gastric emptying in children with and without GER

according to examinations such as pH study, UGI, and scintigraphy. These examinations have quite different sensitivity and specificity to reliably diagnose GER. Moreover, various methods have been used to examine gastric emptying such as scintigraphy, breath tests, and ultrasound (119,168,179–181). In addition, many different test meals have been given, and in some studies included patients have not been given the same test meal (178). There are also trials that have not given a precise information about the test meal, only reporting giving a test meal consisting of "the child`s usual formula" or a "meal appropriate for age" (114,119). Since gastric emptying rate is affected by the volume and composition of the meal, as well as the method used to assess gastric emptying, the lack of a standardized method makes conclusions from different trials hard to compare (57,168,180,182–184).

In adults, guidelines have been published to standardize scintigraphic gastric emptying examinations (185). Furthermore, a multicenter trial has established gastric emptying values using scintigraphy and a standardized test meal in healthy adults (186). No guidelines recommending a standardized meal with corresponding control values are available in children. However, gastric emptying data from healthy children using different meals and methods have been reported in a few small studies (171–174,180,187). Despite these reports, many studies apply various definitions of DGE derived from adult literature or other sources when assessing the association between DGE and GER in children (115,119,163,188). How the definition affects the reported frequency of DGE in patients with GER, can be illustrated by applying the definition used in another study to our patient population (119). In this study, a meal "appropriate for age" was given, and DGE was defined as "more than 50% retained labelled liquid or solid meal within the stomach after 120 minutes in children younger than 2 years and after 60 minutes in children older than 2 years", (119). If we had used this definition three (13%) of the healthy children and nine (18%) of the patients in our study would have been defined to have DGE. We used healthy children as controls and defined DGE as "gastric emptying slower than the range of the healthy children". Thereby, only one GER patient (2%) was defined as having DGE in our study. This example emphasizes the need to establish the range of gastric emptying in healthy children for the method and meal that is used in each laboratory, before a cut-off is used to decide whether or not a patient has DGE (189).

The significance of DGE for outcome of fundoplication is debated (114–116,119,177). There are studies suggesting that children with DGE are more likely to experience recurrence of GER or symptoms of gas bloat and nausea after fundoplication than those with normal gastric emptying (114,116). Some surgeons, therefore, advocate a gastric drainage procedure concomitantly with the fundoplication in children with preoperative DGE (115,177). However, the scientific quality of studies suggesting that DGE is associated with recurrence after fundoplication is not high, and there are no randomized studies comparing outcome after fundoplication with and without a gastric drainage procedure in children with DGE. Among our patients, there was only one child with DGE. No gastric drainage procedure was performed at the time of the fundoplication. Still, $T_{1/2}$ changed from 121 min preoperatively to 61 minutes 6 months postoperatively. Faster gastric emptying of both solid and liquid meals after fundoplication has also been observed in other studies (190–192). Since DGE may improve with fundoplication (190,191), the value of performing a gastric drainage procedure in children with DGE has been questioned (119). Our observations on the only patient with preoperative DGE support this view, as this particular patient has not had recurrence of GER in the six years that have passed since the fundoplication. However, a larger study assessing outcome after fundoplication in children with and without DGE is needed to answer this question.

Although the use of a gastric emptying study to identify candidates for a gastric drainage procedure is debated, there are studies suggesting that the test can be of value in predicting postoperative outcome (178,193). One study reported that patients with postoperative dysphagia had significantly slower preoperative gastric emptying rate and a higher dysphagia risk index than patients with no postoperative dysphagia (178). Another study reported that children with preoperative DGE had a higher occurrence of gas bloat and nausea after fundoplication than those with a normal gastric emptying rate (116). It has also been suggested that children with extremes in gastric emptying rates (either slower or faster than controls) have higher risk of developing retching symptoms postoperatively (193). Retching, gas bloat, nausea, and dysphagia are attributed to upper gastrointestinal dysmotility (116,193). Thus, it is not surprising that patients with DGE may have an increased risk of problems post fundoplication. Nevertheless, although there are indications that DGE may be related to a bit more problems after

fundoplication, the scientific support for this is so far so weak that it seems difficult to make results from gastric emptying studies significantly affect the decision to do a fundoplication (194).

13. Methodological considerations

Parental evaluation

The results after PEG and Nissen fundoplication in Study I and II were mainly obtained by asking the parents to evaluate outcome. It was recently demonstrated that health-related quality of life is assessed differently depending on whether the chronic sick child, its parents or the doctor is asked (139). The disagreement between self-report and proxy-ratings by the doctor or parent was greater on subjective outcomes such as pain, emotion, and cognition than on objective outcomes such as self-care, mobility, speech, and hearing. Overall agreement was somewhat better between parent-child pairs than doctor-child pairs. Although asking the patient remains gold-standard when assessing patient reported outcome measures, we had to rely on proxy-ratings because the majority of patients were neurologically impaired, young and/or non-verbal at the time of surgery.

GER-questionnaires have been validated for different age groups and for different purposes (195–199). However, none of these questionnaires were able to address the main aim of the studies: How satisfied parents were, why they were satisfied/dissatisfied, how the child's overall condition had changed, and how we could improve preoperative information prior to PEG and Nissen fundoplication. In order to obtain these data, talking to the parents was considered most useful. A telephone-interview was chosen for practical reasons. We think it is a strength that all telephone-interviews in Study I, II, and III were performed by medical students (C Kristensen/CK Knatten, TL Åvitsland, and TJ Fyhn) not involved in the decision to inform, operate or perform the surgery. When asking patients or caregivers to assess outcome, there is always a risk that they will report better results than what is true to avoid disappointing the surgeon or be a "good patient". Although it was not the surgeon asking about outcome, the answers may still have been influenced by the way or the intonation with which students asked the questions, as a telephone-interview was chosen as method.

In both study I and II, we reported parental satisfaction with the outcome. Several methodological problems have been described related to measuring patient satisfaction (137,158). Firstly, we used a cross-sectional design in both Study I and II and contacted parents at various follow-up times. It has been reported that patient satisfaction increases with time (158). In addition, the extended and variable time-interval between the surgery and the phone-interviews may have affected the answers due to recall-bias. Secondly, we did not know which expectations the parents had preoperatively. If the parents did not have a clear perception of what to expect after a fundoplication, it is difficult to answer a question concerning if their expectations were met (140). Lastly, the parents' satisfaction with the fundoplication may have been affected by other factors than the disease-specific outcome of surgery, and parents may mean different things when rating satisfaction.

A number of studies have reviewed how expectations, treatment and blinding affects outcome and effect of different treatments (200–202). There is little evidence that lack of blinding affects objective outcomes such as death, result of laboratory procedures, and other objective investigations, but the lack of blinding may exaggerate effect estimates of subjective outcomes such as patient reported outcomes and physician assessed disease outcome (200,203). Moreover, it has been suggested that surgery may have an enhanced placebo-effect compared to other treatment options when subjective outcome is evaluated (201), particularly in cultures rich in technology (204). Therefore, it has been suggested that surgical procedures where only subjective outcome can be measured should be carefully evaluated, if possible with sham-surgery (201,205). However, the reported number of children with improved overall condition of more than 90% in both Study I and II was higher than what could be expected from the placebo-effect alone. Furthermore, fundoplication has been found to improve GER in a number of trials using objective outcome measures such as pH monitoring (90). Nonetheless, we acknowledge that the placebo-effect accounted for some of the improvements parents reported, as could be expected with any treatment (202,206). It is a limitation of Study I and II that we had no objective verification of weight gain, improved growth, or reduction in GER as compared to preoperatively, although this could not be achieved with the retrospective design.

Inclusion and exclusion criteria

The majority of patients included in these four studies were recruited at Rikshospitalet, which is a tertiary care centre. Patients with complex conditions affecting anesthesia- and postoperative care are usually referred to Rikshospitalet for treatment, although other hospitals in the region can perform PEG insertions and Nissen fundoplications. The selection towards more complex patients may affect the generalizability of complication rate and outcome after surgery. In particular, presence of comorbidity may increase the risk of early postoperative complications caused by the general anesthesia and surgery.

For fundoplication, there are no standardized criteria to determine candidates for surgery. The pediatric gastroesophageal reflux clinical practice guidelines from NASPGHAN and ESPGHAN state that a child may be considered as a candidate for fundoplication if it has troublesome symptoms and/or complications of GER despite optimal conservative treatment, or if it is likely to depend on medical therapy for a long time period (1). In addition, a pathological reflux index should have been demonstrated by a 24-hour pH monitoring or 24-hour multichannel impedance monitoring, and other conditions with similar symptoms should be excluded. For gastrostomy, guidelines recommend gastrostomy insertion if enteral tube feeding is needed for more than 1-3 months (77). These general recommendations were followed in our studies, but there may have been variations in the interpretation of the guidelines among surgeons as the guidelines are relatively wide. Different selection criteria among surgical centres also likely results in differences in the patient populations accepted for PEG or fundoplication, and may limit the generalizability of the obtained results.

In Study IV, half of the eligible patients were excluded because the parents reported any form of cow's milk intolerance or allergy, the child was unable to lie still, or the parents refused participation.There was no significant difference in the number of neurologically impaired children between the included and the excluded patients, but the age difference was close to statistically significant. Although age and neurological status did not influence $T_{1/2}$ in the multiple regression analysis, we do not know if the excluded patients had gastric emptying dysmotility. The patient selection and the number of patients that were excluded must be taken into consideration when reading our results.

Complication rate after gastrostomy and fundoplication

Studies that are specifically focused on complications after surgery report a significantly higher number of complications than those who examine other outcomes after surgery as well (113). Furthermore, trials with a prospective design report a higher complication rate than retrospective studies (207). In Study I and II complications were found through chart review. Severe complications requiring prolonged medical treatment, surgical intervention or causing mortality will be reported, but minor complications such as urinary tract infection and wound infections might not be referred in the charts and are therefore not identified and included in the complication rate. Moreover, complications occurring after discharge will be missed unless patients are contacted again to register complications treated at home or at the local hospital. These differences in data collection likely resulted in the difference in complication rate registered between Study II and III, where early complications were reported in 11% and 54% of the patients, respectively. We have no reason to believe that the difference in complication rate is caused by a significant detoriation of surgical or nursing skills from the time period of Study II (1990-2001) to the period when Study III (2003-2009) was performed. Furthermore, we think that it is unlikely that using experienced surgeons such as stated in the protocol of Study III should increase the complication rate. In contrast, no protocol was followed to ensure that the fundoplications were performed in a standardized way and performed by or supervised by experienced surgeons in Study II.

In Study I and II complications were graded as “minor” or “major” by a subjective evaluation of the publishing authors, whereas a predefined classification system was used to classify complications in Study III. Since Study I and II did not compare complication rates or severity of complications between patient groups, the lack of standardisation in complication-grading is of minor importance for the conclusion in these studies. The Clavien Dindo Classification System is a more standardized way of classifying complications, with a high reproducibility and validity (145,208). Therefore, we applied this system when comparing ONF and LNF groups. However, the Clavien Dindo Classification has not been validated for children and there remains a need to develop and validate a classification system for the pediatric patient group (135,147).

In Study III only experienced surgeons performed the laparoscopic fundoplication, whereas some of the open fundoplications were performed by junior doctors supervised by consultants. The randomness of the outcomes would have been better maintained if the four expert laparoscopic surgeons had done all the open as well as the laparoscopic fundoplications. Unfortunately, this was impossible due to the hospitals' obligation to junior doctors' training. However, the expert laparoscopic surgeons performed some of the open operations, and the senior author either operated or assisted in the majority of both the open and laparoscopic operations. We therefore believe that the surgical guidelines for the procedure were followed, and the main difference was the approach of laparoscopy or laparotomy.

In study II, we recorded the number of children which had had a redo fundoplication to give an estimate on the recurrence rate. However, patients may have recurrence of GER without undergoing a second fundoplication (98,99,105). A proper registration of recurrence rate should ideally include patients receiving antireflux medications, jejunal feeding tube or a second fundoplication, and GER should be verified by pH monitoring or other objective tests (105). Due to the design of study II, we were not able to report a proper recurrence rate including all these categories. Although the data on patients undergoing redo fundoplication are easily obtained and frequently used as a proxy for recurrence rate, it generally underestimates the number of patients with recurrence of GER.

Gastric emptying

When examining gastric emptying, it is important that the volume is sufficiently large to induce a postprandial motor response (209). However, the minimum volume that is necessary is not known in different age groups. For simplicity, we therefore used a standard volume and encouraged children less than four years to drink 100 ml, and older children to drink 200 ml. In adults it is not usual to adjust the size of the test meal according to body weight or height, although they may have large variations in body size (185). In line with this, a recent study in children demonstrated that the administration of volumes of 3 and 7 ml per kg body weight did not influence $T_{1/2}$ significantly (210). Nevertheless, the effect of volume was addressed in the statistical analysis to reduce any confounding effect on $T_{1/2}$.

The highest sensitivity for detecting gastric emptying pathology is achieved by giving a solid test meal or a combined solid and liquid test meal (175,176). However, many of the patients with GER referred for fundoplication and gastrostomy are unable to tolerate solid food, and we therefore chose a liquid, caloric meal. Still, we experienced that studying gastric emptying in children with GER was more challenging than expected from previous reports. For instance, scintigraphy is described as "an easy method to study gastric emptying in children with GER" (173,211). The main problem in our setting was that the children refused to drink or did not tolerate a bolus meal. Moreover, we found that scintigraphic study of gastric emptying was labour intensive, as the majority of both controls and patients required continuous supervision from both staff and parents to prevent the child from moving under the gamma camera. In addition, some of the children found the study setting frightening because they had to lie under the large detector of the camera. In retrospect, it would have been easier to perform the study as suggested by guidelines for investigation of adults. According to these, pictures are taken hourly, and the patient is free to move out of the camera field between these time-points (185). However, this could potentially have biased the results of gastric emptying, as gastric emptying is affected by positioning and physical activity (212), and it is reasonable to assume that the patients are less physically active than the healthy children.

There are several different methods to examine gastric emptying rate, including scintigraphy, breath tests, and ultrasound (181). Scintigraphy is non-invasive, provides a direct and quantitative measurement of gastric emptying, and is considered the gold standard (185). Therefore, we chose this method. In comparison, breath tests measures indirect gastric emptying and rely on normal pulmonary and bowel function, whereas ultrasound is operator-dependent and the result depends on the experience of the operator. Ultrasound is usually only applied for liquid meals, whilst both solid and liquid meals can be given using breath test and scintigraphy. However, scintigraphy has the disadvantage of radiation exposure, which is probably why many studies in children have been performed using other methods to examine gastric emptying.

All patients included in Study IV were assessed for inclusion in two different trials where the main outcome was to evaluate outcome after PEG-placement or fundoplication. Since it has been suggested that DGE may affect outcome after surgery

(114,115,177), all patients included in these studies were attempted to perform a gastric emptying study prior to surgery as part of the general preoperative work-up investigations. Therefore, no sample size calculation was performed. However, we have performed a post hoc sample size calculation by using data obtained from a large study investigating gastric emptying of cow`s milk in children from 2006 (164). A difference in $T_{1/2}$ of 15 minutes or more between GER patients and healthy children was considered clinically significant. Using a standard deviation in $T_{1/2}$ of 16 min, a significance level of 0.05 (α), and a power of 0.8 (β), a sample size of 25 patients in each group would be required to detect the predefined interesting difference between the groups. Despite the unexpected high number of GER patients that were excluded, we reached a sufficient number of included patients determined by this calculation. However, the high number of excluded patients limits the conclusions that can be made from our study.

14. Conclusions

1. An overwhelming majority of parents assessed that Nissen fundoplication and PEG insertion had benefited their child
2. Early outcome is similar after LNF and ONF except for operating time
3. Children with GER have similar gastric emptying rate as healthy children

15. References

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