THE EFFECTS AND EFFICACY OF ANTIREFLUX SURGERY IN CHILDREN

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The Effects and Efficacy of Antireflux Surgery in Children

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De effecten en effectiviteit van antirefluxchirurgie bij kinderen
(met samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor aan de Universiteit Utrecht op gezag van de rector magnificus, prof. dr. G.J. van der Zwaan, ingevolge het besluit van het college voor promoties in het openbaar te verdedigen op dinsdag 10 november 2015 des middags te 4.15 uur

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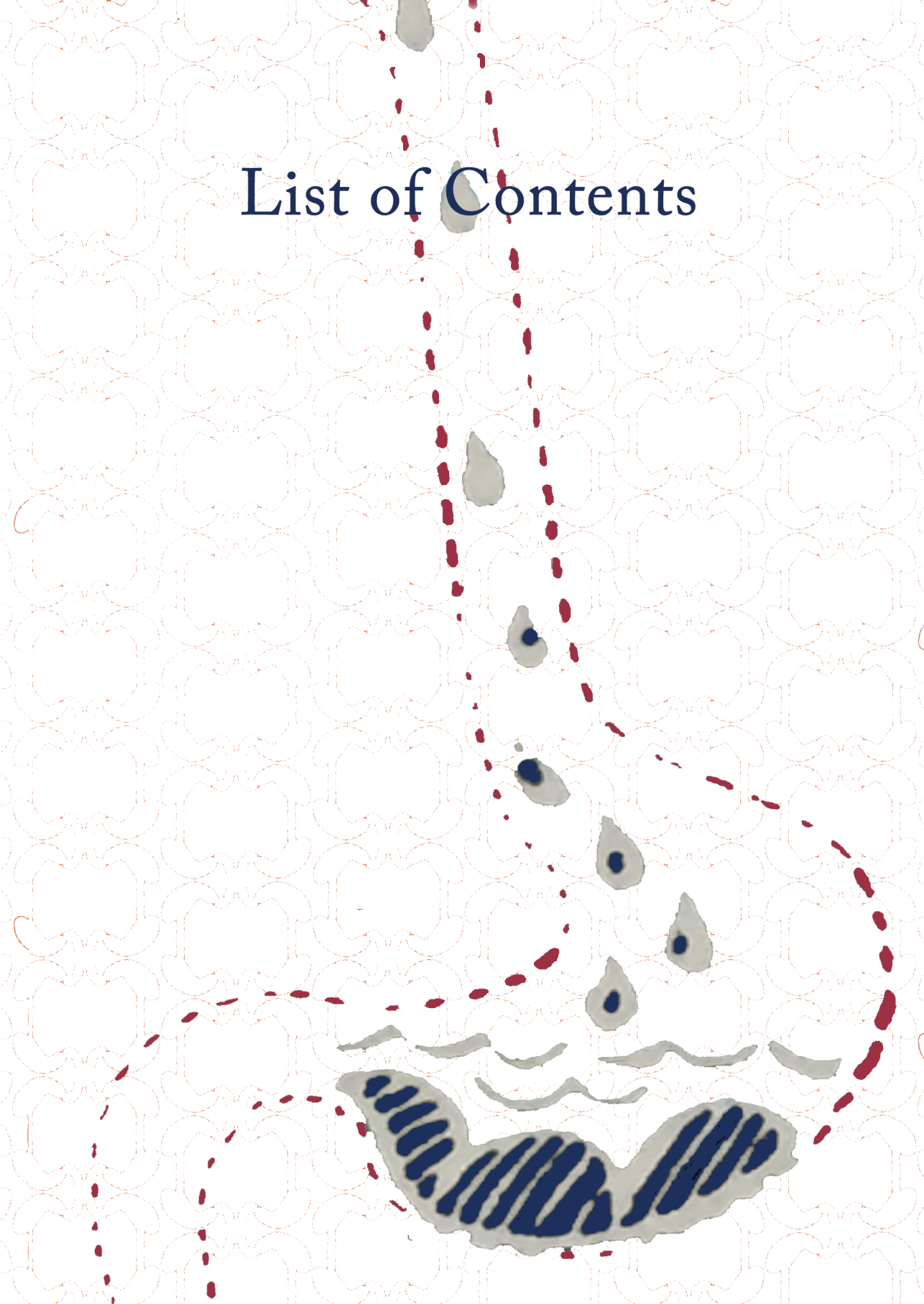
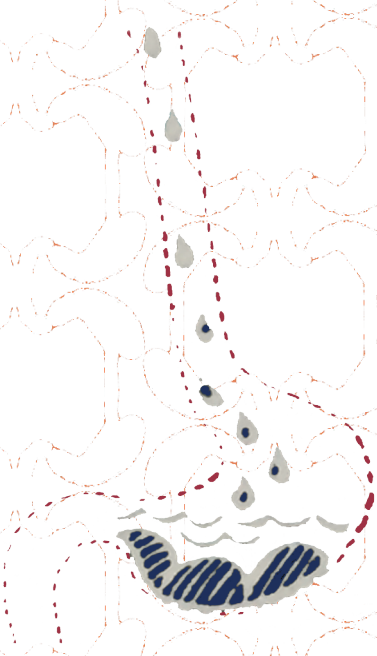


1. General introduction



GASTROESOPHAGEAL REFLUX DISEASE (GERD) IN CHILDREN

Gastroesophageal reflux (GER) is defined as a passive backward flow of gastric content in to the esophagus, with or without regurgitation and vomiting [1-3]. In healthy newborns, infants and adolescents, GER is a normal physiologic process occurring in up to 70% [4;5]. These children are also called "Happy spitters" (**Figure 1**) as GER does not result in troublesome symptoms. GER resolves spontaneously in 95% of the children by the age of 12-14 months [6;7]. When GER results in troublesome symptoms and/or complications, it is defined as gastroesophageal reflux disease (GERD) [2;3;8;9]. Although GERD is less frequent than physiological GER, it is a frequently encountered condition, affecting 7–20% of the pediatric population [10;11].

Figure 1 The "happy spitter"

GERD is a life-long condition, which is demonstrated by the fact that GERD in adults is associated with GERD during childhood [12;13]. GERD puts a high burden on health care costs [14] and decreases Health-related quality of life (HRQoL) [15-18]. Complications of GERD include esophagitis, esophageal stricture and the development of Barrett's esophagus, which can lead to esophageal cancer [19;20].

Children with underlying diseases, such as impaired neurodevelopment, cystic fibrosis and esophageal atresia [21] are predisposed to develop (more severe) GERD and its associated complications [22;22-26]. The prevalence of GERD has been reported in up to 56% of children with impaired neurodevelopment [27].

PATHOPHYSIOLOGY OF GERD

The esophagus has two sphincters, the upper esophageal sphincter (UES) and the lower esophageal sphincter (LES). The LES has a dual function; it opens to allow passage of food into the stomach and thereafter prevents food from moving back from the stomach into the esophagus [28]. The LES and the crural diaphragm together create a high-pressure zone that works as an "antireflux barrier", also known as the esophagogastric junction [29] and is located between the thoracic and abdominal cavity.

GERD is a multifactorial disorder mainly caused by failure of the antireflux mechanisms of the esophagus [30]. Transient lower esophageal sphincter relaxations (TLESRs) are a physiological phenomenon to vent air from the stomach and are considered to be the main

pathophysiological mechanism in GERD [9;31-35]. TLESRs are responsible for almost 70% of acidic reflux events [9;36;37]. TLESRs are triggered by proximal gastric distension [37;38] to accommodate the presence of food in the stomach [36;39].
The presence of a hiatal hernia may also contribute to the development of GERD. A hiatal hernia interferes with the synergistic effect of the LES and the crural diaphragm as the gastroesophageal junction has moved above the diaphragm [40-43]. Furthermore, GERD can also be associated with LES incompetence or low LES pressure [9;35] and delayed gastric emptying. The latter is seen in 40% of GERD patients [44-46].
In children the pathophysiology differs somewhat to that in adults as nearly 50% of pediatric GERD patients have underlying (mostly congenital) disorders, such as esophageal atresia, congenital diaphragmatic hernia and impaired neurodevelopment [3]. In these patients prolonged supine position, spasticity, and generalized gastrointestinal dysmotility contribute to GER [47].

CLINICAL PRESENTATION OF GERD IN CHILDREN

According to the Montreal consensus, symptoms of GERD are classified as esophageal and extra-esophageal [8]. GERD in children is typically associated with excessive regurgitation, vomiting, weight loss or failure to thrive, abdominal pain and irritability after feeds [2]. Older children are more likely to experience typical reflux symptoms, such as heartburn, acidic regurgitation and dysphagia [7]. In contrast, in infants, young children and children with impaired neurodevelopment, symptoms of GERD are predominantly non-specific and include abdominal pain, food refusal, anorexia, unexplained crying and swallowing difficulties [48;49]. Extra-esophageal presentation of GERD in children may include Sandifer's syndrome [50], dental erosions [51], apparent life threatening events, chronic cough, hoarseness, pharyngitis and laryngitis, sinusitis and serous otitis media [2].
A clinical diagnosis of GERD, which is only based on symptoms, cannot be used in infants, young children and children with impaired neurodevelopment as they are not able to reliably report their symptoms. Even if children are verbally able to communicate pain, the description of intensity, location and severity can still be inaccurate [3;52;53].

DIAGNOSTIC TOOLS IN PEDIATRIC GERD

A diagnosis of GERD is predominantly based on symptoms or signs associated with GER in combination with objective measurements.

Questionnaires

For symptom evaluation in young patients with GERD, two age-specific reflux questionnaires have been developed; namely the infant gastroesophageal reflux questionnaire (I-GERQ) [54] and the GERD symptom questionnaire (GSQ) [54-56].

24–hour pH monitoring

Intraluminal pH monitoring measures the frequency and duration of episodes of acidity in the esophagus. It was the first tool to be used for quantifying acid exposure to the esophagus. A drop of pH below 4 is considered an acid reflux episode. Acid exposure time is calculated as the percentage of time during the 24-hour measurement in which pH is below 4. In the adult population, pathological acid exposure is defined as total acid exposure time ≥6% or ≥ 9% in the upright and ≥3% in the supine body position during a 24-hour period [57;58]. Unfortunately in the pediatric population normal values exist only for infants and young children ≤18 months [59].

24–hour multichannel intraluminal impedance pH (MII–pH) monitoring

By adding electrical impedance to a pH-monitoring catheter at various levels in the esophagus, air and fluid moving through the esophagus can be registered irrespective of the acidity of the bolus. During a measurement, gas movement can be registered as a rise in impedance since gas has a low ionic content. In contrast to gas, liquid moving through the esophagus, during either a swallow or a reflux episode, is shown on the tracing as a decrease in electrical impedance. When MII is added to the pH-only catheter acid, weakly acidic and non-acidic, as well as liquid or gas reflux can be observed [60]. It has been demonstrated that most reflux episodes occurring in infants and children are undetectable by standard pH-only monitoring, therefore combining pH monitoring with MII is valuable and possibly superior to diagnose GERD in children [61]. Unfortunately, analyzing 24-hour MII-pH tracing is quite time consuming as automatic analysis is still not as good as manual analysis by experts [62]. Furthermore, similar to pH-only monitoring, no normal values are available for pediatric patients and MII-pH catheters are relatively expensive.

Symptom association

In addition to quantification of acid reflux the association between reflux and symptoms can also be assessed. Using the 24-hour tracings and symptoms that are scored by the patients during the measurement, the symptom index (SI) and the symptom association probability (SAP) can be calculated [63;64].

Baseline impedance assessment

The MII-pH catheter can also be used to assess the esophageal intrinsic electrical conductivity in the absence of GER or swallowing [65], which is referred to as baseline impedance and can be used as an in vivo tool to assess the integrity of the esophagus [66]. Baseline impedance values in healthy volunteers are usually high, whereas GERD patients express low baseline impedance values. Low baseline impedance values have been associated with Barrett's esophagus and severe esophagitis [67]. The effect of acid suppressive drugs on baseline impedance in children and adults with GERD has been studied extensively showing an increase in baseline impedance during acid suppressive therapy [68-70]. However, the effect of antireflux surgery on baseline impedance has not widely been investigated until now.

Barium Swallows

Barium swallow fluoroscopy is useful to detect anatomic anomalies [71]. However, it cannot be used to diagnose GERD as the sensitivity and specificity are low (<60%) [72;73].

Manometry

Esophageal manometry is not a diagnostic tool to diagnose GERD, although it has been shown that in patients with esophagitis due to GERD, ineffective motility is more frequently observed [74]. It is however important to evaluate esophageal motility and LES pressure in order to diagnose (related) motility disorders such as achalasia before antireflux surgery [40;75]. Furthermore it can be used to correctly position the (MII-)pH catheter.

Esophagogastroscopy

Esophagogastroscopy in combination with or without esophageal biopsies is important to document GERD by endoscopic visualization of mucosal changes, such as esophagitis, Barrett's esophagus and stricture formation [76]. The severity of the esophagitis is classified using the Los Angeles (LA-)classification and is based on macroscopic extent of mucosal breaks [77]. Furthermore, esophagogastroscopy with biopsy, is able to rule out other conditions, such as eosinophilic esophagitis [78] and Crohn's disease.

Gastric emptying studies

Gastric emptying can be assessed by using a 13C labeled Na-octanoate breath test [79]. This test allows calculating gastric emptying half time, gastric emptying coefficient and the gastric emptying percentiles. This is the only objective assessment test of gastrointestinal motility for which normal values are available in the pediatric population [80].

CONSERVATIVE MANAGEMENT OF GERD

The goal of therapy in GERD is to control symptoms, heal mucosal injuries and improve HRQoL. At first, treatment of GERD consists of lifestyle changes, although by itself it is almost always ineffective in relieving reflux symptoms completely. Lifestyle changes that may positively influence symptomatology of GERD are elimination of cow's milk from feedings and making the household free of tobacco smoke [81;82], thickening of feedings, sleeping in a more upright or anti-Trendelenburg position [83-85], left lateral position while supine [86] and awareness of overfeeding as a decrease in feedings has been shown to decrease acid reflux [86;87].

In addition to lifestyle changes, in almost all children medical treatment is started. For medical therapy a variety of drugs, such as antacids, histamine- 2 receptor antagonists (H2-antagonists), proton pump inhibitors (PPIs) and prokinetic drugs can be used.

Antacids

Antacids offer good control of heartburn symptoms and quality of life in adults [88], however it does not have any effect on weakly and non-acidic reflux and regurgitation and the effect is only temporary [89]. In children the efficacy has not been proven yet. In a study comparing placebo with antacids no differences in gastroesophageal reflux as measured by MII-pH monitoring [90] were observed.

Histamine– 2 receptor antagonists

H2-antagonists decrease secretion of gastric acid by inhibiting the H2-receptor of the gastric parietal cell, which is located in the stomach wall. H2-antagonists are less effective in acid suppression compared to PPIs in adults [91]. Furthermore, chronic use of H2-receptor antagonists has been shown to be associated with tolerance [92]. The therapeutically effect specifically in pediatric GERD patients remains unclear.

Proton pump inhibitors (PPIs)

PPIs reduce gastric acid secretion by inhibiting the H+/K+ ATPase pump of the gastric parietal cell. PPIs provide the most powerful symptomatic relief of all currently available medication, heal esophagitis in the majority of children and adults and can safely be used for long-term medical treatment [8;91;93;94]. In children, PPIs are well tolerated [95] and have shown to effectively control gastric acidity [96], heal esophagitis [97] and decrease reflux symptoms [98]. Nevertheless, PPIs like antacids and H2-antagonists, do not reduce weakly-acidic and non-acidic reflux events.

Prokinetics

Prokinetics, such as metoclopramide [99] and domperidone [78] may act on GERD by effecting LES pressure, esophageal peristalsis and/or gastric emptying. However, up to now there is no defined role for the use of prokinetic drugs as they have not shown sufficient efficacy in pediatric GERD patients [100]. Moreover, side effects can be serious especially in children with impaired neurodevelopment [101]. Erythromycin, a macrolide antibiotic, is frequently used off-label in the pediatric population as it is thought to promote peristalsis of the esophagus and gastric emptying by binding to the motilin receptor. However, up to now, no studies have investigated the true effect of erythromycin on esophagogastric motility in pediatric GERD patients [102].

ANTIREFLUX SURGERY

Antireflux surgery (ARS), by means of (laparoscopic) fundoplication is reserved for pediatric patients with severe GERD resistant to medical treatment [3;103;104] and is one of the most frequently performed major operations in children.

ARS by means of fundoplication was first performed in 1956 by Rudolph Nissen [105]. Fundoplication is performed by plicating the fundus of the stomach around the esophagus. The most commonly used types of fundoplication are the complete (360 degrees) posterior Nissen [105] fundoplication (**Figure 2**), the partial (270 degrees) posterior Toupet [106] fundoplication (**Figure 3**) and the partial (270 degrees) anterior Thal [107] fundoplication (**Figure 4**). Prior to the fundoplication, the distal esophagus is fully mobilized and the distal part of the esophagus is repositioned back into the abdomen. It is important that both vagal nerves are identified. Furthermore, a crusplasty is usually performed as well.

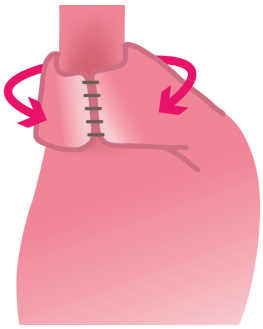


Figure 2 Nissen fundoplication: 360° posterior complete fundoplication

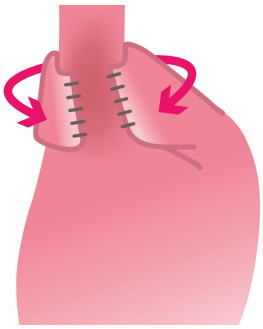


Figure 3 Toupet fundoplication: 270° posterior partial fundoplication

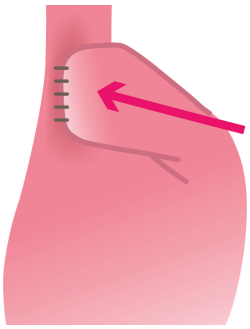


Figure 4 Thal fundoplication: 270° anterior partial fundoplication

ARS is thought to treat GERD by reestablishing the esophagogastric junction, the angle of His and is associated with enhancement of gastric emptying [46;108-110]. Furthermore, in the adult literature it has been shown that ARS reduces the number of TLESRs and its associated reflux episodes [111-113] by reduction of TLESRs that are elicited by proximal gastric distension [33;114].

The overall published success rates of ARS in children are generally good, with a median short-term reflux control in up to 75% [47;115;116]. However, ARS can also lead to complications [117], such as postoperative dysphagia in around one third of the patients [47;118] and gas bloat syndrome in up to 11% of patients [119;120]. Studies on long-term efficacy are scarce and have mostly retrospective study designs [121-124].

Antireflux surgery can be performed by an open or laparoscopic procedure. Nowadays, ARS is predominantly performed by laparoscopy, as it has been shown to result in a shorter hospital stay, less morbidity, and earlier feeding time compared to open ARS. Recurrence rates of GER after both procedures were similar [125-127].

Nissen fundoplication is the most frequently (>60%) performed procedure in the pediatric population [119]. It is however associated with a high risk of postoperative severe dysphagia [119;124;124;128]. Partial fundoplication, either the Toupet or the Thal fundoplication, is performed less frequently as they are still thought to have inferior reflux control, but conversely may result in less postoperative dysphagia compared to Nissen fundoplication [129;130]. Until recently, it was therefore reserved for patients without a history of life-threatening events or with signs of esophageal dysmotility to reduce the risk of complications after ARS [129-131]. Several studies have tried to address the question as to which type of fundoplication is superior in the pediatric GERD population, but up to now no consensus has been reached. Only just recently the first randomized controlled study was published. A meta-analyses of randomized controlled studies in adult GERD patients in 2011 demonstrated that partial fundoplication significantly reduces the risk of postoperative dysphagia and gas bloat syndrome compared to complete fundoplication, while providing excellent reflux control [128]. After this publication a debate started whether or not partial fundoplication should be the fundoplication of first choice and an increasing number of surgeons have changed their practice; however, current guidelines still state that surgeons may decide between complete or partial fundoplication according to their experience and results [132].

AIMS AND OUTLINE OF THIS THESIS

The overall aim of the studies presented in this thesis is to assess the effects and efficacy of antireflux surgery (ARS) in children. This thesis is subdivided into three parts:

- ***Part one: Efficacy of antireflux surgery:*** In this part we address the short-term and long-term efficacy of ARS and aim to identify predictors of failure.
- ***Part two: Effects of antireflux surgery:*** In this part the effects of ARS on gastroesophageal function and health-related quality of life (HRQoL) are investigated.
- ***Part three: Surgical techniques:*** In this part we aim to answer the question which type of fundoplication is the preferred technique in pediatric GERD patients.

Part one: Efficacy of antireflux surgery

In the first part of the thesis, the short-term and long-term efficacy of ARS in children with GERD is studied by means of both reflux symptom control and objective (acid) reflux reduction. Furthermore, we investigate adverse events associated with ARS as efficacy is also influenced by post-fundoplication events such as dysphagia and reinterventions. Finally, up to now predictors for success of ARS in pediatric patients are unavailable. In order to advise parents and children prior to ARS, it is important to identify parameters that are associated with success of therapy and to identify predictors of ARS failure.

In **chapter two** the medical literature is systematically reviewed to obtain an overview of available information on the efficacy of pediatric antireflux surgery and its effects on gastroesophageal function, as measured by gastroesophageal function tests. In **chapter three** the results of a prospective multicenter study are presented. This study aims to objectively assess the efficacy of laparoscopic antireflux surgery in pediatric GERD patients. The efficacy is evaluated by questionnaires for GERD symptoms and by the effects on controlling reflux episodes as measured by MII-pH monitoring. In this study we also aim to identify predictors of LARS failure. Since delayed gastric emptying may contribute to GER, gastric emptying is evaluated by the 13C labeled octanoic acid breath test. In **chapter four** we report on the long-term efficacy of laparoscopic antireflux surgery in a prospectively followed cohort of pediatric patients with GERD.

Part two: Effects of antireflux surgery

The second part aims to address the effects of antireflux surgery on gastroesophageal function and HRQoL. In order to understand the effect of LARS on the pathophysiology of GERD and the association with success of therapy objective measurements of gastroesophageal function should be performed before and after LARS. Furthermore, to better assess the impact of GERD and ARS from the perspective of the pediatric patient and their caregivers, HRQoL assessment has been increasingly recognized as an essential part of patient care outcome.

Chapter five studies the effect of laparoscopic antireflux surgery on esophageal mucosal integrity by using MII-pH monitoring. We hypothesize that laparoscopic antireflux surgery increases health-related quality of life. In **chapter six** HRQoL is investigated by using a validated HRQoL questionnaires in a prospective multicenter cohort. Furthermore, we tried to identify parameters associated with the overall HRQoL and the effect of ARS on HRQoL.

Part three: Surgical techniques

Various techniques of fundoplication (i.e. complete Nissen or partial Thal or Toupet fundoplication) are performed in pediatric GERD patients. However, up to now no consensus on which technique is the preferred type in pediatric GERD patients is available. **Chapter seven** presents a systematic review and meta-analysis of the medical literature comparing complete to partial fundoplication in children with GERD. In this chapter we aim to answer the question which type of fundoplication is the preferred technique in pediatric GERD patients.

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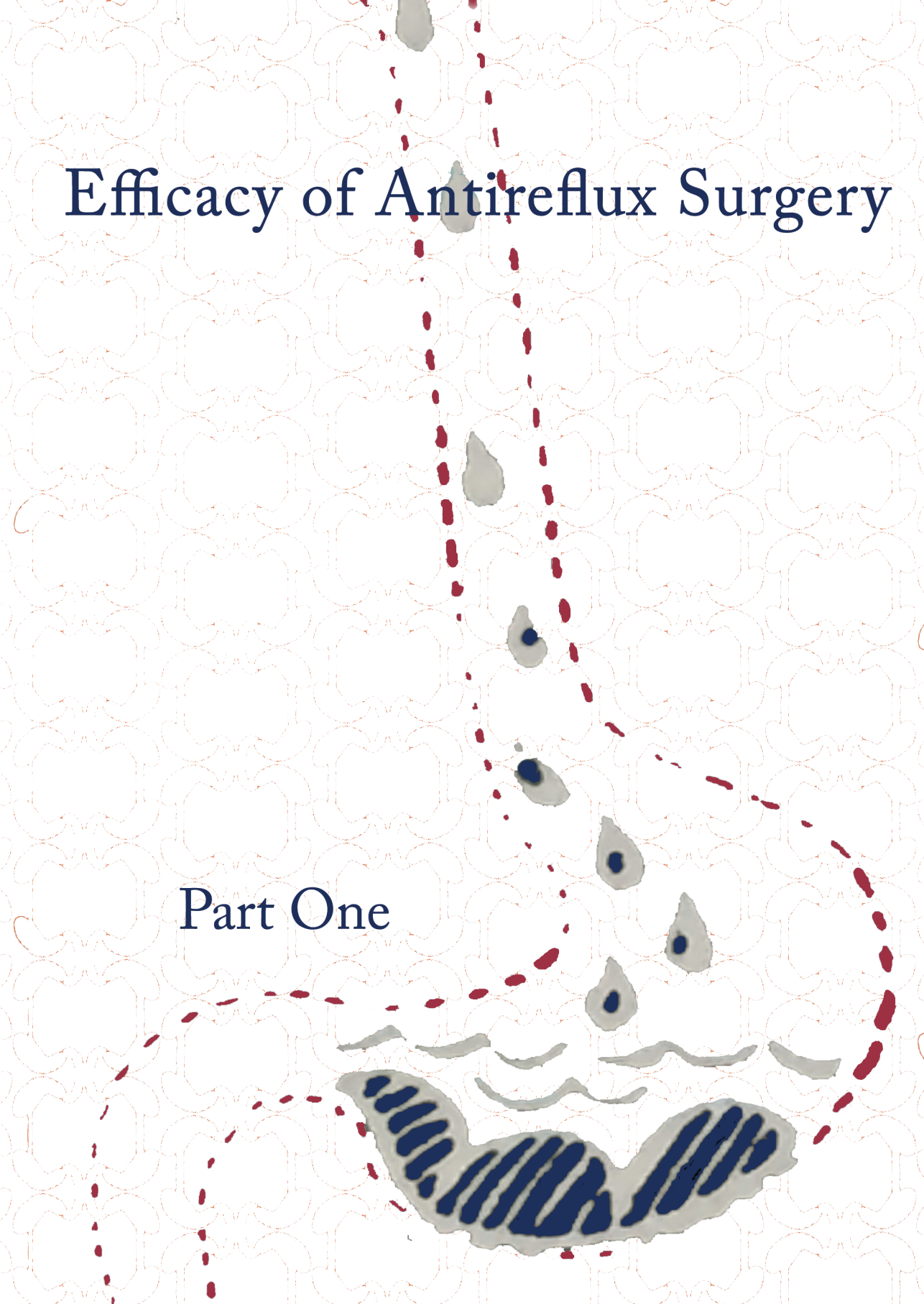
Efficacy of Antireflux Surgery



Part One

2. The effects and efficacy of antireflux surgery in children with gastroesophageal reflux disease: a systematic review

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ABSTRACT

Background: Antireflux surgery (ARS) for gastroesophageal reflux disease (GERD) is one of the most frequently performed major operations in children. Many studies have described the results of ARS in children, however, with a wide difference in outcome. This study aims to systematically review the efficacy of pediatric ARS and its effects on gastroesophageal function, as measured by gastroesophageal function tests. This is the first systematic review comprising only prospective, longitudinal studies, minimizing the risk of bias.

Methods: Three electronic databases (Medline, Embase, and the Cochrane Library) were searched for prospective studies reporting on ARS in children with GERD.

Results: In total, 17 eligible studies were identified, reporting on a total of 1,280 children. The median success rate after ARS was 86% (57–100%). The success rate in neurologically impaired children was worse in one study, but similar in another study compared to normally developed children. Different surgical techniques (total versus partial fundoplication, or laparoscopic versus open approach) showed similar reflux recurrence rates. However, less postoperative dysphagia was observed after partial fundoplication and laparoscopic ARS was associated with less pain medication and a shorter hospital stay. Complications of ARS varied from minimal postoperative complications to severe dysphagia and gas bloating. The reflux index (RI), obtained by 24-h pH monitoring (n=8) decreased after ARS. Manometry, as done in three studies, showed no increase in lower esophageal sphincter pressure after ARS. Gastric emptying (n=3) was reported either unchanged or accelerated after ARS. No studies reported on barium swallow x-ray, endoscopy, or multichannel intraluminal impedance monitoring before and after ARS.

Conclusions: ARS in children shows a good overall success rate (median 86%) in terms of complete relief of symptoms. Efficacy of ARS in neurologically impaired children may be similar to normally developed children. The outcome of ARS does not seem to be influenced by different surgical techniques, although postoperative dysphagia may occur less after partial fundoplication. However, these conclusions are bound by the lack of high-quality prospective studies on pediatric ARS. Similar studies on the effects of pediatric ARS on gastroesophageal function are also very limited. We recommend consistent use of standardized assessment tests to clarify the effects of ARS on gastroesophageal function and to identify possible risk factors for failure of ARS in children.

INTRODUCTION

Gastroeophageal reflux disease (GERD) is a frequently encountered condition, affecting 7–20% of the pediatric population [1–3]. Most symptomatic children respond well to medical treatment [3]. However, when medical treatment fails and reflux symptoms persist, antireflux surgery (ARS) may be considered [4]. ARS is one of the most frequently performed major operations in children, and over the last decades, numerous studies have been published on this subject. The efficacy of ARS and the relationship between ARS and gastroesophageal (GE) function in children is difficult to deduce from these publications, since most studies are underpowered, retrospective, and have heterogeneous study designs, as well as a heterogeneous pediatric patient population. Therefore, in order to provide the best evidence on the efficacy of pediatric ARS, this article aims to systematically review all prospective, longitudinal studies, and randomized controlled trials (RCTs). In addition, this review aims to study the effects of ARS on GE function in children, as measured by pre- and postoperative assessment tests.

MATERIAL AND METHODS

Study Selection

Using predefined search terms, PubMed (from 1960), Embase (from 1980), and the Cochrane library (issue 11, 2010) were systematically searched for all articles published until November 10, 2010. For PubMed, the following search terms were used: (fundoplication[Title/Abstract] OR nissen[Title/Abstract] OR thal[Title/Abstract] OR toupet[Title/Abstract] OR boerema[Title/Abstract] OR antireflux surgery[Title/Abstract]) AND (child[Title/Abstract] OR children[Title/Abstract] OR infant[Title/Abstract] OR infants[Title/Abstract] OR pediatric[Title/Abstract] OR pediatrics[Title/Abstract] OR pediatric[Title/Abstract] OR pediatrics[Title/Abstract]). The same search strategy was used in EMBASE (replacing "[TIAB]" by ":ti,ab"). In addition, the Cochrane library was manually searched.

Assessment of Study Eligibility

Inclusion Criteria

Each article was independently assessed for eligibility using the following criteria: study population—infants and children (0–18 years), who underwent ARS; type of intervention—open or laparoscopic Nissen, Thal, or Toupet fundoplication; study design—only prospective study format; study results—operative results reported using symptom questionnaires, or clearly defined reflux symptoms, or GE function tests, both before and after ARS.

Exclusion Criteria

Studies were excluded if they did not meet the inclusion criteria or if the outcomes of interest were not reported. Articles in non-English languages were excluded. In case of multiple studies reporting on an overlapping population, only the study with the largest patient population was included.

Outcomes of Interest

Reflux specific symptom questionnaires; clearly defined reflux symptoms; reoperation rate; postoperative dilatations and GE functions tests: 24-h pH monitoring; combined 24-h pH-multichannel intraluminal impedance (pH-MII); manometry; endoscopy; scintigraphy of the stomach (gastric emptying studies) and barium swallow radiography. In this systematic review, success of pediatric ARS will be defined as complete relief of reflux symptoms.

Data Extraction

The titles and abstracts of all identified studies were reviewed by two independent authors (WS, MH) according to the MOOSE criteria.5 Full publications were obtained for articles that appeared potentially relevant. References in these selected articles were also screened for cross-reference. The following data were extracted from each selected article: Study design, study population, surgical method, outcome assessment techniques, duration of follow-up, and study outcomes of interest.

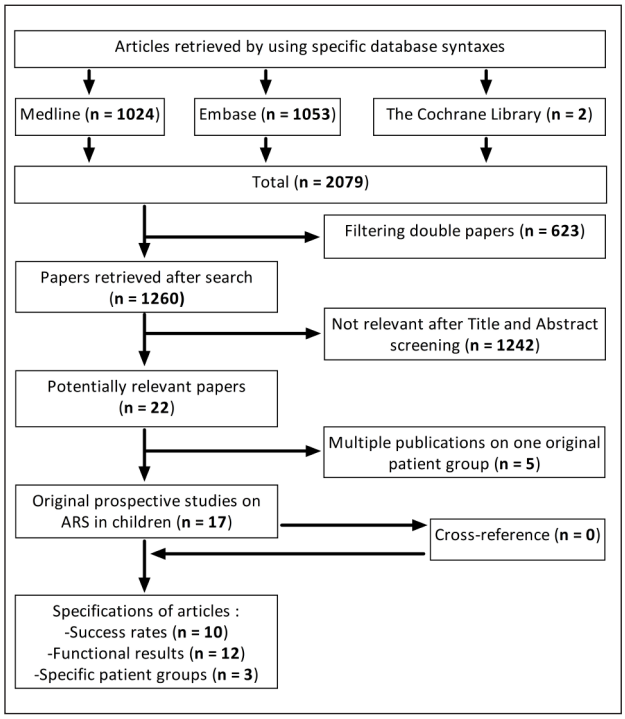

Figure 1 Flow chart illustrating details of selection of studies on results of anti-reflux surgery in children

RESULTS

In total, 1,260 articles were identified and screened. Of these, 17 original prospective studies that met our criteria were selected for inclusion (**Figure 1**) [6–23]. Included trials were published between 1995 and 2010 and reported on a total of 1,280 children. Most studies only presented very short-term follow-up; however, a wide range in follow-up duration was present (1–96 months). Age at time of surgical intervention varied widely between the included studies from 0.25 to 20 years (**Table 1**).

Study (year)	Period	Method	*n*	Follow-up	Patient characteristics	
					Comorbidity	Age: Mean or range (yrs)
Capito (2008)[**6**]	1992-2003	LNF	127	66	All	0.25 – 20
Cheung (2006)[**7**]	1999-2004	ONF + G	9	36 – 60	Only NI	8.5 (SD 3.5)
		LNF + G	11			
Durante (2007)[**8**]	2003-2004	ONF +/- G	7	3	Only NI	0.33 – 12.25
		VGP +/- G	7			
Engelmann (2010)[**9;10**]	2001-2006	LThF	76	6	All	7 (SD 6.1)
Estevão-Costa (2010)[**11**]	NR	ONF	20	6 – 12	All	NR
		LNF	5			
		Boix-ochoa	4			
Kawahara (1998)[**12**]	1996-1997	NF + Stamm	7	1 – 3	All	
Kawahara (2000)[**13**]	1998-1999	LNF	12	1 – 2	All	0.5 – 13
Kubiak (2010)[**14**]	1998-2007	LNF	89	1.5	All	5.2 (SD 4.7)
		LTouF	86			
Mattioli (2002)[**15**]	1998-2002	LNF	254	6-54	All	4.8 (.025–14)
		LTouF	5			
		LThF/LJ	29/10			
Mattioli (2002)[**16**]	1993-2000	ONF	17	6	No NI	5 (SD 6.3)
		LNF	49			
Menon (2002)[**17**]	1993-1999	LNF	11	12	No NI	9 – 15
		LTouF	1			
Mousa (2006)[**18**]	NR	ONF	6	3 – 7	All	0.5 – 18
		LNF	7			
Soyer (2007)[**19**]	2003-2004	NF	13	1 – 3	All	6.7 (SD 3.3)
Srivastava (2007)[**20**]	2005-2006	O+LNF + G	63	1	Only NI	1.8 (SD NR)
Van der Zee (1999)[**21**]	1993-1996	LThF	53	10	All	NR
Weber (1995)[**22**]	1991-1993	ONF	56	12 – 36	Only NI	0.5 – 12
Weber (1999)[**23**]	1990-1997	ONF	102	12 – 96	No NI	0.25 – 16
		LTouF	154			

Method: NF = Nissen fundoplication (open or laparoscopic unknown); ONF = Open Nissen Fundoplication; LNF = Laparoscopic Nissen Fundoplication; LThF = Laparoscopic Thal fundoplication; LTouF = Laparoscopic Toupet Fundoplication; LJ = Lortat Jacob; VGP = Vertical gastric placation; G = Gastrostomy; Stamm = Stamm-gastrostomy
Comorbidity: EA = Esophageal atresia; NI = Neurologically impaired; All = all patients
Yrs = years**; SD =** Standard deviation**; NR =** Not recorded

Table 1 Details on included prospective clinical trials on ars in children

Only two RCTs were identified, and only five articles used control groups to verify their results [6,8–10,14,23]. Most studies used standardized surgical methods and investigation techniques and reported adequate on lost to follow-up. However, the overall methodological quality was generally poor. All potential threats to validity are summarized in **Table 2**.

Study (year)	Capito et al. [6]	Cheung et al. [7]	Durante et al. [8]	Engelmann et al.[9;10]	Estevão-Costa et al.[11]	Kawahara et al.[12]	Kawahara et al.[13]	Kubiak et al.[14]	Mattioli et al.[15]	Mattioli et al.[16]	Menon et al.[17]	Mousa et al.[18]	Soyer et al.[19]	Srivastava et al.[20]	Van der Zee et al.[21]	Weber et al.[22]	Weber et al.[23]
Randomization	-	-	+	-	-	-	-	+	-	-	-	-	-	-	-	-	-
Controlled	+	-	+	+	-	-	-	+	-	-	-	-	-	-	-	-	+
Standardization	+	-	+	+	+	+	+	+	-	+	-	+	+	+	+	-	-
Adequate report on loss to follow-up	+	NA	NA	+	+	+	+	NA	NA	NA	NA	+	NA	-	+	-	-
Potential other source bias			+[‡]	+[†¶]				+[*]	-	+[§]		+[¶]		+[†]			+[¥]

[ʃ] Results from longitudinal follow-up of other surgical intervention (Esophageal atresia) [‡] No power calculation, underpowered; [†] High drop-out percentage; [¶] Male/female imbalance; [*] Significant baseline imbalance in weight between the two arms ; [§] Time horizon determines method of surgical approach (Open vs. Laparoscopic); [¥] Patient assignment (based on patient characteristics): TF (Patients with symptoms or radiological signs of gastroesophageal dysmotility and adolescent patients) and NF (Patients with life-threatening symptoms or esophageal strictures were assigned) NA = Not applicable (no lost to follow-up)

Table 2 Risk of bias summary

Success Rate

Overall Success Rate

In 10 out of 17 (59%) studies (**Table 3**), the success rate of antireflux surgery in eliminating reflux symptoms was reported. Short-term success rates (within 6 months after surgery) were reported in seven of the ten studies and varied from 57–100% (median 86%). Long-term success rates (follow-up period longer than 6 months) were reported in three of the ten studies and varied from 70–96% (median 72%). In one study, the outcome after redo ARS (in 5% of patients) was included, which resulted in a secondary success rate of 99% after long-term follow-up [6]. Symptom severity scores were available in only one study [10], showing a significant reduction in symptom severity after laparoscopic anterior partial (Thal) fundoplication. Failure was not defined in most studies. Some studies reported the failure rate only as the need for reoperation. In nine studies [6,7,9,10,15,19–23], a redo percentage was reported, varying from 0–3.8% (median 1%). The indication for redo operation was recurrent reflux in all cases.

Study	Short term SR (%) (FU < 6 months)	Long term SR (%) (FU > 6 months	Long term SR (%) after second ARS
Capito et al. [**6**]	NR	72	99
Cheung et al. [**7**]	NR	70	NR
Durante et al. [**8**]	57	NR	NR
Kawahara et al. [**12**]	100	NR	NR
Mattioli et al. [**15**]	NR	96.2	NR
Menon et al. [**17**]	100	NR	NR
Soyer et al. [**19**]	86	NR	NR
Van der Zee et al. [**21**]	75	NR	NR
Weber et al. [**22**]	79	NR	NR
Weber et al. [**23**]	93	NR	NR

SR = Success rate; FU = Follow-up; NR = Not recorded.

Table 3 Success rate (complete resolution of gastroesophageal reflux symptoms) of ars in children

Success Rate in Selected Patient Groups

Four studies reported solely on neurologically impaired (NI) children undergoing ARS [7,8,20,22]. Success rates varied from 57–79% (median 70%). Two studies compared outcome of ARS in NI patients to neurologically normal (NN) children. The first study demonstrated that recurrence of reflux was significantly higher in NI patients than in NN patients (18% vs. 2%, p=0.01)[6]. The second study demonstrated a small, but significant difference in favor of NI patients concerning relative postoperative improvement of symptom severity, but no significant differences in 24-h pH monitoring, gastric emptying, or quality of life scores between patient with or without neurological impairment[9,10]. In three studies, patients were included who had previously been operated for esophageal atresia, but none reported results for this group separately[14,19,21]. No prospective studies have been published showing only results in children with esophageal atresia undergoing antireflux surgery.

Success Rate Depending on Surgical Technique

Recently, an RCT was published comparing complete versus partial fundoplication in children [14]. In this study, no significant difference in short-term outcome between laparoscopic Nissen fundoplication and laparoscopic Thal fundoplication was seen. However, a higher rate of severe dysphagia and complications were found after Nissen fundoplication. A prospective, non-randomized study comparing open Nissen fundoplication to open Toupet fundoplication showed similar recurrence rates[23]. In this study, Toupet fundoplication also resulted in less postoperative dysphagia. Furthermore, Toupet fundoplication resulted in

lower reoperation rates, shorter time to first feeding, and shorter hospital stay. Patients were, however, assigned to either technique based on preoperative symptoms, gastroesophageal motility, age, and learning curve of the surgeon (**Table 2**). Durante et al. randomly allocated patients to either Nissen fundoplication or vertical banded gastroplasty and showed no significant differences between these procedures. However, the number of patients included in this trial was very small (seven patients per group) [8]. No RCTs comparing laparoscopic to open fundoplication were published. Two prospective studies comparing open with laparoscopic fundoplication were identified, showing similar recurrence rates [7,16]. However, patients after laparoscopic ARS required less pain medication (one vs. six doses, $p<0.05$), and had a shorter hospital stay (2 vs. 7 days, $p<0.05$).

Complications

Complications were not consistently reported. Perioperative complication rates varied widely between 0% and 54%, including esophageal perforation, pneumonia, and wound infections. The highest complication rates were found in studies that only included neurologically impaired patients [22]. Nine studies reported on dysphagia, demonstrating postoperative dysphagia in zero to 33% of patients [6,9,12–14,16,17,21,23]. However, this rarely lasted after the first few months following surgery. In two studies, balloon dilatation was used to treat postoperative dysphagia [14,17]. Only one study reported prolonged dysphagia postoperatively [6]. Postoperative dysphagia was more commonly reported after complete fundoplication than after partial fundoplication [23]. Postoperative gas bloating was not reported in any of the prospective studies. Overall mortality during follow-up ranged from 0% to 29%. Surgery-related mortality rate was 0% in eight studies [7,8,15,17,19,21–23] and 0.7% in one study [6] In this particular study, the patient died of peritonitis following postoperative detachment of a simultaneously placed gastrostomy.

Pre– and Postoperative Assessment Tests

In most (15/17) studies, 24-h pH monitoring was performed prior to ARS [6–10,12–17,19–23]. Postoperative pH monitoring was routinely performed in eight studies [6–10,12,17,19,21]. All these studies reported a decrease in incidence and/or severity of reflux after ARS, including a reduction in RI (percentage of time with a pH <4) and the number and duration of reflux episodes. Four of these eight studies actually published the numbers of the RI before and after surgery [7,8,12,19] (**Table 4**). Data on symptom association probability scores were not reported. Three studies reported manometry data before and after Nissen fundoplication [12,13,19]. Although the lower esophageal sphincter (LES) pressure seemed to increase after ARS, this was not statistically significant in any of the studies. In one study, the number of transient LES relaxations had significantly decreased postoperatively from 13 to 7 ($p<0.05$) [12]. ARS did not seem to affect esophageal motor function [13,19]. Three studies reported

on gastric emptying before and after ARS using scintigraphy. In two studies, ARS had no significant effect on gastric emptying rate [10,18]. The third study demonstrated a significant acceleration of the gastric emptying rate after ARS [11].

Study	*n*	Reflux index preoperatively (%)	Reflux index postoperatively (%)	p
Cheung et al. [**7**]	20 (NIP)	5.7	0.15	0.009
Durante et al. [**8**]	7 (Nissen)	14.8	4.3	0.002
	7 (VGP)	25.7	12.1	0.042
Kawahara et al. [**12**]	10	15	0	NR
Soyer et al. [**19**]	13	24.7	0.9	<0.05

NIP = Neurologically impaired; VGP = Vertical gastric placation; NR = Not recorded

Table 4 Studies reporting reflux indices pre- and postoperatively in children

In two studies, a reflux specific symptom severity score was employed, showing significantly improved scores after ARS [9,10,17]. In one other study, a quality of life (QoL) questionnaire was performed to evaluate the results of ARS, showing a significant improvement in quality of life after ARS [20]. In none of the studies, MII monitoring, endoscopy, or barium swallow radiography was performed before and after ARS.

DISCUSSION

Our systematic review identified more than 1,000 publications after searching the available databases for pediatric ARS. Most of these articles were found to be retrospective studies or case reports. Only 17 prospective, longitudinal studies, using reflux symptom scores and/or GE tests could be identified that described the outcome of ARS in pediatric GERD patients. This indicates that the vast majority of studies on pediatric ARS are of poor quality. In this systematic review, success was defined as complete relief of reflux symptoms. The median reported success rate after pediatric ARS was 86%, but varied widely (57–100%), due to several reasons. First, in most studies, heterogeneous patient groups and different surgical techniques were included and compiled in one general data pool. Second, although guidelines of the NASPHGAN [4] have been published, an actual unanimous definition of therapy-resistant GERD is lacking. This results in a large variety of presumed GERD and non-GERD patients that are included in studies on pediatric ARS. Our systematic review further shows that the QoL has been highly underexposed in the evaluation of pediatric ARS, even though validated QoL questionnaires are available for different age groups and development

levels [24]. In only one study, QoL questionnaires were performed, showing a significant improvement after ARS [20].
Several studies have postulated that NI patients are predisposed to a worse outcome after ARS. But in fact, only two studies [6,10] actually compared NI patients with NN patients. These two studies reported conflicting results. Capito et al. [6] found a significantly higher recurrence rate in NI patients. Engelmann et al. [10], however, demonstrated that NI patients showed relatively more improvement than NN patients. Nevertheless, we have to realize that drawing conclusions on the efficacy of ARS in specific groups, such as NI patients or patients after esophageal atresia is challenging, because of a lack of well-designed prospective comparative studies.

Clinical trials comparing laparoscopic to open ARS in pediatric GERD patients have not been published. However, prospective studies in this systematic review have shown that the results of laparoscopic ARS were not different from those of open ARS with regard to reflux symptoms during short-term follow-up. The main benefits of laparoscopic ARS include a shorter hospital stay and a reduced need for pain medication [5,12]. Recently, the New Technology Committee of the American Pediatric Surgery Association published a position paper favoring laparoscopic fundoplication. This advice was, however, based on results from case series and retrospective reviews [25]. In only three studies, different types of ARS were compared [8,14,23]. Two of these studies compared complete versus partial fundoplication demonstrating less postoperative dysphagia in the partial fundoplication group. Reflux control, on the other hand, was comparable in both groups [14,23]. Similar results were demonstrated by a recently published systematic review and meta-analysis on RCTs comparing complete posterior (Nissen) with partial posterior (Toupet) fundoplication in adults [26].

Finally, we noticed that following ARS, values of 24-h pH monitoring significantly decreased, LES-pressure seemed to increase, and gastric emptying was either unchanged or accelerated. However, no definite conclusions of the effects of ARS on GE function can be drawn, since too few studies have performed standardized GE function tests and the number of patients included in these studies was too small. Only if GE function tests are consistently performed before and after ARS in a sufficient amount of patients, the effects of ARS on GE function may be clarified. Moreover, these tests may then also provide us with the opportunity to identify prognostic factors for failure of ARS.

In conclusion, ARS in children shows a good overall success rate (median 86%) in terms of complete relief of symptoms. The success rate in NI patients may not be worse compared to NN patients. The outcome of ARS does not seem to be influenced by different surgical techniques, although postoperative dysphagia may occur less after partial fundoplication. The strength of these conclusions is, however, bound by the lack of high-quality prospective

studies on pediatric ARS. Similar studies on the effects of pediatric ARS on gastroesophageal function are also very limited. Therefore, future studies should be performed in a well-designed prospective format, either as an RCT comparing different types of ARS, or as a prospective, age- and sex-matched study comparing different patient groups. But, even more crucial is the use of standardized GE function tests to clarify the effects of ARS on GE function and to identify possible risk factors of failure of ARS in children

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3. Effects and efficacy of laparoscopic fundoplication in children with GERD: a prospective, multicenter study

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ABSTRACT

Introduction: Laparoscopic antireflux surgery (LARS) in children primarily aims to decrease (acid) reflux events and reduce reflux symptoms in children with therapy-resistant gastroesophageal reflux disease (GERD). The aim was to objectively assess the effect and efficacy of LARS in pediatric GERD patients. Furthermore, we aimed to identify parameters associated with failure of LARS.

Methods: We performed a prospective multicenter study in pediatric patients with therapy-resistant GERD to undergo LARS. From July 2011 until December 2013, 25 patients (12 males, 5 with impaired neurodevelopment, median age 6 (2-18) years) were included. Before and 3-4 months after LARS, clinical assessment was performed using reflux-specific questionnaires, stationary manometry, 24-hour multichannel intraluminal impedance pH monitoring (MII-pH monitoring) and a 13C-labeled Na-octanoate breath test.

Results: In all patients fundoplication was completed laparoscopically. Perioperative complications did not occur. After LARS, 3/25 (12%) patients had persisting/recurrent reflux symptoms (one also had persistent pathological acid exposure on MII-pH monitoring). New-onset postoperative dysphagia was present in 3/25 (12%) patients 3-4 months after LARS. Twenty-four hour MII-pH monitoring showed a significant decrease in total acid exposure time (AET) (8.5% (2.5-32.8%) to 0.8% (0-2.8%), $p<0.0001$) and total number of reflux episodes (91 (8-230) to 14 (2-153), $p<0.001$), both acidic and weakly acidic. Lower esophageal sphincter (LES) resting pressure significantly increased after fundoplication from 10 mmHg (7-18) to 24 mmHg (17-26), $p<0.0001$. Complete LES relaxation, peristaltic contractions and gastric emptying time did not change after LARS. The total number of reflux episodes on MII-pH monitoring before LARS was a significant predictor for the effect of the procedure on reflux reduction (Estimate = 0.8; $p<0.0001$, 95% CI 0.52 – 1.10).

Conclusion: In children with therapy-resistant GERD, LARS significantly reduces reflux symptoms, total AET and number of (acidic) reflux episodes. LES resting pressure increases significantly after LARS, but esophageal function and gastric emptying are not affected by the procedure. LARS showed better reflux reduction in children with a higher number of reflux episodes on preoperative MII-pH monitoring.

INTRODUCTION

Gastroesophageal reflux disease (GERD) frequently occurs in the pediatric population [1;2]. In severe GERD resistant to medical treatment, laparoscopic antireflux surgery (LARS) can be warranted [2-4]. Many studies have been published on pediatric LARS [5-12]. Most of these studies had a retrospective design and could only concluded that the procedure resulted in symptom control in 57 to 100 percent of patients [11;13;14]. To assess the efficacy of LARS it is important to use validated questionnaires before and after LARS. Such questionnaires, however, have not been used in the majority of pediatric LARS studies [15]. In addition to evaluation of reflux symptoms, more objective assessments of (acid) reflux, like multichannel intraluminal impedance pH (MII-pH) monitoring should be performed [9;10;16].

In previous published pediatric studies, objective assessments were primarily performed using only pH monitoring [6;9;10;12]. MII-pH monitoring enables quantification of both acid and weakly acidic reflux and the proximal extent of the refluxate [17] and therefore increases the yield of symptom association assessments in children [18]. Studies in children using MII in addition to pH monitoring so far were either retrospective [19] or only investigated efficacy in a selected patient population [20]. However, up to now none of the studies quantifying both reflux symptoms and more objective assessments of GERD after LARS have shown a correlation between both measurements [9;10]. It is therefore important to evaluate effects and efficacy of LARS using both validated questionnaires and objective assessment tools.

The success of LARS is determined by the disappearance or reduction of GERD, but is also influenced by postoperative sequelae, such as severe dysphagia and gas/bloating [21]. It is therefore indicated to identify predictors for failure in order to enable optimal preoperative counseling on the risk of persisting or recurrent GERD after LARS. Rosen et al [19] addressed this issue in a retrospective study by trying to identify predictors for failure of LARS in children using preoperative MII-pH monitoring in 37 patients. However, no predictors could be identified in this study.

The aim of the current prospective study was to objectively assess the effect and efficacy of LARS in pediatric patients and to identify predictors of LARS failure.

METHODS

We performed a prospective multicenter study in three University Medical Centers in the Netherlands that are specialized in performing laparoscopic fundoplication in children (Wilhelmina children's Hospital, University Medical Center Utrecht (UMCU); Sophia's Children's Hospital, Erasmus University Medical Center (Erasmus MC) and Maastricht University Medical Center (MUMC). From July 2011 till December 2013 we prospectively included all pediatric patients diagnosed with PPI-therapy resistant GERD. Patients who underwent any previous

esophageal or gastric surgery (except previous gastrostomy placement) and those with structural abnormalities other than an esophageal hiatal hernia were excluded.

Surgical Procedures

All laparoscopic fundoplication procedures were performed by experienced pediatric surgeons. In the UMCU Utrecht the anterior, partial fundoplication according to Thal [22] was used to perform fundoplication. In the other two UMC's (EMC and MUMC) the posterior, total fundoplication according to Nissen [23] was performed. Before fundoplication, the distal esophagus was fully mobilized; the distal 3 cm of the esophagus was repositioned back into the abdomen. Both vagal nerves were identified, and a crusplasty was performed routinely (UMCU and EMC). Thereafter, the fundoplication was constructed. The Thal fundoplication was performed by plicating the fundus of the stomach over 270 degrees against the distal anterior intra-abdominal part of the esophagus and the diaphragmatic crus [9;22]. A floppy Nissen was constructed with one of the sutures of the 360 degrees posterior wrap incorporated in the esophageal wall [23].

Clinical Assessment

Before and three months after laparoscopic fundoplication, clinical assessment was performed using stationary manometry, 24-hour multichannel intraluminal impedance pH monitoring (MII-pH monitoring), 13C labeled Na-octanoate breath test and a reflux-specific symptom questionnaire. Surgical reinterventions, type and indication for reintervention, endoscopic procedures, use of antireflux medication, complications, and comorbidities were registered in a prospective database.

Reflux–specific symptom questionnaires

To assess reflux symptoms, patients and/or their parents were asked to fill-out the validated age adjusted Gastroesophageal Reflux Symptom Questionnaire (GSQ) before and after LARS [24]. Reflux symptoms and dysphagia were scored for frequency and severity on a score ranging from 1 (none) to 7 (most severe). Symptoms were defined as; no symptoms (no symptoms reported); mild (mild symptoms, weekly); moderate (mild symptoms daily or severe symptoms weekly) and severe (severe symptoms daily). Reflux symptoms were scored using the symptoms heartburn, regurgitation, food refusal and vomiting. Furthermore, the need for acid suppressive therapy after LARS was registered.

Nutritional status

Weight and height measurements were converted to weight-for-length and length-for-age z-scores based on the Netherlands Organization for Applied Scientific Research (TNO) growth standards [25]. Z-scores allow comparison of an individual's weight or height, adjusting for age and sex relative to a reference population, expressed in standard deviations from the reference mean.

Stationary Manometry

For esophageal stationary manometry, age-adjusted stationary water-perfused sleeve-manometry catheters were used (Mui Scientific, Mississauga, Ontario, Canada). The sleeve-manometry catheter was positioned with the sleeve at the level of the lower esophageal sphincter (LES) using the pull-trough technique. In a semi-recumbent position, patients received 10 liquid bolus challenges using saline combined with lemonade (5ml) in order to study the manometric response. During the study, data were recorded on the stationary Solar Gastro System (Medical Measurement Systems, Enschede, The Netherlands). Manometry tracings were analyzed for LES resting and nadir pressure, LES relaxations, number of peristaltic contractions and peak amplitude of the contractions according to previously accepted standards [26].

Ambulatory 24–Hour MII–pH monitoring

Ambulatory 24-hour MII-pH testing was conducted after cessation of all medication that may have an effect on gastrointestinal motility and acid secretion for at least 3 days. MII-pH monitoring was performed using an age-adjusted combined impedance-pH catheter with six impedance segments and one ISFET pH electrode (Unisensor AG, Attikon, Switzerland). The pH electrode was positioned above the upper border of the manometrically localized lower esophageal sphincter. Impedance and pH signals were stored on a digital data logger (Ohmega, Medical Measurement Systems, Enschede, The Netherlands), using a sampling frequency of 50 Hz. Patients were instructed to record reflux symptoms, supine resting periods, and meals, including drinks, in a diary and by marking the symptom using the recording button on the data logger. The 24-h MII-pH tracings were analyzed for the number and acidity of reflux episodes according to previously described definitions [17]. Pathological acid exposure was defined as total acid exposure time (AET) ≥6%, ≥ 9% in upright, and ≥3% in the supine body position [27;28]. The symptom index (SI) and the symptom association probability (SAP) were calculated if patients had experienced symptoms during the measurement [29;30].

Gastric emptying breath test

To assess gastric emptying (GE) half time, we used a 13C labeled Na-octanoate breath test [31]. Subjects fasted for at least 6 hours before the study. In children >4 years of age, a

solid test meal containing 13C Labeled Na-octanoate was performed with 375-g pancake containing 45mg of 13C labelled Na-octanoate (a stable isotope).
For younger children or children who were unable to eat the pancake within 15 minutes, 100mg of 13C labelled Na-octanoate was added to a liquid formula (infant formula, full cream milk or chocolate milk). Breath samples were obtained in duplicate at 15-minute intervals during the course of 4 hours (for the liquid test, breath samples were obtained at 5-minute intervals during the first 30 minutes). Hereafter, the ratio between 12CO2 and 13CO2 content in breath samples was analyzed with an isotope ratio mass spectrometer. Finally, three parameters were calculated. Gastric half-emptying time (GGE-T½) was defined as the time when the first half of the 13C labelled substrate had been metabolized, that is, when the cumulative excretion of 13C in the breath was half the ingested amount. Gastric emptying percentiles (P) were calculated according to the reference values obtained by van den Driessche et al. [32]. GE percentiles higher than 75 were considered delayed; and above 95 severely delayed. The gastric emptying coefficient (GEC) reflects a global index for GE, influenced by both the rate of appearance and disappearance of 13C in breath.

Sample size calculation

A sample size of 50 patients was calculated based on the assumption that approximately 20 percent of pediatric GERD patients will fail after LARS. Success of LARS was defined as: 1) Complete symptom relief and normalized MII-pH monitoring, or 2) Complete symptom relief and near-normal MII-pH monitoring or 3) Normalized MII-pH monitoring combined with a significant improvement of reflux symptoms (complaints less than moderate/weekly). Using the logistic regression model according to Frank Harrell [33] 5 failures were required to reliably identify a determinant of failure. Determinant of interest were gastric emptying and age at time of operation.

Patients

In total 25 children were included in our study. After enrolment of the 25th patient, the study was stopped prematurely, because the inclusion rate was lower than anticipated. Mean age of the included patients was 6 (range 2-18) years at the time of fundoplication (**Table 1**). Five children (80%) had normal neurodevelopment (NN), while impaired neurodevelopment (NI) was seen in 5 children (20%). Cause of NI are shown in **Table 2**.

	(Median; IQR)
Age at time of operation (years)	6.0 (3.0-11.0)
Duration of hospital admission (days)	3.0 (2.0-4.5)
	n (%)
Male gender	12 (48.0%)
Impaired neurodevelopment	5 (20.0%)
Gastrostomy preoperatively in situ	4 (16.0%)

Table1 Baseline charateristics

Charge syndrome
Mitochondrial complex II deficiency
Post hypoxic encephalopathy
Congenital rubella infection
Impaired neurodevelopment of unknown origin with autistic behavior

Table 2 Impaired neurodevelopment (n = 5)

Ethical approval and trial registration

This study was registered at the start of the study in the Dutch national trial registry (www.trailregister.nl; Identifier: 2934). Ethical approval for this prospective multicenter study was obtained from the University Medical Center Utrecht Ethics Committee and local approval was obtained by the remaining two participating centers. Prior to study procedures, informed consent from the patients' parents and children (≥12 years) was obtained.

Statistical analysis

Continuous variables, when symmetric, were expressed as mean ± standard error. Skewed variables were expressed as median with interquartile ranges (IQR). For statistical analysis we used the paired sample t-test or the Wilcoxon signed ranks test, whenever appropriate. The McNemar-Bowker test was used to compare groups in case of nominal outcome measures.

Exploratory subgroups analysis for all outcome measures was performed comparing neurodevelopment and type of fundoplication. The primary aim was to perform a logistic regression analysis if sufficient LARS failures were identified. Linear regression analysis was performed to identify determinants influencing the effect of LARS on reflux control measured by 24-hour MII-pH monitoring. Determinant of interest were age at time of operation, neurodevelopment, type of fundoplication, preoperative number of reflux episodes on 24-hour MII-pH monitoring and preoperative gastric emptying rate. Differences with a $p < 0.05$ were considered statistically significant. All analyses were performed using IBM®22.0.0 SPSS statistical package (IBM, Armonk, NY).

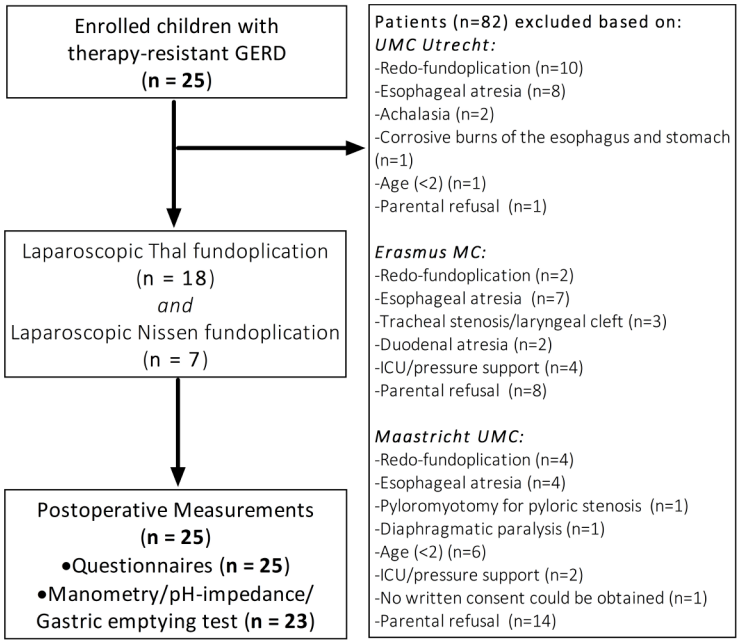

Figure 1 Flow-chart of patient selection and enrollment

RESULTS

In total 18 Thal and 7 Nissen fundoplications were performed (**Figure 1**). In all patients fundoplication could be completed by laparoscopy. Perioperative complications were not observed. Median hospital admission time was 3.0 (2.0-4.5) days (**Table 1**). In one patient with retching based on impaired neurodevelopment a redo-fundoplication was indicated because of severe recurrent reflux (pathological reflux on 24-hour pH-monitoring and severe reflux symptoms) caused by hiatal herniation. Another patient required emergency gastroscopy to remove a food bolus impacted in the esophagus one day after LARS. In six children temporary nasogastric tube feeding was required to obtain sufficient caloric intake. Insufficient caloric intake was caused by transient dysphagia (n=4), persistent dysphagia (n=1) or rejection of oral feedings without dysphagia (n=1).

Symptom assessment

All patients and/or parents completed the reflux-specific symptom questionnaire (**Figure 1**). Overall reflux symptoms significantly decreased after LARS (p =0.001). In three of 25 (12%) patients, reflux symptoms persisted (1/3 also had persistent pathological acid exposure on MII-pH monitoring) (**Table 3**). The use of acid suppressive medication decreased from 100% of all patients preoperatively to 16% (n=4) after operation. Analysis in subgroups comparing children with NI to NN (NN (5%) vs NI (40%); p = 0.099) and Nissen compared to Thal fundoplication (Nissen (11%) vs Thal (17%); p = 0.597) did not show significant differences in the presence of GERD symptoms after LARS.

Moderate to severe dysphagia was reported in eight (32%) patients before LARS and in seven (28%) patients three months after LARS (p=0.887) (**Table 3**). New-onset dysphagia was seen in three of these seven patients with dysphagia after LARS. Dysphagia more frequently occurred in NI children (NI (80%) vs NN (15%), p =0.012) after LARS compared to NN patients. Furthermore, there was a trend showing that children undergoing Nissen fundoplication had more frequently dysphagia compared to those undergoing Thal fundoplication (Nissen (57%) vs Thal (17%), p=0.066).

Nutritional status

Height-for-weight (-0.2SD (-1.0-0.7) to -0.5SD (-1.3-0.1); p=0.57) and height-for-age (-0.9SD (-1.2-0.1) to -1.0SD (-1.5-0.4); p=0.42) scores remained similar when comparing preoperative to 3-months postoperative measurements.

	Preoperative (n; %)		3-4 months postoperative (n; %)		p-value
Reflux symptoms					
None	0	(0%)	17	(68%)	
Mild	2	(8%)	5	(20%)	0.001
Moderate	7	(28%)	2	(8%)	
Severe	16	(64%)	1	(4%)	
Dysphagia					
None	13	(52%)	15	(60%)	
Mild	4	(16%)	3	(12%)	0.887
Moderate	3	(12%)	3	(12%)	
Severe	5	(20%)	4	(16%)	

Table 3 Symptom assessment

Clinical assessment tests

Postoperative manometry, 24-hour MII-pH monitoring and gastric emptying breath test were not performed in two patients because of parental refusal (**Figure 1**). LES resting pressure significantly increased after fundoplication from 10 mmHg (7-18) to 24 mmHg (17-26), p<0.0001. Nadir LES pressure also significantly increased from 0 mmHg (0-8) to 3.5 mmHg (0-8) after LARS, p<0.0001. Complete LES relaxation, percentage of continued peristaltic contractions and peak amplitude all remained similar (**Table 4**). Subgroups analysis showed no differences comparing NI to NN children. Children undergoing Thal fundoplication had a significantly higher preoperative LES resting pressure compared to those who underwent Nissen fundoplication (Thal (14.6 mmHg) vs Nissen (6.5 mmHg); p = 0.001); however, after LARS no statistical difference was found (Thal (22.7 mmHg) vs Nissen (19.8 mmHg); p= 0.525). All other manometry outcome measures were similar when comparing Thal to Nissen fundoplication.

Twenty-four hour MII-pH monitoring showed a significant decrease in total acid exposure time and number of reflux episodes (p<0.001; **Table 4**). Acidic, weakly acidic, liquid and mixed reflux episodes also decreased significantly (**Table 4**). In two patients pathological reflux persisted after LARS, although in one of these patients total acid exposure time (AET) decreased from 32.8 percent (severe pathological) to 9.7 percent (near-normal). Subgroup analysis comparing NI to NN children revealed that preoperative acid exposure time and total number of reflux episodes (RE) before LARS were significantly higher in NI children (AET: NN

(9.5%) vs NI (19.3%); p = 0.006 and RE: NN (91.5) vs NI (181.4); p = 0.002). After LARS NI children still had more reflux, although it was not statistically significant (AET: NN (1.2%) vs NI (7.2%); p = 0.22 and RE: NN (16.6) vs NI (41.8); p = 0.42). Other 24-hour MII-pH outcome measures were similar comparing NI to NN children. Comparing Thal to Nissen fundoplication only identified a significant difference in preoperative total number of reflux episodes on 24-hour MII-pH monitoring (AET: Thal (121.4) vs Nissen (76.7); p = 0.03); however, after LARS outcomes were not significantly different (AET: Thal (25.9) versus Nissen (11.4); p = 0.33).

GE half time (77 min (0-113) to 56 min (14-103); p=0.102) and GE percentiles did not significantly change after LARS (**Table 4**). However, looking at a subset of patients with preoperative delayed (n=13) or severely delayed (n=8) GE, GE half time (84 min (58-106) to 54.4 min (40.3-87.3); p=0.023) and GE percentiles (85 (75-95) to 75 (10-85); p=0.029)improved significantly. Furthermore, in 4 patients GE normalized after LARS (**Figure 2**). Subgroup analysis comparing gastric emptying in NI to NN children and Thal to Nissen fundoplication did not show any significant differences.

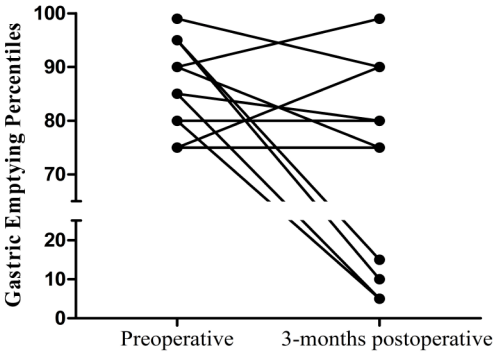

Figure 2 Effect of LARS on gastric emptying in patients with preoperative delayed gastric emptying

24-hour MII-pH measurement:	Preoperative (IQR)		3-4 months postoperative (IQR)		p-value
Total GER episodes	91.5	(8-230)	14	(2-153)	<0.0001
Acid GER episodes	61.5	(34.3-93.8)	8	(1-13)	<0.0001
Weakly acid GER episodes	23	(10.5-42)	5	(3-11)	0.002
Liquid GER episodes	55.5	(11-153)	10	(2-96)	<0.0001
Mixed GER episodes	37.5	(3-176)	3	(0-57)	<0.0001
Proximal extend					
Z1 (Proximal esophagus)	26.5	(14.5-55.3)	2	(0-8)	<0.001
Z3 (Mid esophagus)	75.5	(64.8-88)	57	(44-71)	0.009
Z5 (distal esophagus)	100	(100-100)	100	(100-100)	NA
Total acid exposure (%)	8.5	(2.5-32.8)	0.8	(0-2.8)	<0.0001
Longest reflux episode (min)	20,7	(3.4-66.7)	3.8	(0-21.6)	<0.0001
SI (%)	75	(18.8-100)	50	(0-100)	0.111
SAP (%)	100	(97.3-100)	93.2	(22.1-98.7)	0.048
Stationary manometry:					
LES resting pressure (mmHg)	10	(6.5-18)	23.5	(17-26)	<0.0001
LES nadir pressure (mmHg)	0	(0-8)	3.5	(0-8)	<0.0001
Complete LES relaxation (%)	100	(100-100)	100	(100-100)	0.311
Continued peristaltic contraction (%)	100	(100-100)	100	(100-100)	0.149
Peak amplitude (mmHg)	74	(39-109)	66	(24-139)	0.299
Gastric Emptying test:					
Gastric emptying half time (min)	76.5	(49.3-89)	56	(47-78)	0.102
Gastric emptying percentile	75	(0-99)	70	(2-99)	0.530
GEC	3.0	(2,5-5,6)	3.6	(2.3-4.7)	0.463

GER = Gastroesophageal Reflux; SI- Symptom Index; SAP = Symptom Association Probability; NA = Not Applicable; LES = Lower Esophageal Sphincter; GEC = Gastric Emptying Coefficient

Table 4 Results of clinical assessment tests

Predictors of LARS failure

After LARS only one patient had persistent reflux symptoms and pathological reflux. As only one patient failed LARS a logistic regression analysis was therefore not feasible.

Predictors of the effect of LARS on reflux control

Linear regression analysis identified preoperative reflux episodes on MII-pH monitoring as a determinant influencing the effect of LARS reflux episodes (Estimate = 0.791; p<0.0001). Age at the time of operation, neurodevelopment, type of fundoplication and GE did not show any significant effect (**Table 5**).

	Estimate	p-value	95% CI
Age at time of operation	-6.1	0.76	-47.2 – 34.9
Neurodevelopment	0.8	0.61	-2.7 – 4.4
Type of fundoplication	3.4	0.85	-33.8 – 40.6
Preoperative total number of reflux episodes	0.8	<0.0001	0.5 – 1.1
Preoperative gastric emptying	-0.2	0.34	-0.6 – 0.2
Linear regression analysis (95% CI = 95% confidence interval)			

Table 5 Predictors of the effect of lars on reflux reduction

DISCUSSION

In the present study LARS was successful in 96% of children with therapy-resistant GERD according to both the symptom and clinical response. LARS reduced not only acidic reflux episodes, but weakly acidic reflux was also significantly reduced.

Reflux symptoms significantly decreased after LARS and in three (12%) patients reflux symptoms persisted at 3-months follow-up. This short-term success rate is similar to other prospective studies in pediatric antireflux surgery [7;11;12]. Subgroups analysis showed that the incidence of persistent or recurrent reflux symptoms was similar after both Thal and Nissen fundoplication (p=0.597). A recent meta-analysis in both adults and children also reported no differences between partial and complete fundoplication techniques in reduction of reflux symptoms [34;35]. It must be noted that our study was not powered to study the differences between both techniques and therefore results may differ in a larger study population.

When comparing reflux symptoms after LARS in children with NI to children with NN, we found that reflux symptoms were present in only 5% (1/20) of NN patients versus almost half (40%; 2/5) of NI children. This difference was not statistically different possibly because the current study was not powered to identify differences between both groups. Before LARS total acid exposure time and number of reflux episodes were significantly higher in NI children, however after LARS no significant differences were observed. Some authors hypothesized that NI children may insufficiently benefit from LARS [5;36;37]; however we found no statistical significant differences in our study.

Only one of the three patients with persistent reflux symptoms also had pathological acid exposure on MII-pH monitoring; conversely, only one of the two (both NI) patients with pathological reflux had reflux symptoms after LARS. In the other NI patient reflux symptoms completely resolved and 24-hour MII-pH monitoring decreased to near-normal acid exposure. In adults a lack of correlation between reflux symptoms and objective assessment of the prevalence of (acid) refluxate in the esophagus has been reported as well [38;39]. It is thought that recurrent or persistent symptoms may be caused by concomitant functional disease such as functional dyspepsia or hypersensitivity [39]. Moreover, in NI patients symptom assessment may be even more challenging because NI children are frequently verbally restricted and often have more (co-) morbidity, which underscores the importance of objective assessment of GERD in these children.

Objective assessment of reflux using 24-hour MII-pH monitoring showed that LARS resulted in a significant decrease in acidic and also weakly acidic reflux. An earlier published pilot study by Loots et al [8] did not show significant reduction in weakly acidic reflux. However, in this study only 10 patients were included, which may result in a type 2 error. Weakly acidic reflux is often not successfully treated by acid suppressive therapy (i.e. proton pump inhibitors) as it only decreases the acidity of the refluxate but does not treat the actual retrograde movement of gastric content [40]. Furthermore, in young children gastric content is buffered by frequent feeds and is therefore often not acidic.

LES resting and nadir pressure increased significantly after LARS, which is in accordance with previous studies on pediatric antireflux surgery [12;36]. Increase in the esophagogastric junction competence is expected, as it is one of the mechanisms in which LARS prevents GERD [41-43]. It has been reported that LARS may affect LES relaxations and esophageal motility thereby inducing postoperative dysphagia [44]. In this current study LARS did however not affect LES relaxations and esophageal motility.
In seven patients dysphagia was found after LARS. New-onset dysphagia was seen in three of these patients and was significantly more prevalent in NI children. Furthermore, a non-significant trend was shown in favor of Thal fundoplication [17% vs 57%, compared to Nissen fundoplication. New-onset dysphagia is thought to be caused by fundoplication-induced

restriction and postoperative swelling at the esophagogastric junction. LES pressure testing in our cohort did show a significant increase in LES resting and nadir pressure, which may reflect this restriction. Complete [eg. Nissen) and partial (eg. Thal and Toupet) fundoplication are all currently used in the pediatric population and reported dysphagia rates differ between these techniques, but are mostly less prominent after partial fundoplication [7;15;35]. Finally, dysphagia may be a manifestation of GERD, as dysmotility of the distal esophagus is frequently seen in adult patients with esophagitis [45;46].

In the current study only one patient failed after LARS, which made a logistic regression analysis for the identification of predictors of LARS failure not possible. Rosen et al. also used MII-pH monitoring trying to identify predictors for LARS failure using a Cox-regression analysis, however their study was underpowered with only 37 patients and few failures and was not able to identify any predictors [19]. Despite the fact that logistic regression was not feasible, we still could perform a linear regression analysis that identified that the number of preoperative reflux episodes on MII-pH monitoring is a significant determinant influencing the effect of LARS. Patients with a higher number of reflux episodes on MII-pH monitoring had significantly more reflux reduction after LARS. Age at the time of operation, neurodevelopment and type of fundoplication did not show a significant effect. In the adult literature preoperative delayed GE negatively influenced the success of LARS [45;46]. In children with GERD delayed GE may influence the severity of GERD [47;48]. Therefore, for this study we hypothesized that preoperative delayed GE could be a risk factor for failure of LARS in our pediatric cohort. In linear regression analysis, GE was however not a significant predictor. LARS did significantly improve GE in patients with preoperative delayed or severely delayed GE, which has also been demonstrated in adults [47;48] and children [49] that have undergone LARS.

One of the limitations of this current study was that we enrolled fewer patients than anticipated. Although most results on the efficacy of LARS showed statistically significant differences, the number of included patients limited our linear regression analysis and therefore we were only able to investigate 5 determinants assuming enough statistical power with 5 included patients per chosen predictor. As only one patient failed after LARS a logistic regression analysis to identify predictors of failure was not possible. Furthermore, three months follow-up time may be too short. As published in a previous study [9], reflux symptoms may increase over time and therefore it is important that we closely follow-up this current group over the years.
In conclusion, LARS significantly reduces reflux complaints, total AET and number of (acidic) reflux episodes in children with therapy-resistant GERD. LES resting pressure increases significantly after LARS, but esophageal function was not affected by the procedure. GE significantly improved in patients with preoperative delayed gastric emptying, but in the overall group no differences were observed. LARS showed better reflux reduction in children

with a higher number of reflux episodes on preoperative MII-pH monitoring. Identifying predictors for failure was not possible due to the low failure rate of LARS in this cohort at 3-months follow-up. Future studies should entail multicenter prospective trials with a higher number of patients and long-term follow-up to assess parameters in predicting success of therapy.

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4. Laparoscopic Thal fundoplication in children a prospective 10- to 15-year follow-up study

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ABSTRACT

Background: To study long-term (10–15 years) efficacy of antireflux surgery (ARS) in a prospectively followed cohort of pediatric patients with gastroesophageal reflux disease, using 24-hour pH monitoring and reflux-specific questionnaires. Background: Studies on short-term outcome of ARS in pediatric patients with gastroesophageal reflux disease have shown good to excellent results; however, long-term follow-up studies are scarce, retrospective, and have not used objective measurements.

Methods: Between 1993 and 1998, a cohort of 57 pediatric patients (ages 1 month to 18 years; 46% with neurological impairment) underwent laparoscopic anterior partial fundoplication (Thal). Preoperatively and postoperatively (at 3–4 months and at 1–5 and 10–15 years), reflux-specific questionnaires were filled out, and 24-hour pH monitoring was performed.

Results: At 3 to 4 months, at 1 to 5 years, and at 10 to 15 years after ARS, 81%, 80%, and 73% of patients, respectively, were completely free of reflux symptoms. Disease-free survival analysis, however, demonstrated that only 57% of patients were symptom free at 10 to 15 years after ARS. Total acid exposure time significantly decreased from 13.4% before ARS to 0.7% ($P < 0.001$) at 3 to 4 months after ARS; however, at 3 to 4 months after ARS, pH monitoring was still pathological in 18% of patients. At 10 to 15 years after ARS, the number of patients with pathological reflux had even significantly increased to 43% ($P = 0.008$). No significant differences were found comparing neurologically impaired and normally developed patients.

Conclusions: As gastroesophageal reflux persists or recurs in 43% of children 10 to 15 years after laparoscopic Thal fundoplication, it is crucial to implement routine long-term follow-up after ARS in pediatric patients with gastroesophageal reflux disease.

INTRODUCTION

Antireflux surgery (ARS), by means of (laparoscopic) fundoplication, is an established treatment option performed in pediatric patients with severe gastroesophageal reflux disease (GERD) resistant to medical treatment [1,2]. We recently published a systematic review that clearly demonstrated a lack of well-designed prospective studies, particularly of those using standardized questionnaires and objective gastroesophageal function tests [3]. A limited number of prospective studies that fitted our inclusion criteria showed that pediatric ARS had good to excellent results after short-term follow-up. This is in line with one of our previous studies in which we showed that 90% of pediatric GERD patients were completely free of reflux symptoms at 3 to 4 months after ARS [4]. Publications with a longer follow-up duration after pediatric ARS are scarce, and long-term (>5 years follow-up) efficacy of ARS has

never been investigated prospectively [5–9]. International guidelines on pediatric GERD [1,2] recommend diagnosing GERD based on typical GERD symptoms, preferably in combination with objective function tests, such as 24-hour pH monitoring [10]. To strengthen the diagnosis of GERD, a good correlation between reflux symptoms and objective measurements is needed. Long-term follow-up studies have never used gastroesophageal function tests before and after operation. This is the first prospective study on long-term results (10–15 years) of pediatric ARS, using reflux symptom questionnaires and 24-hour pH monitoring.

MATERIAL AND METHODS

Study Design

The aim of the study was to evaluate long-term (10–15 years) efficacy of ARS in a prospectively followed cohort of pediatric GERD patients. Between 1993 and 1998, a total of 57 consecutive patients underwent laparoscopic anterior Thal fundoplication for therapy-resistant GERD and were prospectively followed for at least 10 years. All clinical and laboratory data were recorded in a prospective database. Data of short-term follow-up of this prospective trial were published in 1996 [4].

Ethical Approval

Ethical approval for this long-term follow-up study, using 24-hour pH monitoring, was obtained from the University Medical Center Utrecht Ethics Committee.

Surgical Procedures

All children underwent laparoscopic anterior, partial fundoplication according to Thal [11,12]. All operations were performed by 2 senior pediatric surgeons, experienced in pediatric laparoscopic surgery. Depending on age, an 8-, 9-, or 10-mm orogastric tube was placed in the esophagus as a guide for dissection and as a bougie for calibration of the hiatus during crural repair. Patients were placed either in a froglike position, with bended legs on a short operating table, or with both legs abducted, depending on the age and length of the child. The Thal fundoplication was performed by plicating the fundus of the stomach in 2 layers over 180 to 270 degrees against the distal anterior intra-abdominal part of the esophagus and the diaphragmatic crus [4]. The first layer of the fundoplication is created by suturing the fundus to halfway the intra-abdominal esophagus, using three 3/0-Ethibond nonabsorbable sutures. In the second layer, the fundus is hitched up approximately 1 cm more distally on the fundus, depending on the age and size of the child, and sutured against both the esophagus at the highest intra-abdominal point and the diaphragmatic ridge. Before the fundoplication, the distal esophagus was fully mobilized, the distal 3 cm of the esophagus was repositioned

back into the abdomen, both vagal nerves were identified, and closure of the hiatus was performed using one or two 3/0-Ethibond nonabsorbable sutures. If adequate energy intake could only be obtained by prolonged enteral feeding [13], concomitant gastrostomy tube placement was performed during the procedure.

Clinical Assessment

Long-term clinical outcome was analyzed using reflux-specific questionnaires and 24-hour pH monitoring. Surgical reinterventions, type and reason of reintervention, endoscopic procedures, Antireflux medication, complications, and comorbidities were registered up to 15 years after ARS.

Reflux–Specific Questionnaire

All patients and/or their caretakers were asked to fill out reflux symptom questionnaires before operation and both at 3 to 4 months and at 1 to 5 years after operation. After this time period, more superior questionnaires became available, such as the Gastroesophageal Reflux Symptom Questionnaire [14] for patients younger than 18 years and the Reflux Diagnostic Questionnaire [15] for patients older than 18 years. These questionnaires were added to assess reflux symptoms at 10 to 15 years after ARS.

Ambulatory 24–Hour pH Monitoring

We performed 24-hour pH monitoring at 3 different time points: before ARS and at 3 to 4 months and at 10 to 15 years after ARS. Ambulatory 24-hour pH testing was conducted after termination of at least 7 days of all medications that affect gastrointestinal motility and acid secretion. A single-use ISFET-pH-only catheter (Unisensor, Unisensor AG, Attikon, Switzerland) was introduced through the nose. The pH sensor was positioned 5 cm above the upper margin of the lower esophageal sphincter. The upper margin of the lower esophageal sphincter was manometrically determined in patients older than 18 years [16]. In patients younger than 18 years, adequate catheter position was determined using fluoroscopy. During the 24-hour measurement period, data were recorded with a portable digital data recorder (Ohmega, Medical Measurements Systems, Enschede, The Netherlands), with a sampling frequency of 1 Hz. Patients were instructed to record reflux symptoms, supine resting periods, and meals, including drinks, in a diary. After 24 hours, the pH recordings were analyzed automatically using a commercial software program (MMS, Enschede, The Netherlands). Pathological acid exposure was defined as total acid exposure time 6% or more, or 9% or more in upright, and 3% or more in the supine body position [17,18]. In patients who had undergone 24-hour pH monitoring at 10 to 15 years after ARS, we calculated the symptom association probability (SAP) if they experienced symptoms during measurement. Before and at 3 to 4 months after operation, this analysis had not been performed, because symptoms were not routinely

recorded during measurement then. The SAP was considered positive if the probability was more than 95%.

Statistical Analysis

Continuous variables, when parametric, were expressed as mean ± standard error of the mean. Nonparametric variables were expressed as median, with interquartile ranges (IQR). Longitudinal data were analyzed using the generalized estimating equation (GEE) analysis, with an unstructured working correlation matrix to take repeated measurements into account. All available data from patients were used in this GEE analysis. To deal with missing information in our data set, GEE analysis produces unbiased estimators for data that are missing completely at random. Factors that may possibly be of influence (gastrostomy tube placement, sex, and age at the time of intervention) were explored within the GEE analysis. A post hoc subgroup analysis was performed to compare neurologically impaired (NI) and neurologically normal (NN) developed children. Kaplan-Meier survival curves were constructed for disease-free survival analysis. Patients lost to follow-up were censored within the Kaplan-Meier analysis. To identify difference in disease-free survival between patient groups, the log-rank testwas used. Differences with a P<0.05 were considered statistically significant. All analyses were performed using PASW 18.0.0 SPSS statistical package (IBM, Armonk, NY).

Demographics		
	Median (years)	
Age at time of operation	5.2 (range 0.08 – 18, IQR 1.4 – 8.7)	
Follow-up time	12.8 (range 10 – 15, IQR 12 – 14)	
	n	**(%)**
Male gender	25	(43.9%)
Neurological impaired development	26	(45.6%)
Esophageal atresia	2	(3.5%)
Hiatal Hernia	19	(33.3%)
Concomitant gastrostomy placement	21	(36.8%)

Table 1 baseline characteristics of included patients

RESULTS

Patients and Follow-up

Between 1993 and 1998, we performed laparoscopic anterior, partial Thal fundoplication in 57 children with severe GERD. Age at the time of inclusion varied from 1 month to 18 years. Almost half (45.6%) of the included patients were NI. Two children (3.5%) underwent prior esophageal correction for esophageal atresia. A hiatal hernia was present in 19 (33.3%) patients. In 21 children (36.8%), concomitant gastrostomy tube placement was performed; because adequate energy intake could be obtained only by prolonged enteral feeding [13]. The majority (90.5%) of these patients were NI. Baseline characteristics are depicted in **Table 1**. In total, 15 patients were lost to follow-up, of whom 3 patients had emigrated. Twelve of the 15 patients had died from a cause unrelated to ARS. These 12 patients were all NI with severe comorbidities. Causes of death were neuropathy based on mitochondrial deficits, aspiration pneumonia, acute cardiac infarction, apnea in known epilepsy, acute respiratory stress syndrome, and bilateral pneumonia. Median follow-up of the included patients was 13 years (range, 10–15 years; IQR = 12–14 years). All 57 patients or their caretakers completed the reflux-specific questionnaire before and 3 to 4 months after ARS. At 1 to 5 years and at 10 to 15 years after ARS, 54 and 42 patients or their caretakers, respectively, completed the reflux-specific questionnaire. Twenty-four-hour pH monitoring was also performed in all 57 patients before and at 3 to 4 months after ARS. At 10 to 15 years after ARS, 24-hour pH monitoring could not be repeated in 13 of the 42 patients because of patient refusal (n=12) and exclusion in 1 patient because of a gastric bypass that had been performed. In 1 patient, 24-hour measurement failed because of accidental removal of the pH catheter after 2 hours of recording (**Figure 1**).

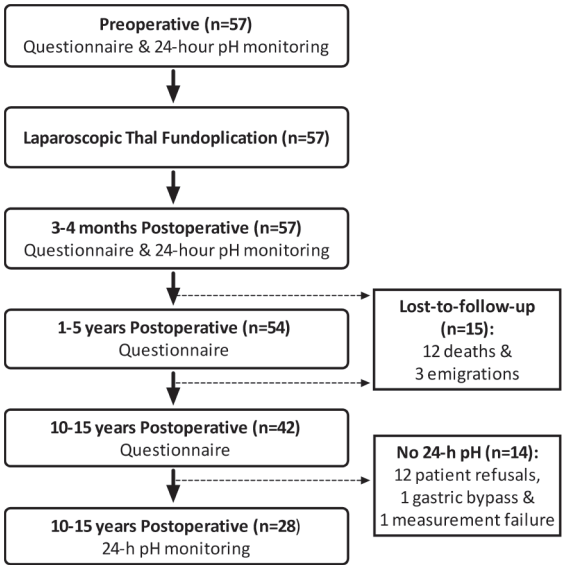

Figure 1 Flow-chart of follow-up

Reflux-Specific Questionnaire

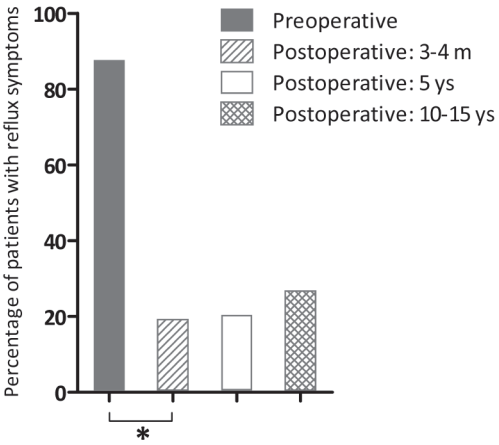

Figure 2 Percentage of patients with reflux symptoms per time point in follow-up.

Before surgery, 7 (12.3%) patients did not have typical reflux complaints. At 3 to 4 months after ARS, 80.7% of patients were completely free of reflux symptoms, whereas at 1 to 5 years after ARS, this was seen in 79.6% of patients and at 10 to 15 years after ARS in 73.2% of patients. No significant differences could be observed between the different postoperative time points (**Figure 2**). However, taking into account patients lost-to-follow-up and patients with reflux symptoms in earlier follow-up using the disease-free survival analysis, only 57.2% of patients were symptom free at 15 years after ARS (**Figure 3**). No dependent variables influencing reflux symptoms could be identified.

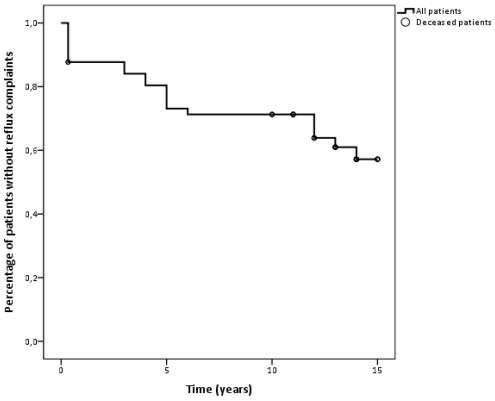

Figure 3 Kaplan–Meier curves showing the percentage of patients free from reflux symptoms after laparoscopic Thal fundoplication *p<0.001

Twenty-four-Hour pH Monitoring

The ARS significantly reduced median total acid exposure time of the esophagus from 13.4% (IQR = 8.8%–22.8%) to 0.7% (IQR = 0.0%–3.5%) (P < 0.001) after 3 to 4 months. At 10 to 15 years after ARS, median total acid exposure time remained equally low (2.7%, IQR = 1.0%–5.9%; P = 0.145). The number of patients with pathological reflux before ARS was 48 of 57 (84.2%). At 3 to 4 months after ARS, this number had significantly decreased, but 24-hour pH monitoring was still pathological in 18.2% of patients (P < 0.001). But at 10 to 15 years after ARS, this had increased significantly, because 42.9% of patients (P = 0.008) had a pathological 24-hour pH monitoring (**Figure 4**). The reflux pattern in patients with pathological reflux at 10 to 15 years after ARS was predominantly supine pathological reflux in 75.0% of patients. In a subset of patients with pathological reflux, median total acid exposure time was also significantly reduced from 14.0% (IQR = 10.1%–25.3%) before ARS to 7.5% (IQR = 5.5%–13.3%) (P < 0.001) at 3 to 4 months after ARS and remained equal at 10 to 15 years after ARS (6.0%, IQR = 4.75%–9.25%;

P = 0.159) (**Figure 5**). No dependent variables influencing 24-hour pH monitoring were identified. In only 15 of 28 patients who underwent pH monitoring at 10 to 15 years after ARS, a SAP analysis was possible. Median SAP in these patients was 89.2% (IQR = 0.0%–0.958%). In 7 patients, SAP was considered positive (>95%). However, one of the patients with a positive SAP indicated reflux complaints on the reflux-specific questionnaire.

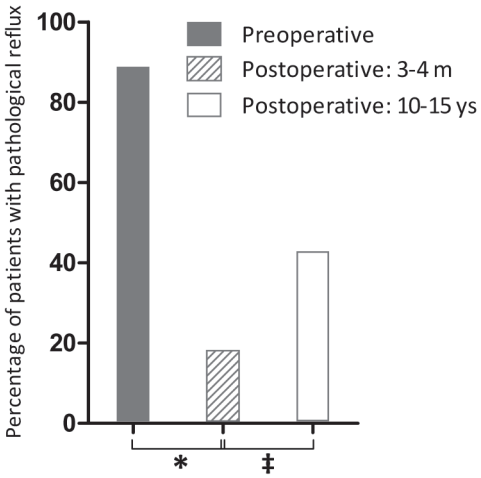

Figure 4 Percentage of patients with pathological reflux on 24-hour pH monitoring per time point of follow-up. *p<0.001; ‡ p=0.008

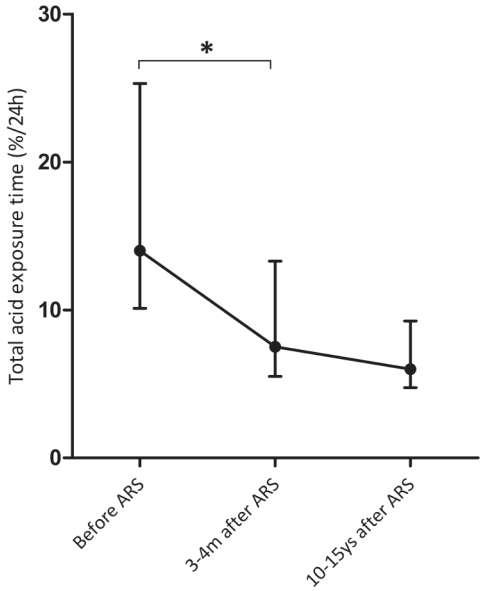

Figure 5 Median (IQR) total acid exposure time (%/24h) on 24-hour pH monitoring in patients with pathological reflux per time point of follow-up. *p<0.001

Postoperative Dysphagia

In 5 patients, dysphagia was present before operation (8.8%). After ARS, we identified dysphagia in 6 of 57 (10.5%) patients at 3 to 4 months follow-up. One patient with postoperative dysphagia had preexisting dysphagia before operation. Five of these 6 patients developed new-onset postoperative dysphagia, of whom 4 patients had coexisting GERD. In 2 of the patients with coexisting GERD, endoscopic balloon dilatations were needed for a peptic esophageal stricture. Only one patient had new-onset postoperative dysphagia, without reflux complaints. This patient was treated with 1 endoscopic balloon dilatation, which resulted in a complete resolution of symptoms. Further follow-up revealed postoperative dysphagia in 8.2% of patients at 1 to 5 years after ARS and in 12.2% of patients at 10 to 15

years after ARS. No significant differences were found between the different time points, and no dependent variables influencing postoperative dysphagia were identified.

Complications and Reinterventions

In total, 8 (14.0%) of all included patients had intra- or postoperative complications. Two patients had a minimal intraoperative bleeding that did not warrant an intervention, nor did it influence postoperative recovery. One NI patient with known epilepsy had an episode of apnea during operation. Postoperative complications were urinary tract infection (n = 1), pneumonia (n = 1), and trocar site hernia (n = 2). One of the patients with a trocar site hernia underwent a surgical repair. One patient underwent a reintervention twice due to leakage at the gastrostomy site insertion 3 months after ARS and due to a gastric blowout caused by an obstructing gastrostomy balloon 2 years after ARS. Six (10.5%) patients underwent redo-fundoplication because of recurrent reflux symptoms and pathological reflux on 24-hour pH monitoring. Median time interval between primary fundoplication and redo-fundoplication for recurrent reflux was 2.3 years (range = 0.4–8.9 years). Five patients received a laparoscopic redo-fundoplication (2 Thal, 2 Nissen, and 1 Toupet). In 1 patient, a laparoscopic procedure was not possible because of adhesions caused by a prior revision of the concomitant gastrostomy. This patient received a conventional Nissen fundoplication. Intraoperative findings during redo-fundoplication were a widened hiatus in 3 patients, a warp failure in 2 patients, and an intrathoracic herniation of the wrap in 1 patient. Redo-fundoplication had good results with regard to symptoms and 24-hour pH monitoring in all but one patient. No reinterventions were warranted for postoperative dysphagia.

Subgroup Analysis Comparing NI Patients With NN Patients

The percentages of patients completely free of symptoms were similar for both NI and NN patients at 3 to 4 months after ARS (80.2% vs 80.6%, respectively). After longer follow-up, NI patients seemed to have slightly less effective subjective reflux control, with 76.9% of NI patients versus 82.1% of NN patients being completely free of reflux symptoms at 1 to 5 years. At 10 to 15 years, 69.2% of NI patients versus 75.0% of NN patients were completely free of reflux symptoms (**Figure 6**). These differences were not statistically significant. The disease-free survival also showed that fewer NI patients were symptom free at 10 to 15 years after ARS than NN patients (49.0% of NI patients vs 64.7% of NN patients; P = 0.182). At 3 to 4 months after ARS, 24-hour pH monitoring was still pathological (13.8% of NN patients vs 23.1% of NI patients; NS). At 10 to 15 years, this difference had even increased to 38.1% for NN patients versus 57.1% for NI patients (NS). However, none of the results on 24-hour pH monitoring showed statistically significant differences between NN and NI patients. Postoperative dysphagia was seen more frequently in NN patients. At 3 to 4 months follow-up, we identified 3.8% of NI patients, compared with 16.1% of NN patients, with postoperative dysphagia (NS). After longer follow-up, these differences, although not significant, remained present (at 5 years: 4.8% vs 10.7% patients; at 10–15 years: 7.7% vs 14.3% patients). Finally, no dependent

variables influencing outcomes in subgroup analysis, such as concomitant gastrostomy tube placement, were identified.

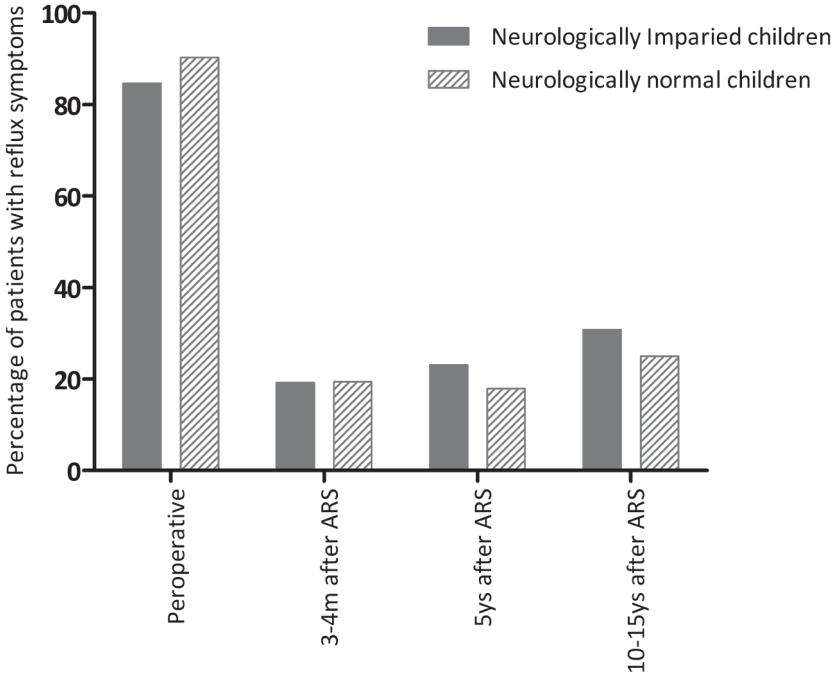

Figure 6 Percentage of patients with reflux symptoms comparing neurologically impaired (NI) and neurologically normal (NN) developed children per time point of follow-up

DISCUSSION

In this prospective longitudinal follow-up study on the efficacy of laparoscopic Thal fundoplication with a follow-up duration of 10 years or more, we found that approximately 40% of patients had recurrent or persistent reflux symptoms. Remarkably, this high recurrence rate is in contrast to the majority of previously published studies [5–8], and in particular the only published study on follow-up 10 years after ARS by Esposito et al. [9], which showed long-term reflux control in up to 87% of patients. A possible factor causing this difference is that all previous studies on long-term efficacy of pediatric ARS were of retrospective cohort designs and therefore introduced selection bias by including only alive and available patients into the analysis. To more reliably address this risk, we performed a disease-free survival analysis and included all patients, irrespectively whether they were lost to follow-up. We believe that these analyses are necessary in this population, because a large proportion of the patients were NI. These patients have a high incidence of comorbidities, and death due to these

comorbidities may influence the outcome of ARS. The fact that our study demonstrates a difference between the efficacy analysis of pediatric ARS in available patients (73.2%) and efficacy of pediatric ARS in the entire study population (57.2%) underlines this. Furthermore, the endpoint in our study was completely free of symptoms, whereas the endpoints are less strict in many other studies [5,6]. Many studies consider redo-fundoplication as a failure of ARS [7]. Therefore, these studies will have much higher success rates than our study. Finally, it may also be possible that during long-term follow-up, the Thal fundoplication might be less favorable than the Nissen fundoplication in terms of reflux control. However, to compare long-term reflux control after both Thal and Nissen fundoplication, we also need studies on Nissen fundoplication to perform disease-free survival analyses, as we have performed in our study on the Thal fundoplication.

We identified pathological reflux in 18% of patients at 3 to 4 months after ARS. After 10 to 15 years, the proportion of patients with pathological reflux significantly increased to 43%. In contrast, median total acid exposure time of the esophagus in these patients with pathological reflux decreased over time, meaning that results of 24-hour pH monitoring were less pronounced at 10 to 15 years after ARS. A problem of interpreting 24-hour pH monitoring in the pediatric and adolescent population is that, with the exception of early infancy [19,20], normal values are not available. Moreover, even in adulthood, different cutoff values are used by different groups [17,18,21]. Therefore, a more reliable tool in assessing reflux control may be the SAP analysis [22–24]. However, assessing symptoms in children can be difficult, especially at a young age and/or in NI children, and is not yet used widely for that reason in the pediatric population. In this study, symptom assessment was possible in only half of the patients who underwent 24-hour pH monitoring at 10 to 15 years after ARS. In 25% (7/28) of patients, SAP was positive (>95%), but only 1 of these 7 patients had significant reflux complaints as defined in the reflux questionnaire. This underscores the difficulty in analyzing and interpreting symptom association.

In our cohort, the prevalence of dysphagia before and after ARS is rather high compared with other studies reporting on pediatric ARS [6,25,26]. We scored all types of dysphagia after ARS in this cohort. However, the majority of these patients with postoperative dysphagia had coexisting GERD or preexisting (preoperative) dysphagia. Dysphagia may be a manifestation of GERD, as dysmotility of the lower esophagus is frequently seen in adult patients with esophagitis [27,28]. Ultimately, only 1 (1.8%) patient developed true new-onset postoperative dysphagia.

After subgroup analysis, no significant differences were identified between NI and NN children, but a trend in less effective reflux control in NI children was observed in the disease-free survival analysis and in 24-hour pH monitoring. In the NI group, 75% of patients received concomitant gastrostomy tube placement. Effects of gastrostomy tube placement (either

alone or in combination with an antireflux procedure) on gastroesophageal reflux are still unclear [29,30].

With our GEE analysis, we demonstrated that concomitant gastrostomy tube placement had no influence on reflux control and other outcomes. Interestingly, dysphagia in NI children, in whom this could be evaluated, was less frequently seen. It is well known that dysphagia is a difficult symptom to diagnose. In NI children, who are frequently verbally restricted, it is even more complex to diagnose and this may create a risk for underestimation of postoperative dysphagia in this group. Furthermore, almost all NI children underwent gastrostomy tube placement and did not receive orally administered feedings. Excluding these NI patients for the analysis resulted in similar postoperative dysphagia rates between NN and NI patients at 1 to 5 years and at 10 to 15 years after ARS, but not at 3 to 4 months after ARS. Of note, however, this study was not designed to identify differences between NI and NN children and sample size would have to be increased to investigate this more accurately. The GEE analysis produces unbiased estimators for data that are missing completely at random. This missing completely at random assumption may not have been completely met in our study, because data were often missing due to death. However, the patients with missing data were evenly distributed and an analysis on only patients with complete data produced similar results (data not shown), indicating that the inclusion of patients with some missing data did not bias the estimated effect sizes and confirmed the reliability of the GEE analysis.

In adult studies, it has been shown that fundic capacity increases during the years after ARS [31]. Next to wrap failure, this could provide a potential explanation for the decrease in efficacy of ARS over time. Another contributing factor could be that the child may outgrow the fundoplication over time. Patients with untreated GERD are at risk of developing Barrett epithelium and ultimately adenocarcinoma of the esophagus. The development of Barrett esophagus and adenocarcinoma of the esophagus is not limited to older age groups but is even encountered in children [32]. This risk depends on the duration and severity of symptoms [33,34].

CONCLUSIONS

In conclusion, as gastroesophageal reflux still persists or recurs in 43% of children 10 to 15 years after laparoscopic Thal fundoplication and recurrence of disease as measured by pathological 24-hour pH monitoring significantly increases in up to 43% of patients over time, it is crucial to implement routine long-term follow-up after ARS in pediatric GERD patients using objective measurements, preferably in combination with reflux-specific questionnaires and SAP analysis to make a timely diagnosis of GERD recurrence.

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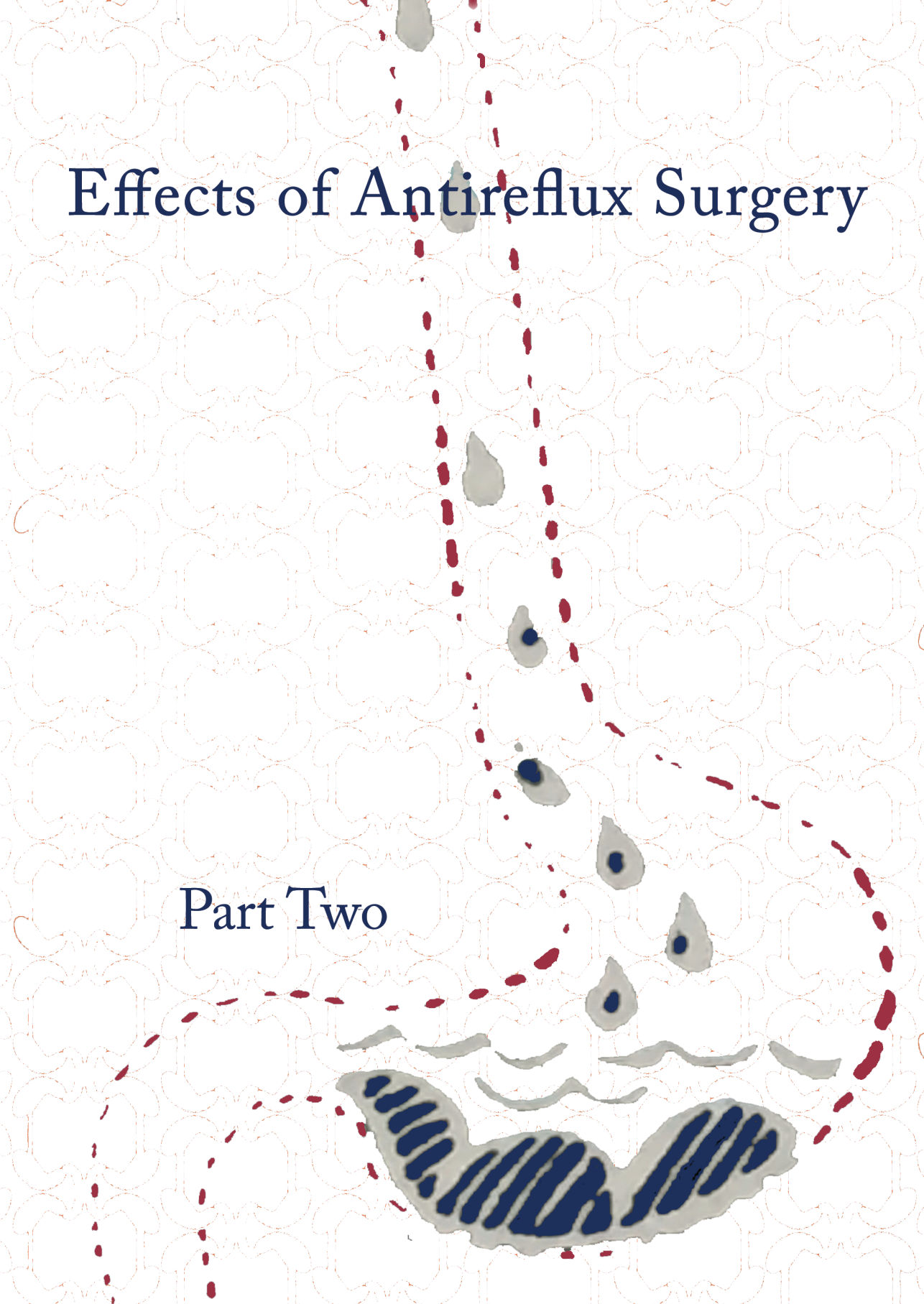
Effects of Antireflux Surgery



Part Two

5. Esophageal mucosal integrity recovers after laparoscopic antireflux surgery in children with gastroesophageal reflux disease

Submitted

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ABSTRACT

Background: Esophageal intraluminal baseline impedance reflects the conductivity of the esophageal mucosa and may be an instrument for in vivo evaluation of mucosal integrity in children with gastroesophageal reflux disease (GERD). Laparoscopic antireflux surgery (LARS) is a well-established treatment option for children with proton pump inhibitory (PPI) therapy resistant GERD. The effect of LARS in children on baseline impedance has not been studied in detail. The aim of this study was to evaluate the effect of LARS on baseline impedance in children with GERD.

Methods: This is a prospective, multicenter, nationwide cohort study (Dutch national trial registry: NTR2934) including 25 patients (12 males, median age 6 (range 2-18) years) with PPI-resistant GERD scheduled to undergo LARS. Twenty-four hour multichannel intraluminal impedance pH monitoring (MII-pH monitoring) was performed before and 3 months after LARS. Baseline impedance was evaluated during consecutive two-hour intervals in the 24-h tracings.

Results: LARS reduced acid exposure time from 8.5% (6.0-16.2%) to 0.8% (0.2-2.8%), $p<0.001$. Distal baseline impedance increased after LARS from 2445 Ω (1147-3277 Ω) to 3792 Ω (3087-4700 Ω), $p<0.001$. Preoperative baseline impedance strongly correlated with acid exposure time (r:-0.76, $p<0.001$); however, no association between symptomatic outcome and baseline impedance was identified.

Conclusions: LARS significantly increased baseline impedance likely reflecting recovery of mucosal integrity. As the change in baseline impedance was not associated with the clinical outcome of LARS, other factors besides mucosal integrity may contribute to symptom perception in children with GERD.

INTRODUCTION

Multichannel intraluminal impedance (MII) combined with pH monitoring is a well-established technique for the assessment of gastroesophageal reflux disease (GERD) in both children and adults [1-4]. Changes in conductivity between multiple electrode pairs on a single sensor MII-catheter allow detection of intra-esophageal movement of saliva during swallowing and the occurrence of gastroesophageal reflux (GER). In the absence of GER or swallowing, the esophagus is collapsed and the esophageal wall comes directly in contact with the MII-pH sensor catheter [5]. The impedance value during these periods, commonly referred to as baseline impedance, reflects the intrinsic electrical conductivity of the esophageal wall and may offer an in vivo tool to assess the integrity of the esophageal mucosa [6]. Baseline

impedance values in healthy volunteers are usually high, whereas GERD patients express low baseline impedance values. Low baseline impedance values have been associated with Barrett's esophagus or severe esophagitis [7], but recently they were also linked to acid-induced mucosal changes in patients with non-erosive reflux disease [6,8]. Recovery of impaired mucosal integrity, reflected by increased baseline impedance, may relief symptoms in GERD patients and be a marker for the clinical outcome of therapy [6,9]. Previous studies evaluating the effect of proton pump inhibitors (PPIs) on baseline impedance in children and adults with GERD, showed an increase of baseline impedance during acid suppressive therapy [9-11]. However, these studies did not reveal a correlation between the recovery of baseline impedance and symptomatic outcome [10,11].
Laparoscopic antireflux surgery (LARS) to treat severe, PPI-therapy resistant GERD aims to reduce reflux episodes and symptoms [12]. At present, the effect of LARS on esophageal mucosal integrity has not previously been studied in detail. The aim of this study is to assess the effect of LARS on baseline impedance and to explore if changes in baseline impedance are associated with the clinical outcome of LARS.

METHODS

Study design

We performed a prospective multicenter study in three University Medical Centers in the Netherlands that are specialized in performing fundoplication in children (Wilhelmina children's Hospital, University Medical Center Utrecht (UMCU); Sophia's Childrens Hospital, Erasmus University Medical Center (Erasmus MC) and Maastricht University Medical Center (MUMC)). From July 2011 until December 2013 we prospectively included 25 pediatric patients (12 males, median age 6 (range 2-18 years) diagnosed with PPI-therapy resistant GERD. Twenty of these 25 (80%) patients had normal neurological development. Patients who underwent previous esophageal or gastric surgery (except previous gastrostomy placement) and those with structural abnormalities other than esophageal hiatal hernia were excluded. Patients were studied before and 3 months after the surgical procedure.

Surgical procedure

All laparoscopic fundoplication procedures were performed by pediatric surgeons experienced in minimal invasive pediatric surgery. In the UMCU, the anterior, partial fundoplication according to Thal [13] was used to perform fundoplication. The other two centers (Erasmus MC and MUMC) used the posterior, total fundoplication according to Nissen [14]. Before fundoplication, the distal esophagus was fully mobilized, the distal 3 cm of the esophagus was repositioned back into the abdomen. Both vagal nerves were identified, and a crusplasty was performed routinely (UMCU and EMC). Thereafter, the fundoplication was constructed. The Thal fundoplication was performed by plicating the fundus of the stomach

over 270 degrees against the distal anterior intra-abdominal part of the esophagus and the diaphragmatic crus [15]. A floppy Nissen was constructed with one of the sutures of the 360 degrees posterior wrap incorporated in the esophageal wall [14].

Ambulatory 24–Hour multichannel intraluminal impedance pH monitoring

Ambulatory 24-hour MII-pH testing was conducted after at least 3 days cessation of all medications that affect gastrointestinal motility and/or acid secretion. Measurements were performed using a combined pH–impedance catheter assembly that consisted of six impedance segments and one ISFET pH electrode (Unisensor AG, Attikon, Switzerland). The pH electrode was positioned 5 cm above the upper border of the manometrically localized lower esophageal sphincter (LES). Impedance and pH signals were stored on a digital datalogger (Ohmega, Medical Measurement Systems, Enschede, The Netherlands), using a sampling frequency of 50 Hz. Patients and/or their parents were instructed to continue their regular diet, to report GERD symptoms and to keep a diary of their consumptions and body position (supine or upright) during the measurement.

Reflux–specific questionnaires

To assess reflux symptoms patients and/or their parents were asked to fill-out the validated age adjusted Gastroesophageal Reflux Symptom Questionnaire (GSQ) before and 3 months after LARS.16 Reflux symptoms and dysphagia were scored for frequency and severity on a score ranging from 1 (none) to 7 (most severe). Symptoms were defined as: no symptoms (no symptoms reported); mild (mild symptoms, weekly); moderate (mild symptoms, daily or severe symptoms, weekly) and severe (severe symptoms, daily). Reflux symptoms were scored using the symptoms heartburn, regurgitation, food refusal and vomiting.

Data analysis

Baseline impedance values were calculated for two specific segments in the esophagus during consecutive 2-hour intervals in the 24- MII-pH tracings as previously described [9]. Periods of ≥ 30 seconds not containing any swallows or gastroesophageal reflux episodes were selected and the averaged impedance value over this specific time period at two of the in total six impedance segments (Z6 – distal and Z2-proximal) was calculated, using a specific function incorporated in the analysis software (Ohmega, MMS, Enschede, the Netherlands). The 2-hourly obtained baseline impedance values for each segment were averaged and used for further analysis. The 24-h MII-pH tracings were further analyzed for acid exposure time, the number and acidity of reflux episodes according to previously described definitions [17]. Acid exposure time was defined as pathological when pH<4 during >6.0% of time during 24-h monitoring [18,19]. Reflux episodes reaching the proximal (z2) impedance segment were

classified as proximal. Baseline impedance throughout the manuscript refers to baseline impedance in the distal (z6) segment, unless stated otherwise.

Ethical Approval and trial registration

This study was registered with the Dutch national trial registry www.trialregister.nl; Identifier: 2934). Ethical approval for this prospective multicenter study was obtained from the University Medical Center Utrecht Ethics Committee and local approval was obtained by the two participating centers (Erasmus MC and MUMC). Prior to initiating any trial-related study procedure, informed consent from the patients' parents was obtained.

Statistical analysis

Continuous parametric variables were expressed as mean ± standard error of the mean (SEM). Non-parametric variables were expressed as median, with interquartile ranges (IQR). For continuous parametric outcomes a paired sample T test was performed. Non-parametric continuous outcomes were analyzed using the Wilcoxon signed-rank test. Correlations between different parameters were calculated using the Pearson correlation coefficient or Spearman's rank correlation coefficient as appropriate. Linear regression analysis was performed to identify possible determinants of the effect of LARS on baseline impedance. Determinants of interest included: age, type of fundoplication and changes in acid exposure time. A p-value below 0.05 was considered statistically significant. All statistical analyses were performed using commercially available computer software (IBM SPSS Statistics for Windows, Version 22. Armonk, NY: IBM Corp.).

RESULTS

The caregivers of all 25 patients filled out both pre- and postoperative reflux symptom questionnaires. Pre-operative 24-hr pH-MII tracings were completed in all 25 patients. After surgery, 24-hr pH-MII could not be performed in 2 patients due to refusal of the tracing by the caregivers. Postoperative tracings were successfully completed in 23 of the 25 children. Preoperative esophagogastroduodenoscopy was performed in 18 patients. In 13 of these patients macroscopic and/or microscopic acid-induced changes in the esophagus were observed.

Baseline impedance before antireflux surgery

Median baseline impedance before surgery was 2245 Ω, with a range from 430 Ω to 4401Ω. Spearman's rho correlation coefficient showed a strong negative correlation between distal

baseline impedance and acid exposure time (r:-0.76, p<0.001) before surgery (**Figure 1a**). Baseline impedance also negatively correlated with other reflux parameters, such as reflux episodes lasting longer than 5 minutes (r:-0.55, p=0.005) and number of acid reflux episodes (r:-0.55, p=0.005). The number of non-acid reflux episodes showed no correlation with baseline impedance (r:-0.03, NS).

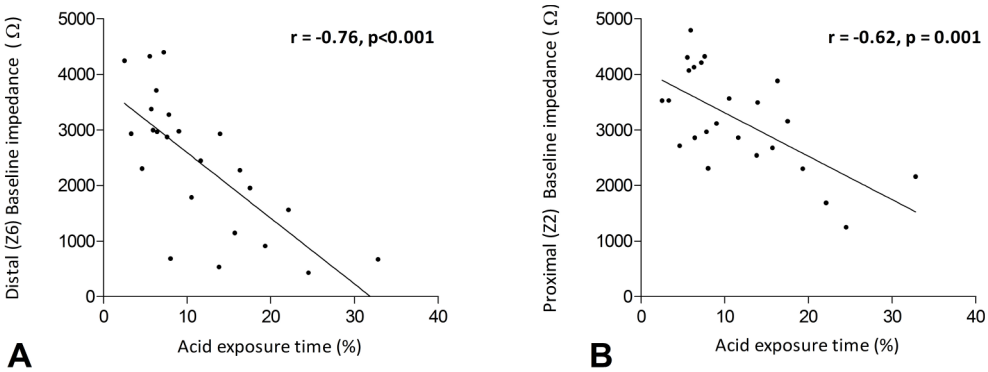

Figure 1 Correlation between esophageal acid exposure time (%) and (A) distal baseline impedance (Ω) and (B) proximal baseline impedance (Ω) in GERD patients before LARS.

In patients who underwent preoperative endoscopy, a trend towards significance was observed when comparing baseline impedance in patients with macroscopic and/or microscopic signs of esophagitis (n=13) to those with no sign of inflammation (n=5) (resp. 1788 Ω (IQR: 677-3187Ω) vs. 2928 Ω (IQR: 2591-4364 Ω), p=0.09). Baseline impedance showed no correlation with severity of reflux symptoms (severe symptoms 2376 Ω (IQR: 1251-3275 Ω) vs. mild/moderate symptoms 2925 Ω (IQR: 1083-3207 Ω), NS).
Proximal baseline impedance was significantly higher when compared to distal baseline impedance (3116 Ω (IQR: 2539-4071 Ω) vs. 2445 Ω (IQR: 1147-3277 Ω), p<0.05). Baseline impedance in the proximal segment also showed a negative correlation with acid exposure time (r:-0.62, p=0.001; **Figure 1b**) and number of acid reflux episodes (r:-0.50, p=0.01).
Proximal extension of reflux episodes occurred on average in 44.8% (SEM: 4.8%) of all reflux episodes. The number of reflux episodes reaching the proximal esophagus did not correlate with proximal baseline impedance (r:-0.18, NS).

Effects of laparoscopic antireflux surgery

LARS reduced acid exposure time from 8.5% (6.0-16.2%) to 0.8% (0.2-2.8%), p<0.001, at 3-month follow-up. All other reflux parameters, including the number of proximal and non-acid GER episodes on 24-h MII-pH monitoring were also significantly reduced after LARS (**Table 1**).

	Preoperative	Postoperative	p-value
Acid exposure total (%, IQR)	8.5 (6.0- 16.2)	0.8 (0.2-2.8)	<0.001
Upright (%, IQR)	12.1 (4.8-19.2)	1.8 (0.5-5.9)	0.001
Supine (%, IQR)	7.1 (0.9-15.3)	0 (0-0)	<0.001
Total GER (n, IQR)	92 (66-139)	14 (11-22)	<0.001
Acid GER (n, IQR)	61 (34-94)	8 (1-13)	<0.001
Non-acid GER (n, IQR)	23 (11-42)	5 (3-11)	<0.001
Proximal reflux (n, IQR)	36 (14-87)	1 (0-3)	<0.001

GER = Gastroesophageal reflux; **n** = number of reflux episodes; **IQR** = interquartile range

Table 1. Reflux Parameters On Mii-Ph Monitoring

LARS significantly increased baseline impedance in both the distal and proximal impedance segment (**Figure 2**). Distal baseline impedance showed a significant correlation with remaining postoperative acid exposure time (r: -0.67, p<0.001) (**Figure 3**). Furthermore, the change in distal baseline impedance after LARS correlated to the reduction in acid exposure time (r: 0.48, p=0.02).
The median preoperative baseline impedance was 2445 Ω. After LARS, the baseline impedance value in three patients was lower than this median preoperative baseline impedance value (**Figure 3**). In two of these three patients, persisting pathologic acid exposure was found. The third patient with lower postoperative baseline impedance after the procedure, had esophageal gastric metaplasia in the distal esophagus. Despite normalization of acid exposure, low baseline impedance persisted only in the most distal segment of the esophagus likely due to increased conductivity of gastric epithelium.

Overall reflux symptoms significantly decreased after LARS (p =0.001). In 15 (65%) patients complete remission of reflux symptoms was achieved and in an additional 6 (26%) patients symptom scores improved. In two of the 23 (9%) patients reflux symptoms were unaltered; one of these patients showed a low baseline value (536 Ω). Deterioration of reflux symptoms did not occur (**Table 2**). Similar to preoperative analysis, no association between postoperative symptoms and baseline impedance could be identified (no symptoms (n=15) vs. persistent symptoms (n=8): 3917 Ω (IQR: 3087-4490) vs. 3706 Ω (2983-4373), NS.

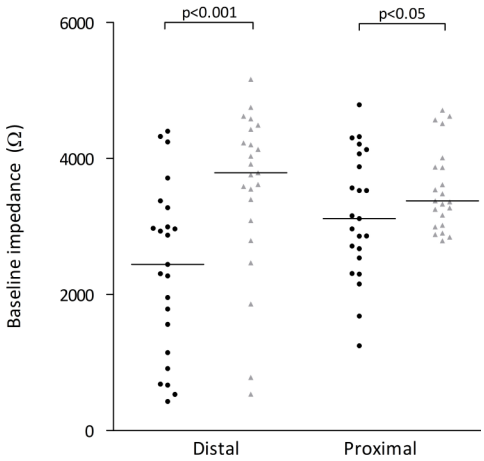

Figure 2 Baseline impedance in distal (z6) and proximal (z2) esophageal segments before (red) and after (blue) LARS.

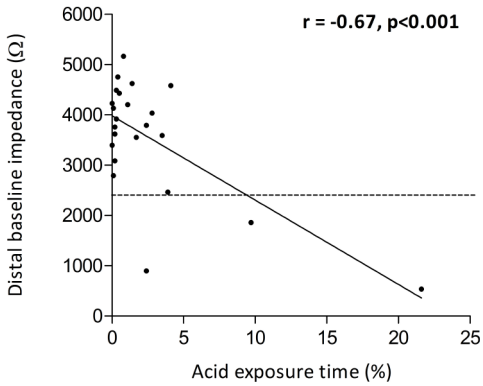

Figure 3 Correlation of distal baseline impedance and acid exposure after LARS. The horizontal dashed line indicates preoperative median baseline impedance.

Determinants of the effect of LARS on baseline impedance

A linear regression analysis was performed to explore determinants of the effect of LARS on baseline impedance. Age (β: -3.5 Ω; 95% CI: -114.6; 107.7, p=0.95) and type of fundoplication (β: -105.1 Ω; 95% CI: -1274.7; 1064.5, p=0.95) did not affect the change in baseline impedance after LARS. Also, the change in acid exposure time (β: 50.7 Ω; 95% CI: -10.3; 111.7, p=0.098) did not reach statistical significance.

	Preoperative (n; %)		Postoperative (n; %)		p-value
Reflux symptoms					
None	0	(0%)	15	(65%)	
Mild	2	(9%)	5	(22%)	0.001
Moderate	6	(26%)	2	(9%)	
Severe	15	(65%)	1	(4%)	

Table 2 Symptom assessment

DISCUSSION

In the present study we investigated the effect of laparoscopic antireflux surgery (LARS) on baseline impedance as a reflection of mucosal integrity in pediatric patients with gastroesophageal reflux disease (GERD). Our main findings were that LARS resulted in recovery of baseline impedance, that reflux symptoms significantly decreased after LARS, without an association with an increase in baseline impedance and finally that no factors affecting the effect of LARS on baseline impedance could be identified.

LARS aims to prevent reflux events from the stomach thereby protecting the esophageal mucosa from potential stressors in the refluxate. Previous studies have shown a strong inverse correlation between baseline impedance and acid exposure in pediatric GERD patients [10,20,21]. Accordingly, we hypothesized that successful elimination of esophageal acid exposure by LARS would increase baseline impedance. Our current study confirms this hypothesis as it demonstrates a significant decrease in acid exposure time and an increase in baseline impedance, which likely reflects the recovery of the esophageal mucosa. Furthermore, postoperative low distal baseline impedance was observed in patients with persistent pathologic acid exposure time and in one patient with gastric metaplasia. In the latter patient this could be due to the intrinsic higher conductive properties of columnar epithelium when compared to esophageal squamous epithelium [22].

Impaired mucosal integrity has been proposed as an important mechanism in symptom generation, as it allows acid reflux to permeate into the deeper layers of the mucosa and activate sensory nerve endings [23]. Previous studies have shown an association between esophageal mucosal integrity and acid sensitivity using a standardized acid perfusion test [24,27]. Lower baseline impedance, as a marker of impaired mucosal integrity, has also been shown to correlate with clinical signs of GERD in the pediatric population [10]. Related to these findings, recovery of impaired mucosal integrity could hypothetically result in improvement of reflux symptoms in GERD patients [6]. Laparoscopic antireflux surgery showed good clinical outcome, but an association between GERD symptoms and baseline impedance despite the use of validated questionnaires could not be identified. These results are in accordance with previous studies attempting to identify a similar association after PPI treatment in children or after endoscopic fundoplication in adults [10,11]. Together, these outcomes suggest that in addition to the mucosal integrity, also content, proximal extent and volume of the refluxate, as well as peripheral and central mediated sensitivity affect GERD symptom perception [25,26].

Baseline impedance may allow identification of patients with impaired mucosal integrity after LARS, as it has been associated with esophagitis and microscopic changes of the mucosa [6,20,27,28]. Post-procedural evaluation of GERD is important as patients with

persistent GERD may be at risk of developing complications, such as esophagitis, stenosis, Barrett's epithelium and ultimately adenocarcinoma of the esophagus [29]. GERD symptoms may not always be evident, especially in younger children or children with impaired neurodevelopment. Evaluation of mucosal impedance during ambulatory 24-hour MII-pH testing may help to detect impaired mucosal integrity. MII-pH analysis is however a time-consuming and the procedure itself may be uncomfortable for pediatric patients. Recently, other groups have reported on endoscopy guided single-sensor catheters to measure mucosal impedance during endoscopy [30,31]. These catheters enable instant evaluation of mucosal integrity during endoscopy instead of the normal 24-hour MII-pH monitoring. Unfortunately, in children endoscopy is generally performed under general anesthesia. Because of the impact and risks of the anesthesia and the invasive way endoscopy is performed, this method in its current form seems unsuitable in pediatric patients. Future developments may lead to alternative methods that allow a similar instant evaluation of the esophageal mucosa without using endoscopy [32].

In the proximal esophagus an inverse correlation between baseline impedance and (distal) acid exposure time was seen, whereas no correlation with the number of proximal reflux episodes was found. As the MII-pH catheter used in this study only had a distal pH-sensor, it is not entirely clear whether proximal baseline impedance is directly affected by acid reflux reaching the proximal esophagus or by indirect mechanisms, activated by distal acid exposure [33]. Previously, Farré et al. showed that distal acid perfusion resulted in changes in the mucosal integrity of the non-exposed proximal esophagus, which is suggestive for an indirect mucosal reaction spreading more proximally than the site of mucosal injury [33]. Further insights in this possible mechanism of impaired mucosal integrity in the proximal esophagus may be of clinical importance as the proximal esophagus is often linked to symptom perception [34-36].

Determinants, such as age, type of fundoplication or change in acid exposure time, influencing the effect of LARS on baseline impedance could not be identified. Infants and young children previously were shown to have a lower baseline impedance when compared to older (pediatric) patients [37]. Age, however, did not influence the effect of LARS on baseline impedance. Until now, studies on efficacy of different types of fundoplication in both the adult and pediatric population were not able to show differences in reflux control [38,39]. In this study type of fundoplication also was not a significant determinant for the effect of LARS on baseline impedance. The change in acid exposure time after LARS showed a tendency to influence the effect of LARS on baseline impedance and may have been a significant determinant, if more patients had been included.

The main limitation in this current study is the number of patients. A larger number of patients would have allowed us to investigate determinants of interest in a linear regression

model with higher statistical power. Furthermore, in the current study endoscopy was not performed per protocol. In 18 out of 25 (72%) patients endoscopy was performed before LARS and in only a few of the patients after the procedure. Data to correlate the changes in baseline impedance with endoscopic and/or histological mucosal findings are therefore not available. Pardon et al. showed in adults that baseline impedance is closely correlated to evaluation of mucosal integrity by established ex vivo methodology (Ussing Chamber technique) [28]. Together with previous findings from an experimental model [6], these observations indicate that baseline impedance is a reliable tool for the evaluation of mucosal integrity in vivo.

In conclusion, LARS increased baseline impedance, which is likely to reflect the recovery of mucosal integrity. Although both baseline impedance and symptomatic reflux control increased, these two parameters were not mutually associated. Factors influencing the effect of LARS on baseline impedance could not be identified.

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6. Health-related quality of life increases after laparoscopic antireflux surgery in children with GERD: results of a prospective, multicenter study

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ABSTRACT

Objectives: To evaluate the effect of laparoscopic antireflux surgery (LARS) on health related quality of life (HRQoL) in children with gastroesophageal reflux disease (GERD) and to identify predictors that influence HRQoL outcome after LARS.

Summary background data: Improving HRQoL is increasingly recognized as an essential part of patient care outcome. Little is known about the effect of LARS on the HRQoL in the pediatric patients

Methods: Between 2011 and 2013, 25 patients with therapy-resistant GERD (12 males, median age 6 (2-18) years) were included prospectively. Caregivers and children with normal neurodevelopment (> 4 years) were asked to fill-out the validated PedsQL 4.0 Generic Core Scales before and 3-4 months after LARS

Results: The PedsQL was completed by all caregivers (n=25) and 12 children. HRQoL total score improved significantly after LARS, both from a parental (p=0.009) and child's perspective (p=0.018). The psychosocial health summary and physical health summary scores also improved significantly after LARS. HRQoL before and after LARS was significantly lower in children with impaired neurodevelopment (p<0.001). However, neurodevelopment did not influence the effect of LARS on HRQoL. The only significant predictor for improvement in HRQoL after LARS was age at the time of operation (p=0.001).

Conclusions: HRQoL significantly improves after LARS. Although children with impaired neurodevelopment had lower overall HRQoL, neurodevelopment by itself does not predict inferior improvement in HRQoL after LARS. Older children have a more favorable HRQoL outcome after LARS compared to younger children. This may suggest caution when considering LARS in younger GERD patients.

INTRODUCTION

Laparoscopic antireflux surgery (LARS), is an established treatment option performed in pediatric patients with severe gastroesophageal reflux disease (GERD) resistant to medical treatment [1;2]. LARS primarily aims to decrease (acid) reflux events and to reduce reflux symptoms. However, as shown in earlier studies the effect on reflux symptoms does not always correlate to more objective assessments of success of therapy [3;4]. Furthermore, co-morbidities (e.g. impaired neurodevelopment) and complications, such as dysphagia and gas-bloat syndrome [5] may also affect success of therapy.

To better assess the impact of pediatric diseases and treatments from the perspective of the pediatric patient and their caregivers health-related quality of life (HRQoL) assessment has been increasingly recognized as an essential part of patient care outcome [6]. Effects of LARS on HRQoL have been mainly investigated in adult population. These studies almost all showed that HRQoL improves after LARS [7-9]. In the pediatric population only few studies have focused on this outcome parameter [10-12]. HRQoL in these studies improves, however none of these studies have used pediatric validated questionnaires. In two studies [10;11] a questionnaire designed for adults had been modified for pediatric use and one study had only used parental proxy-report to score HRQoL [12]. Furthermore, none of these studies could identify determinants that influence HRQoL outcome after LARS. The Pediatric Quality of Life Inventory (http://www.pedsql.org) 4.0 Generic Core Scales (PedsQL) is a reliable and valid tool (also for the Dutch language) for parental proxy-report and parallel child's self-report on HRQoL. It has been used to assess HRQoL in children with numerous acute and chronic health conditions, as well as in healthy populations [6;13-17]. The aim of this study was to evaluate the effect of LARS on HRQoL using the PedsQL and to identify predictors that may influence HRQoL outcome after LARS.

METHODS

We performed a prospective multicenter study in three University Medical Centers in the Netherlands performing laparoscopic fundoplication in children (Wilhelmina children's Hospital, University Medical Center Utrecht (UMCU); Sophia children's Hospital, Erasmus University Medical Center (EMC) and Maastricht University Medical Center (MUMC). From July 2011 until December 2013 we prospectively included all pediatric patients diagnosed with PPI-therapy resistant GERD. Patients that had undergone previous esophageal or gastric surgery (except previous gastrostomy placement) and those who had structural abnormalities other than an esophageal hiatal hernia were excluded.

Patients

In total 25 children were included. Mean age of the included patients was six (range 2-18) years at the time of fundoplication (**Table 1**). Impaired neurodevelopment was present in 20 percent of patients (5/25 patients). Causes of impaired neurodevelopment are shown in **Table 2**.

	Median (IQR)
Age at time of operation (years)	6.0 (3.0-11.0)
Duration of hospital admission (days)	3.0 (2.0-4.5)
	n (%)
Male gender	12 (48.0%)
Neurological Normal Development	20 (80.0%)
Gastrostomy preoperatively in situ	4 (16.0%)

Table 1. Baseline characteristics

Charge syndrome
Mitochondrial complex II deficiency
Post hypoxic encephalopathy
Congenital rubella infection
Neurologically impairment of unknown origin with autistic behavior

Table 2. Neurological impairment (n = 5)

Surgical Procedures

All laparoscopic fundoplications were performed by experienced pediatric surgeons in pediatric laparoscopic surgery. In the UMCU the anterior, partial fundoplication according to Thal [18] was used to perform fundoplication. In the other two UMC's (EMC and MUMC) the posterior, total fundoplication according to Nissen [19] was performed. Before fundoplication, the distal esophagus was fully mobilized; the distal 3 cm of the esophagus was repositioned back into the abdomen. Both vagal nerves were identified, and a crusplasty was performed routinely (UMCU and EMC). Thereafter, the fundoplication was constructed. The Thal

fundoplication was performed by plicating the fundus of the stomach over 270 degrees against the distal anterior intra-abdominal part of the esophagus and the diaphragmatic crus [3;18]. A floppy Nissen was constructed with one of the sutures of the 360 degrees posterior wrap incorporated in the esophageal wall [19].

Clinical Assessment

Before and three months after laparoscopic fundoplication clinical assessment was performed using the PedsQL 4.0 Generic Core Scale for HRQoL, a reflux specific symptom questionnaire, 24-hour multichannel intraluminal impedance pH monitoring (MII-pH monitoring) and an 13C labeled Na-octanoate breath test. Surgical re-interventions, type and indication for re-intervention, endoscopic procedures, complications, and co-morbidities were registered in a prospective database.

1. Health-related Quality of Life

Caregivers and children with normal neurodevelopment (> 4 years) were asked to fill-out the 23-items PedsQL 4.0 Generic Core Scales [14;17;19-21]. The scales are available for parental proxy-report, subdivided in four age-adjusted questionnaires (ages: 2-4; 5-7; 8-12 and 13-18 years) and as a parallel child's self-report (ages: 5-7; 8-12 and 13-18 years). The PedsQL 4.0 Generic Core Scales comprises four domains: physical functioning (8 items), emotional functioning (5 items), social functioning (5 items), and school functioning (5 items). With the four domains the physical health summary score, the psychosocial summary score and the total score is calculated. The physical health summary score is reflected by the physical functioning scale. The psychosocial health summary score is reflected by the mean of the other three domains (emotional, social, and school functioning). Scale scores per domain were computed as the sum of the items divided by the number of items answered. Thereafter, items were reverse-scored and transformed to a 0-100 scale. Higher scale scores indicate better HRQoL.

2. Reflux-specific questionnaire

Patients and/or their parents were asked to fill out the Gastroesophageal Reflux Symptom Questionnaire [22].

3. Ambulatory 24-Hour MII-pH monitoring

MII-pH monitoring was performed using an age-adjusted combined impedance-pH catheter (Unisensor AG, Attikon, Switzerland). Pathological acid exposure was defined as total acid exposure time ≥6%, ≥ 9% in upright, and ≥3% in the supine body position [23;24]. The symptom index (SI) and the symptom association probability (SAP) was calculated when the patients experienced symptoms during measurement [25;26].

4. Gastric emptying breath test

To assess gastric emptying time we used a 13C labeled Na-octanoate breath test [27]. Gastric emptying half time is defined as the time when the first half of the 13C-labeled substrate has been metabolized, that is, when the cumulative excretion of 13C in the breath is half the ingested amount. Gastric emptying percentiles were calculated according to the reference values obtained by van den Driessche et al [28].

Ethical approval and trial registration

This study was registered at the start of the study in the Dutch national trial registry (www.trailregister.nl; Identifier: 2934). Ethical approval for this prospective multicenter study was obtained from the University Medical Center Utrecht Ethics Committee and local approval was obtained by the remaining two participating centers. Prior to any trial-related study procedure, informed consent from the patients' parents and children (≥12 years) was obtained.

Statistical analysis

Continuous variables, when symmetric, were expressed as mean ± standard error. Skewed variables were expressed as median with interquartile ranges (IQR). For statistical analysis we used the paired sample T-test or the Wilcoxon signed ranks test. The McNemar-Bowker test was used to compare groups in case of nominal outcome measures. To assess the relationship between HRQoL and age at the time of operation, impaired neurodevelopment, reflux symptoms, acid exposure and gastric emptying, we used a linear mixed model with a random intercept per patient. A mixed model allowed us to analyze preoperative and postoperative measurements simultaneously, while taking into account correlation of measurements from the same subjects. Backwards selection was performed using the AIC. A linear regression analysis was performed to identify determinants influencing HRQoL and the effect of LARS on HRQoL. Determinant of interest included: age at the time of operation, impaired neurodevelopment, reflux symptoms, preoperative acid exposure time and preoperative gastric emptying rate. Differences with a $P < 0.05$ were considered statistically significant. All analyses were performed using IBM®22.0.0 SPSS statistical package (IBM, Armonk, NY).

RESULTS

In total 18 Thal and 7 Nissen fundoplications were performed. In all patients fundoplication was completed by laparoscopy. Perioperative complications were not observed. One patient with retching due to impaired neurodevelopment developed severe recurrent reflux caused by hiatal herniation that required re-fundoplication. In six children, temporary nasogastric tube feedings were required to obtain sufficient caloric intake. This was caused by transient dysphagia (dysphagia dissolved within 3-4 months after LARS; n=4), persistent dysphagia (>3-4 months after LARS; n=1) or refusal of oral feedings (n=1).

Health–related quality of life

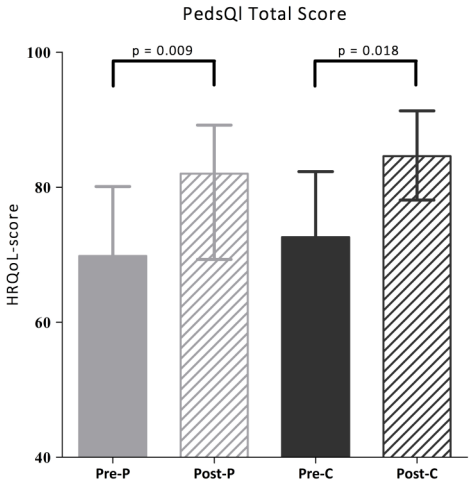

Figure 1a HRQoL assessment using the PedsQL – Total Score (Pre = before LARS; Post = After LARS; P = Parental proxy report; C = child's self-report)

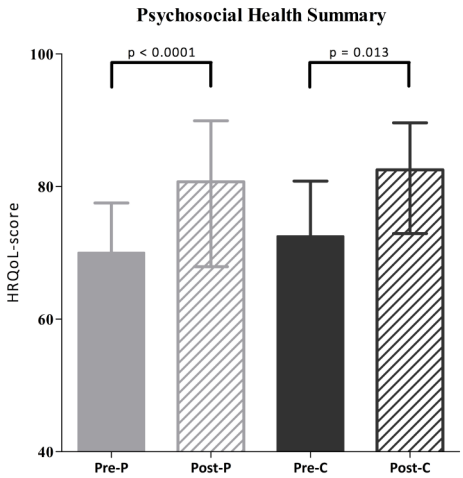

Figure 1b. HRQoL assessment using the PedsQL – Psychosocial Health Summary (Pre = before LARS; Post = After LARS; P = Parental proxy report; C = child's self-report)

The PedsQL was completed by all caregivers both before and after LARS for all included patients (n=25). The HRQoL total score improved significantly after LARS from 69.8 (57.2-80.1) to 82.0 (69.3-89.2; p=0.009; **Figure 1a**). Twelve children were able to fill-out the parallel self-report and their total score also improved significantly from 72.6 (7.4-82.3) to 84.6 (78.1-91.3; p=0.018; **Figure 1a**).

Furthermore, the psychosocial (54.2 (69.7 – 77.5) to 82.5 (72.9 – 89.6); p < 0.0001) and the physical health summary (75.0 (59.4 – 89.1) to 92.2 (80.5 – 99.2); p<0.0001) also significantly improved for both caregivers as well as children's self-report after LARS (**Figure 1b** and **1c**).

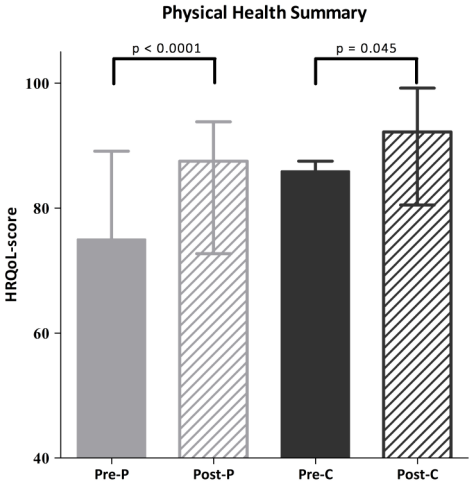

Figure 1c. HRQoL assessment using the PedsQL – Physical Health Summary (Pre = before LARS; Post = After LARS; P = Parental proxy report; C = child's self-report)

Patients' self-report of overall HRQoL outcomes was significantly higher (p=0.037) than parental proxy-report before LARS; self-reported and proxy-reported HRQoL scores after LARS were not different.

Reflux symptoms

Reflux symptoms significantly decreased from 16 (64%) patients with severe reflux symptoms before LARS to one (4%) patient after LARS (p=0.001). Deterioration of symptom severity or frequency was not seen in any of the patients. Dysphagia was reported in seven (28%) patients before and in eight (32%) patients after LARS (p=0.887). New-onset dysphagia was seen in three of these eight patients after LARS (**Table 3**).

	Preoperative (n; %)		3-4 months postoperative (n; %)		p-value
Reflux symptoms					
No symptoms	0	(0%)	17	(68%)	0.001
Mild reflux symptoms	2	(8%)	5	(20%)	
Moderate reflux symptoms	7	(28%)	2	(8%)	
Severe reflux symptoms	16	(64%)	1	(4%)	
Dysphagia	7	(28%)	8	(32%)	0.887

Table 3 Symptoms (n=25)

Gastroesophageal functional assessment tests – Total acid exposure decreased significantly from 8.5% (IQR 2.5-32.8) to 0.8% (IQR 0-21.6) after LARS (p<0.0001). Median gastric emptying rate before LARS (percentile 75, IQR 3-99) was similar to that after LARS (70, IQR 5-99, p=0.530).

Factors influencing HRQoL

Patients with impaired neurodevelopment (NI) had significantly lower HRQoL compared to patients with normal neurodevelopment (NN) (estimate 23.4; p = 0.006; (95% CI 7.2 – 39.5). Furthermore, reflux symptoms were also negatively associated with lower HRQoL (estimate = -4.3l; p = 0.006; 95% CI -7.5 – -1.3). Age at time the of operation (p = 0.11), gastric emptying (p = 0.82) and total acid exposure (p = 0.75) did not significantly influence HRQoL.

Predictors for the effect of LARS on HRQoL

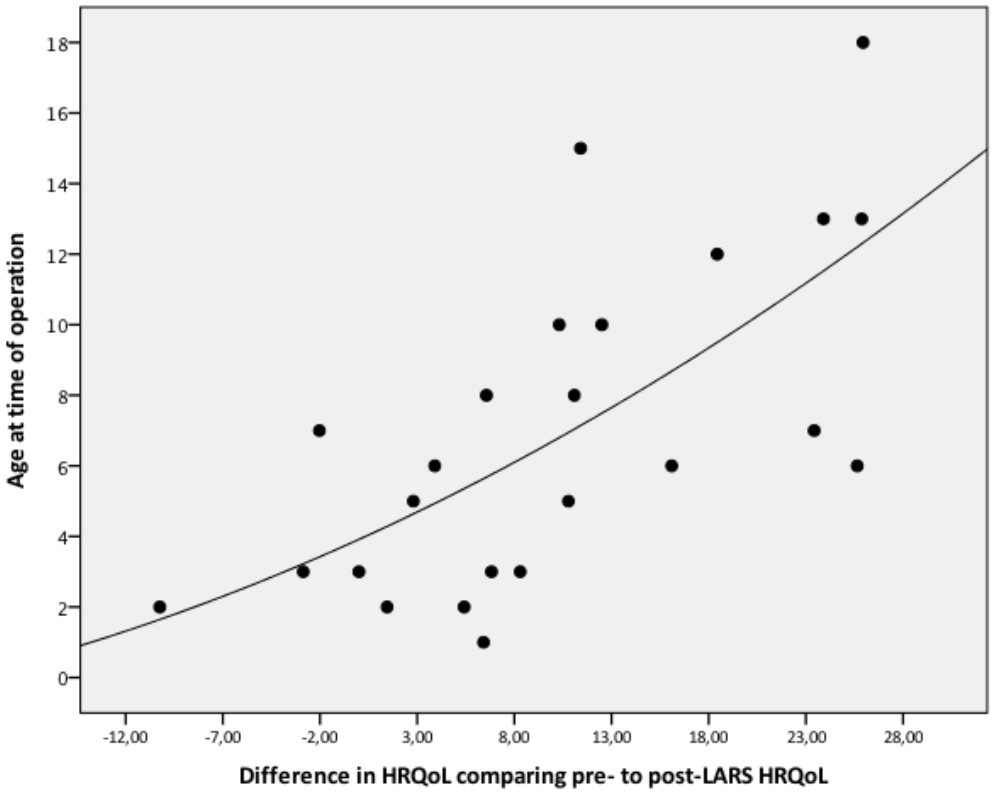

Figure 2. Scatterplot illustrating difference in HRQoL comparing pre- to post-LARS HRQoL

Linear regression analysis showed that an increase in age at the time of operation was a significant predictor for improvement in HRQoL after LARS (p=0.001; estimate = 1.6; 95% CI = 0.8 – 2.5; **Figure 2**). Although HRQoL was significantly lower in NI children, neurodevelopment itself did not influence the change in HRQoL (p=0.73). Preoperative gastric emptying rate, total acid exposure time and reflux symptoms also did not significantly influence the change in HRQoL (**Table 4**).

	Estimate	p-value	95% CI
Age at time of operation	1.7	0.001	0.8 – 2.5
Neurological development	1.8	0.73	-9.3 – 12.9
Preoperative reflux symptoms	2.8	0.61	-8.7 – 14.4
Preoperative acid exposure time (%)	0.3	0.28	-0.3 – 0.9
Preoperative gastric emptying	-0.004	0.94	-0.1 – 0.1
Linear regression analysis (95% CI = 95% confidence interval)			

Table 4 Predictors for the effect of lars on hrqol

DISCUSSION

This is the first study on HRQoL in children undergoing LARS that used a validated pediatric HRQoL questionnaire [6;13-17]. We demonstrate that after LARS HRQoL significantly increases and after LARS HRQoL scored were comparable to the normal HRQoL scores measured in a healthy population [13]. Furthermore, age at the time of operation is a significant predictor for improvement in HRQoL after LARS. Previous studies also showed a significant increase of HRQoL [10-12]. In two studies [10;11] a questionnaire designed for adults had been modified for pediatric use and the third study only used parental proxy-report. In contrast to these previous studies this is the first study in pediatric LARS using a validated questionnaire for HRQoL. Using validated questionnaires in the pediatric population is important as results and questionnaires are not simply translatable for pediatric uses because pathophysiology, and patterns and symptoms of diseases may be different in children compared to adults [29]. Furthermore, this is the first study using both parental proxy-reports as well as child's self-reports.

Some authors hypothesize that children with impaired neurodevelopment (NI) may not benefit to the same extent from LARS as those with normal development [30-32]. In the current study, overall HRQoL was significantly lower in NI children. However, the neurodevelopment itself did not influence the change in HRQoL. This indicates that while NI children with GERD had a lower overall HRQoL LARS was equally effective regarding the change in HRQoL compared to children with normal neurodevelopment (NN). It is not surprising that NI children, who have more (co-) morbidity than NN children, scored lower in HRQoL; the PedsQL is able to distinguish between healthy children and pediatric patients with acute or chronic health conditions and it is related to indicators of morbidity and illness burden [21].

The HRQoL scores of NI children for physical, social and school functioning were scored significantly lower compared to NN children. Emotional function, however, was not scored different from NN (data not shown). As NI children have more (co-)morbidities and associated disabilities they will likely score lower in physical and social functioning. The scores in the domain school functioning may be influenced by the possibility for caregivers or patients to leave these questions open if they are not applicable. If at least 50% is filled-out in a specific domain the score over that domain can however still be calculated. In the domain school functioning questions regarding attitude and performance at school were generally not filled out, whereas questions regarding presence/absence due to sickness or hospital visits were almost completely filled out by the caregivers.

Before LARS, children reported a significantly higher HRQoL than their parental proxies. This difference remained when only the child's self-report was compared to the score of their parents and the scores of the parents with children aged < 5 or NI children were not taken into account. After LARS, this difference resolved as parents scored the HRQoL higher than children. It is not entirely clear why this difference in HRQoL resolves after LAR. We hypothesize that before LARS caregivers experience more burden from GERD on their child's HRQoL compared to their children's own perception. After LARS, GERD resolves in almost all children and it may therefore be possible that HRQoL assessments after LARS are therefore comparable.

Various studies on HRQoL in children indicate that information provided by caregivers does not always correspond to what children report themselves [33;34]. Pediatric patient self-report is considered to be the standard for measuring HRQoL, as it is the only genuine patient-reported outcome [35]. It can, however, be difficult to obtain self-reports in young children and children with impaired neurodevelopment. In these cases a parental proxy-report may be the only way to assess HRQoL [36]. Furthermore, it has been shown that the parents' perception of their child's HRQoL influences health care utilization more than the perception of the child itself [37;38].

Age at the time of operation was a statistically significant predictor of improvement in HRQoL after LARS. This means that LARS has more effect on HRQoL in older children and may suggest caution when younger children are referred for therapy-resistant GERD. It has been suggested that recurrence of GERD and even the necessity for redo-fundoplication are more frequently seen in young patients. These suggestions were based on two retrospective studies both using regression analysis to identify risk factors [39;40]. Bearg et al [39] showed that redo-fundoplication is significantly more frequent if patients are younger or have retching. Ngerncham et al [40] reported that age less than 6 years was independently associated with increased risk of recurrence of GERD. Furthermore, it may also be possible that older children can specify their (reflux) complaints better, allowing a more precise diagnosis of

therapy-resistant GERD to be made. Finally, it has been hypothesized that a young child may outgrow its fundoplication [4].

We initially hypothesized that preoperative gastric emptying might influence the success of LARS and thereby the effect on HRQoL as this has been shown in adult literature [41]. In this study, however, we did not find an effect of gastric emptying on HRQoL.

It is plausible that reflux symptoms and acid exposure influence HRQoL assessment. In the current study reflux symptoms were negatively associated with lower HRQoL. Remarkably, however, recurrence or persisting pathological acid exposure did not significantly influence HRQoL. It has been described before that reflux symptoms do not correlate to objective measurements of GERD, which may underscore the difficulty in symptom assessment [3;4;42]. One of the limitations in the current study were the limited number of 25 patients included. It was therefore only possible to investigate 5 determinants in linear regression assuming that we have sufficient statistical power with 5 patients per predictor. If more patients were included in this study, we would have had more power to detect the influence of these variables, and we had been able to investigate more potential determinants of changes in HRQoL. Furthermore, not all patients were able to fill out the self-report because of impaired neurodevelopment or age and as mentioned previously not all questions could be filled out by their caregivers, because in specific domains the questions were not always suitable when considering comorbidities and patient's limitations.

In conclusion, health-related quality of life, scored by both pediatric patients and their caregivers, significantly improves after LARS. Although patients with impaired neurodevelopment have lower overall HRQoL compared to neurologically normal developed patients, neurodevelopment itself is not a predictor of inferior improvement in HRQoL after LARS. Older children have a more favorable outcome of LARS on HRQoL compared to younger children. This suggests that with the diagnosis of therapy-resistant GERD in younger children, one should possibly be cautious to perform LARS.

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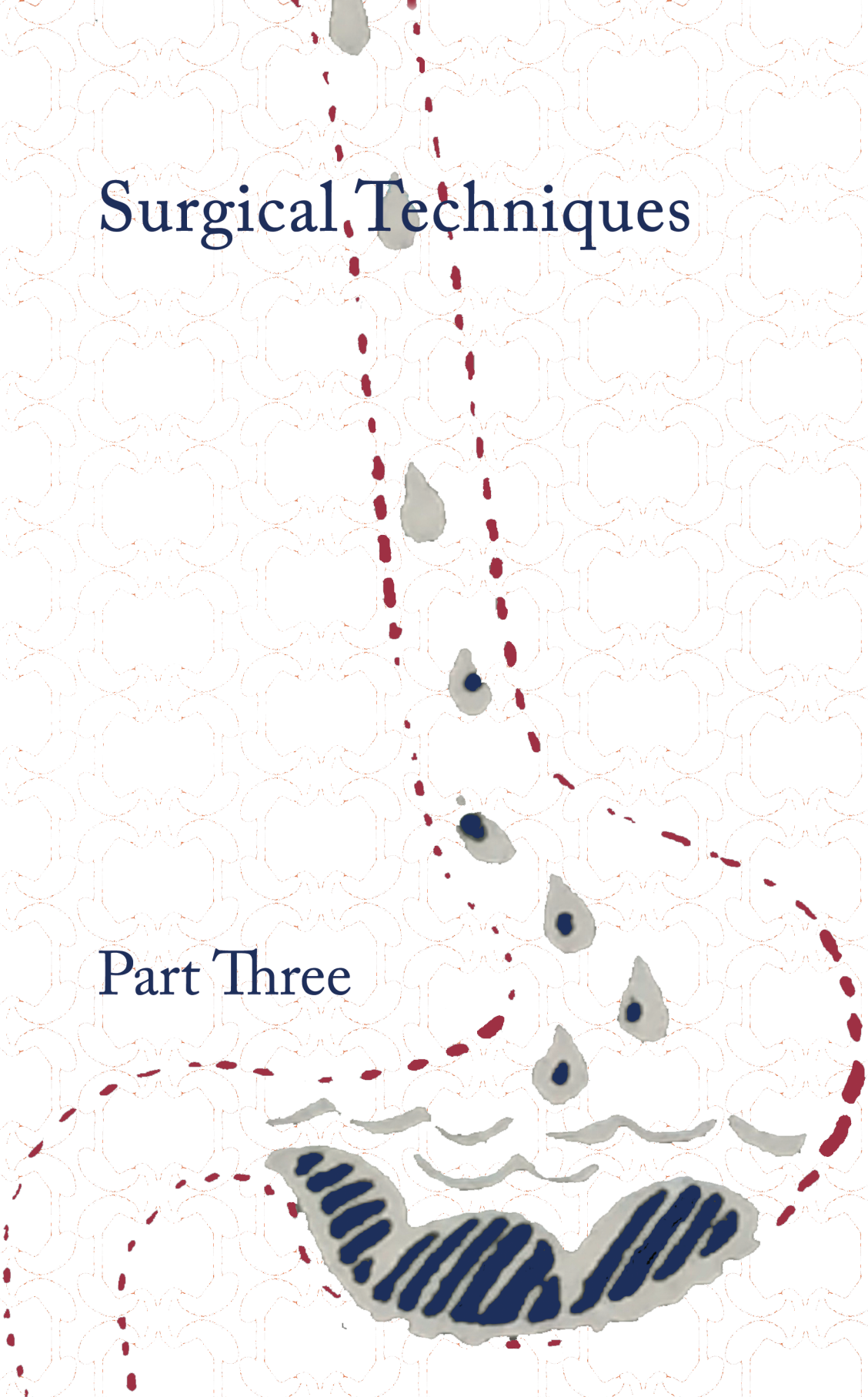
Surgical Techniques



Part Three

7. Complete versus partial fundoplication in children with gastroesophageal reflux disease: results of a systematic review and meta-analysis

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ABSTRACT

Background: Complete fundoplication (Nissen) has long been accepted as the gold standard surgical procedure in children with therapy-resistant gastroesophageal reflux disease (GERD); however, increasingly more evidence has become available for partial fundoplication as an alternative. The aim of this study was to perform a systematic review and meta-analysis comparing complete versus partial fundoplication in children with therapy-resistant GERD.

Methods: PubMed (1960 to 2011), EMBASE (from 1980 to 2011), and the Cochrane Library (issue 3, 2011) were systematically searched according to the PRISMA statement. Results were pooled in meta-analyses and expressed as risk ratios (RRs).

Results: In total, eight original trials comparing complete to partial fundoplication were identified. Seven of these studies had a retrospective study design. Short-term (RR 0.64; p=0.28) and long-term (RR 0.85; p=0.42) postoperative reflux control was similar for complete and partial fundoplication. Complete fundoplication required significantly more endoscopic dilatations for severe dysphagia (RR 7.26; p=0.007) than partial fundoplication.

Conclusions: This systematic review and meta-analysis showed that reflux control is similar after both complete and partial fundoplication, while partial fundoplication significantly reduces the number of dilatations to treat severe dysphagia. However, because of the lack of a well-designed study, we have to be cautious in making definitive conclusions. To decide which type of fundoplication is the best practice in pediatric GERD patients, more randomized controlled trials comparing complete to partial fundoplication in children with GERD are warranted.

INTRODUCTION

Gastroesophageal reflux disease (GERD) in children is defined as pathologic reflux of gastric contents into the esophagus causing symptoms [1,2]. Antireflux surgery, by means of (laparoscopic) fundoplication is reserved for pediatric patients with severe GERD resistant to medical treatment [2, 4]. Overall success rates of antireflux surgery are generally good, with a median short-term reflux control of 86 % (57-100 %) [5]. However, antireflux surgery can also lead to complications [6], such as postoperative dysphagia in up to 33 %5 and gas bloat syndrome in up to 11% of patients [7,8]. Several different types of fundoplication are performed in pediatric GERD patients [9]. Complete posterior (Nissen) fundoplication (360°) is performed in up to two thirds of children undergoing antireflux surgery [7]. However, it may be associated with a higher risk of postoperative dysphagia compared to a partial fundoplication (<360°) [5 - 10]. A partial fundoplication can be constructed by wrapping the fundus either anterior (Thal) or posterior (Toupet) around the esophagus. Until now, partial fundoplication has not been widely used because it is still thought to have less effective reflux control [11,12]. In the past, it was therefore reserved for patients without a history of life-threatening events or patients with signs of esophageal dysmotility to reduce the risk of postfundoplication complaints [11 - 15]. Recent meta-analyses and comparative studies in adult GERD patients have demonstrated that partial fundoplication significantly reduces the risk of postoperative dysphagia and gas bloat syndrome compared to complete fundoplication, while providing excellent reflux control [16, 18]. Several retrospective studies tried to address this question in pediatric GERD patients, but the first randomized controlled trial comparing Nissen to Thal fundoplication was published only recently [10,19]. These studies, individually, are not able to conclude which type of fundoplication is the best procedure in the pediatric GERD population. Therefore, the current study aimed to compare complete fundoplication to partial fundoplication in pediatric GERD patients in a systematic review and to perform a meta-analysis on all available literature.

METHODS

Search Strategy

This systematic review was conducted according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) statement [20,21]. Using predefined search terms PubMed (1960 to 2011), EMBASE (from 1980 to 2011), and the Cochrane Library (issue 3, 2011) were systematically searched until March 16, 2011 to identify all articles comparing complete to partial fundoplication in children with GERD. For PubMed, the following search terms were used: (child*[Title/Abstract] OR infant*[Title/Abstract] OR adolescent*[Title/Abstract] OR pediatric*[Title/Abstract] OR paediatric*[Title/Abstract]) AND (nissen[Title/Abstract] OR toupet[Title/Abstract] OR thal[Title/Abstract] OR antireflux*[Title/Abstract] OR antireflux*[Title/Abstract] OR fundoplication[Title/Abstract] OR fundoplication[MeSH Terms]) AND gastroesophageal reflux[MeSH Terms]. The same search strategy was used in EMBASE (replacing "[Title/Abstract]" by; "ti,ab" and "[MeSH Terms]" by/exp). Human, child and adolescent were used as search limits in both databases. In addition, the Cochrane Library was manually searched. Language restrictions and time horizons were not applied (**Figure 1**).

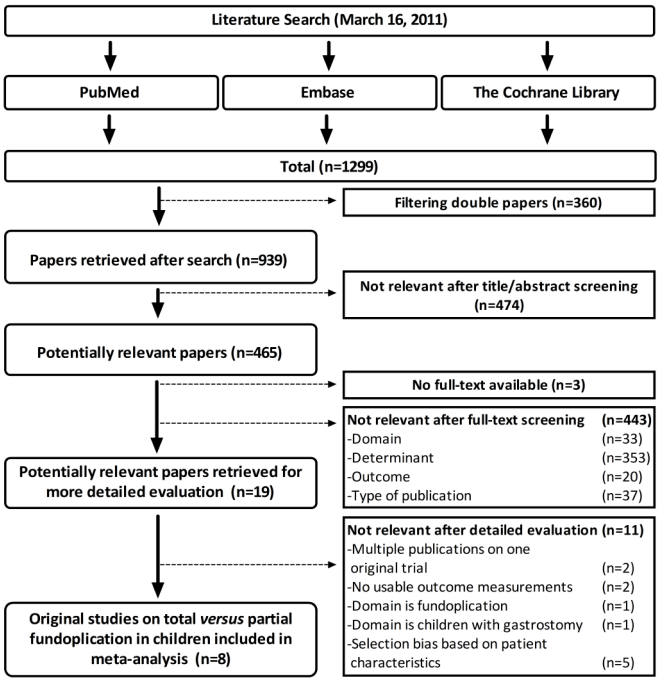

Figure 1 Flow-chart illustrating details of the search strategy and the study selection process according to the PRISMA statement

Study Selection Criteria

Each article was independently assessed for eligibility using the following predefined criteria:

– Study population: neurologically normal (NN) and impaired (NI) infants and children (0–18 years) undergoing primary antireflux surgery for GERD, irrespective of prior or concomitant gastrostomy placement.

– Intervention: complete fundoplication documented as open or laparoscopic posterior 360° complete fundoplication, irrespective of division of the short gastric vessels [22] and partial fundoplication as open or laparoscopic posterior (Toupet) or anterior (Thal or Watson) partial fundoplication.

– Study outcomes: at least one of the outcome measures reported below.

– Study design: originally published articles.

Studies were excluded from analysis if they allocated patients to either surgical technique based on patient characteristics, if they did not meet the inclusion criteria, or if primary outcome parameters of interest were not reported. In case of multiple studies reporting on an overlapping population, only the study with the largest patient population was included.

Outcomes of Interest

Primary outcomes of interest were descriptive symptoms or standardized questionnaires on GERD, 24-h (with or without multichannel intraluminal impedance) pH monitoring, postoperative dysphagia and dilatations for dysphagia. Secondary outcomes of interest were surgical reinterventions (and reasons for reintervention), manometry, gastroscopy, inability to belch, gas bloat syndrome, quality of life, patient satisfaction, in-hospital complications, mortality, operating time and length of hospital stay. A follow-up time of less than 6 months was considered short-term follow up, while a follow-up time of more than 12 months was considered long-term follow-up.

Data Extraction

Titles and abstracts of all retrieved records, and subsequently full-text articles (full-texts were obtained for articles that appeared potentially relevant), were examined independently by two authors (F.M. and B.B.) according to the PRISMA statement [20,21]. A cross-reference check of included articles was performed to identify articles possibly missed by our search strategy. The following data were extracted separately by the same two authors for all studies meeting the inclusion criteria: study population characteristics, study design, surgical

method, duration of follow-up, number of participating subjects and events for each of the study outcomes of interest. In case of discrepancies, a third author (MvH-L.) was consulted and agreement was reached by consensus.

Methodological Quality

Using predefined criteria, two authors (F.M. and B.B) included studies and assessed their methodological quality and risk of bias according to the PRISMA statement [20,21] and the Cochrane Collaboration's tool for risk of bias assessment [23].

Statistical Analysis

Inter-rater agreement was assessed using κ statistic. If more than two studies reported on one of the outcomes of interest, studies were pooled in a meta-analysis. Subgroup analysis was performed to compare specific types of surgical techniques. Surgical techniques of interest were complete posterior (Nissen), partial posterior (Toupet), and partial anterior (Thal) fundoplication. Results were presented as risk ratios (RRs) with 95 % confidence intervals (CI). Data were pooled using the Mantel–Haenszel random-effects meta-analysis model [24]. The random effects model was chosen to take into account suspected heterogeneity caused by differences in study design and patient population, as it generates a more conservative estimate than an analysis using the fixed-effects model [25]. Studies were weighted on sample size and the number of events. Trials with zero events in one arm were included in the analysis by adding a continuity correction of 0.5 to all cells in the two-by-two table for that study. Trials with zero events in both arms were excluded from the meta-analysis. Heterogeneity was calculated using Higgins χ^2 test (χ^2 p value>0.1) [26] and inconsistency in study effects was quantified by I^2 values (I^2>50%) [23,27]. Funnel plots were used to help identify the presence of publication or other types of bias [28]. All analyses were performed using the Review Manager software (version 5.1.7) provided by the Cochrane Collaboration.

RESULTS

In total, 939 potentially relevant publications were identified. After title/abstract and full-text screening we selected eight original studies that met the inclusion and exclusion criteria (**Figure 1**) [9,10,19,29–34]. Inter-rater agreements were high for both title/abstract (κ=0.91) and full-text (κ=0.83) screening. Included studies were published between 1994 and 2011 and reported on a total of 1183 (588 complete and 595 partial fundoplications) children. Most studies only reported data on short-term follow-up. We detected a wide range in follow-up duration (0–192 months) and age at time of surgical intervention (7 days–21 years) between the included studies (**Table 1**). The overall methodological quality of included studies was

generally poor. All except one of the included studies used a retrospective cohort design. Only Kubiak et al. [10,19] randomly allocated patients to either complete or partial fundoplication. Three studies [10,19,29,31] performed investigation techniques and/or questionnaires according to a predefined study protocol and only five studies reported data on the number of patients lost to follow-up. The potential threats to validity are summarized in **Table 1**.

Study	Year	Period	Technique	*n*	FU (months) in mean or range	Patients	Age(years) in mean (SD) or median (range)	Prospective Randomisation	Study conducted according to protocol	complete report on	lost to follow-up	Potential other bias
								Risk of bias summary				
Kazerooni et al.[32]	1994	1974 - 1991	NF	126	50,4	All	0.8	-	-	-	-	(a)
			ThF	34			(SD 0.6)					
Ceriati et al.[30]	1998	1977 - 1995	NF	27	32	Only NI	0.5 - 20	-	-	-	NA	(b)
			ThF	20								
Strecker-McGraw et al.[33]	1998	1983 - 1997	ONF	135	NR - 3	All	0.02 - 15					
			OThF	195				-	-	-	NA	(a)
			TouF	16								
			ThF	16								
Bacewicz et al.[29]	2004	1982 - 1998	NF	30	18 - 192	All	6	-	-	+	-	(d)
			TouF	16			(0.08 - 17)					
Esposito et al.[9]	2006	1993 - 2004	LNF	90	60	No NI	0.4 - 16					
			LTouF	96				-	-	-	NA	(a)
			LThF	48								
Goessler et al.[31]	2007	1985 - 1999	NF	15	28,8	Only NI	12.2					
			TouF	4			(SD NR)	-	-	+	NA	(a)
			ThF	25								
Wagener et al.[34]	2007	1995-2002	ONF	76	0-90	All	0.04 – 16.9	-	-	-	+	(a,b,e)
			OWF	55								
Kubiak et al.[10,19]	2011	1998 - 2007	LNF	89	30	All	3.1	+	+	+	-	(c,f)
			LThF	86	(1 - 109)		(0.1 - 21.0)					

FU = Follow-up; **NR** = Not Recorded; **NA** = Not Applicable (No lost to follow-up)
Patients: NI = Neurologically impaired; All = Neurologically normal and impaired
Techniques: L = Laparoscopic; O = Open = conventional; NF =Nissen Fundoplication; TouF = Toupet fundoplication; ThF = Thal Fundoplication; WF = Watson Fundoplication;
Potential other bias: a = Patient number imbalance between groups; b = Time horizon determines surgical technique; c = Statistically significant baseline imbalance neurological impairment versus neurologically normal developed patients; d = Not all patient underwent investigation techniques; e = OWF performed by a single surgeon, while ONF was performed by 4 surgeons; f = Statistically significant baseline imbalance in weight at time of operation

Table 1 Clinical trials (in chronological order) comparing complete to partial fundoplication in pediatric gerd patients

Study	Technique	n	Acid exposure time preoperative (%, SD)	Acid exposure time after 6 months FU (%; SD)	Acid exposure time after 12 months FU (%; SD)
Goessler et al.[31]	NF	15	17.7±2.5	4.0±1.9	3.6±0.7
	TouF	4	12.6±0	2.8±0.2	3.9±0.8
	ThF	25	22.6±3.0	6.7±1.2	13.6±3.0

FU = Follow-up; **SD** = Standard deviation
Techniques: NF =Nissen Fundoplication; TouF = Toupet fundoplication; ThF = Thal Fundoplication

Table 2 total acid exposure time by 24-hour ph monitoring

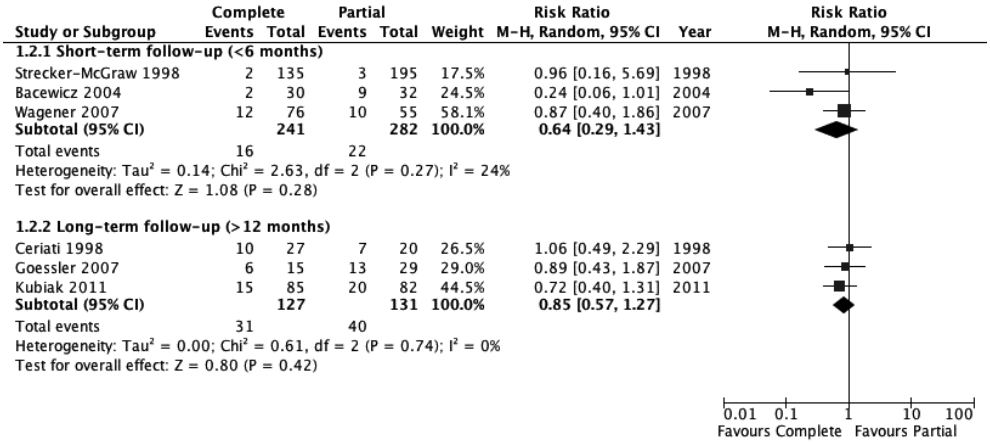

Figure 2 Meta-analysis of subjective recurrence of reflux after a short-term (<6 months) and long-term (>12 months) follow-up following complete versus partial fundoplication. Risk ratios are shown with 95 % confidence intervals (Mantel–Haenszel random-effects model))

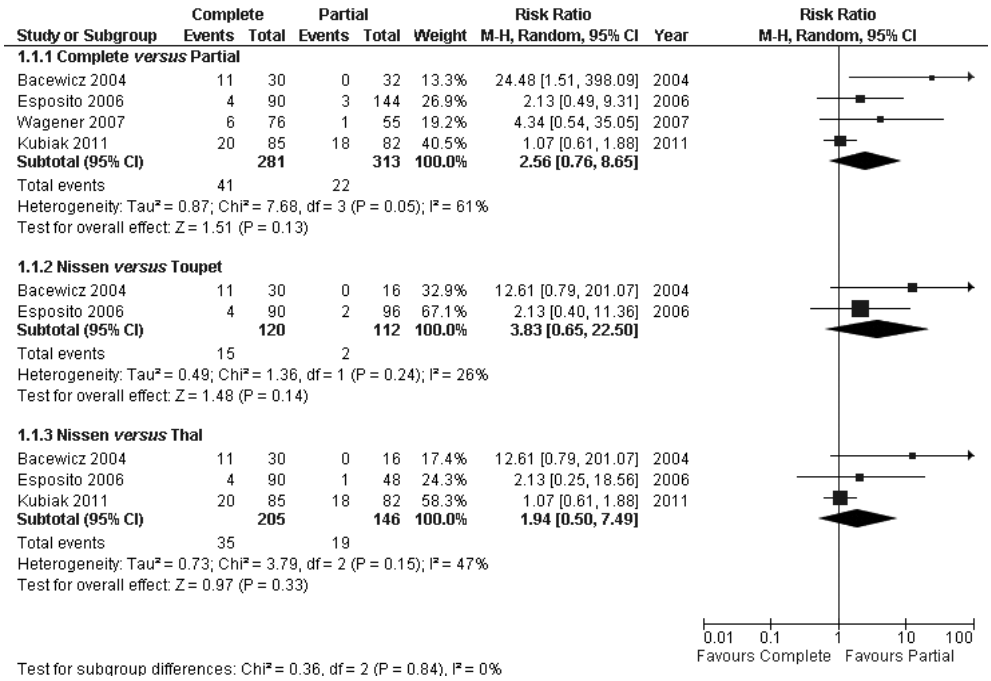

Figure 3 Meta-analysis of postoperative dysphagia following a complete versus partial; b Nissen versus Toupet, and c Nissen versus Thal fundoplication. Risk ratios are shown with 95 % confidence intervals (Mantel–Haenszel random-effects model)

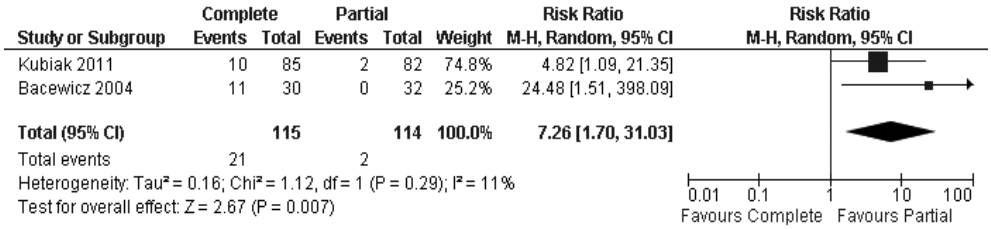

Figure 4 Meta-analysis of dilatations for dysphagia following complete versus partial fundoplication. Risk ratios are shownwith 95%confidence intervals (Mantel–Haenszel random-effects model)

Results of Primary Outcomes

Meta-analysis could be performed on all primary outcomes, except for 24-h pH monitoring. None of the studies used standardized reflux questionnaires. Only the absence or presence of reflux symptoms was reported. Short-term (RR 0.64; p=0.28; **Figure 2a**) and long-term (RR 0.85; p=0.42; **Figure 2b**) subjective reflux control was similar for complete and partial fundoplication. The relative risk of developing postoperative dysphagia in children who underwent complete fundoplication was 2.56 compared to partial fundoplication; however,

this was not statistically significant (p=0.13; **Figure 3a**). Analysis of uniformity among the reported results showed excessive heterogeneity for postoperative dysphagia (I^2=61 %). This was probably caused by the high dysphagia rates for both complete and partial fundoplication in the study performed by Kubiak et al. [10] Follow-up time of studies reporting on postoperative dysphagia varied widely (2 months–16 years). Only three studies reported on dysphagia more than 12 months after operation. These studies also found a higher rate of postoperative dysphagia after complete fundoplication compared to partial fundoplication (18.5 % vs. 11.3 %; p=0.21), however this was not significantly different. Partial fundoplication was associated with significantly fewer endoscopic dilatations to treat severe dysphagia (RR 7.26; p=0.007; **Figure 4**) compared to complete fundoplication. Only one study published total acid exposure times, measured by 24-h pH monitoring per different type of surgical technique [31]. Patients who underwent a Thal fundoplication had a higher acid exposure time before operation and at short-term (6 months) and long-term (12months) follow-up (**Table 2**). However, in this study no statistical significant differences were found. To identify possible selection bias funnel plots were constructed. The funnel plot on dysphagia indicated a lack of larger studies in favor of a partial fundoplication, but it is unclear whether this is due to publication bias or other mechanisms. Other funnel plots did not show clear evidence of publication bias and none of the studies lay outside the 95 % CI limits.

Results of Secondary Outcomes

In three of the secondary outcomes (i.e., reintervention rate, gas bloat syndrome and in-hospital complications) a meta-analysis was possible. The relative risk to develop postoperative gas bloat syndrome comparing complete to partial fundoplication was 2.01. However, this was not statistically significant in the meta-analysis (10.1 % vs. 5.1 %; p=0.18). Reintervention rates after complete and partial fundoplication were similar, but meta-analysis demonstrated a non-significant trend slightly in favor of a complete fundoplication (4.7 % vs. 5.9 %; RR 0.58; p=0.08). The percentage of patients with in-hospital complications was also similar after both procedures (11.0 % vs. 9.2 %; RR 1.12; p=0.65). Two [19,33] of the six studies reporting on reintervention rates published their indications for reintervention. An ineffective wrap was seen in eight patients (complete n=2; partial n=6), recurrence of hiatal hernia in seven patients (complete n=2; partial n=5), recurrence of reflux in four patients (complete n=1; partial n=3) and a bowel obstruction in one patient (complete fundoplication). One study specified in-hospital complications, reporting in both complete and partial fundoplication two patients with intraoperative bleeding and one patient with a bowel perforation [10,19]. Four studies recorded length of hospital stay. In three of these four studies, an open [12,30,34] and in one a laparoscopic technique was used [10,19]. In two studies [12,30], length of hospital stay was significantly longer after complete fundoplication (p<0.01). This was due to delay in resumption of oral feedings and changes in hospital discharge policy over time. In the other studies [10,19,34] hospital stay also appeared longer

after complete fundoplication; however, this difference was not statistically different. Only two studies reported on operating time [10,19,30]. Ceriati et al. [30] reported a significantly longer operating time constructing a complete fundoplication than a partial fundoplication (180 vs. 120 min; p<0.001), whereas in the study by Kubiak et al. [10,19] operating time was similar after both procedures (102 vs. 109min; p=NS). Only one study reported on esophageal motility [29] showing significantly higher postoperative LES pressures after complete fundoplication. None of the included studies reported data on upper endoscopy, inability to belch, quality of life or patient satisfaction. After constructing funnel plots we did not identify evidence indicating publication bias for these secondary outcomes and none of the studies lay outside the 95 % CI limits.

Subgroup Analysis of Specific Types of Fundoplication

Nissen Versus Toupet Fundoplication

Three studies [9,29,31] reported separate data comparing Nissen to Toupet fundoplication. However, only one study [29] with a limited number of patients reported separate data on short-term (93.3 % vs. 93.8 %; p=0.96) reflux control. One other study [31] reported separate data on long-term reflux control, 60.0 % after Nissen versus 83.3 % after Toupet (p=0.64), but also had a limited number of patients. Two studies published data comparing Nissen and Toupet by incidence of postoperative dysphagia [9,29]. These studies reported on a total of 232 children (120 Nissen and 112 Toupet fundoplication). The relative risk of developing postoperative dysphagia was 3.83 after complete fundoplication compared to partial fundoplication; however, this was not statistically significant (12.5 % vs. 1.8 %; p=0.14). Finally, reintervention rates were similar after both procedures (2.9 % vs. 2 %; RR 1.03; p=0.97).

Nissen Versus Thal Fundoplication

Six studies [9,10,19,29–33] reported data comparing Nissen to Thal fundoplication. Two studies [29,33] reported on short-term reflux control, comparing a total of 165 children who underwent Nissen fundoplication to 211 with a Thal fundoplication. In this subgroup analysis, a non-significant trend towards better short-term reflux control (97.6 % vs. 94.8 %; RR 0.36; p=0.08) after Nissen fundoplication was identified. Three studies10,19,22,31 investigated reflux control after long-term follow-up. These three studies reported on a total of 254 children (127 in either arm). Meta-analysis of studies reporting on long-term subjective reflux control resulted in similar results after Thal and Nissen fundoplication (75.6 % vs. 69.3 %; RR 0.76; p=0.26). Postoperative dysphagia was not significantly different after Nissen and Thal fundoplication (17.1 % vs. 13.0 %; RR 1.94; p=0.33). Comparing reintervention rates showed a non-significant trend in favor of Nissen fundoplication (4.7 % vs. 6.9 %; RR 0.54; p=0.06). Directly comparing Thal to Toupet fundoplication was not possible, since none of the included studies reported useable data on the primary endpoints. Funnel plots did not

demonstrate clear evidence of publication bias and none of the studies lay outside the 95% CI limits.

DISCUSSION

For many years, Nissen fundoplication was considered the gold standard for treatment of severe GERD in pediatric patients. Recent meta-analyses of several randomized controlled trials (RCTs) on antireflux surgery have suggested, however, that partial fundoplication should be the therapy of first choice in refractory adult GERD patients [16,17]. Unfortunately, data in the pediatric literature is scarce: several individual retrospective studies and only one RCT have been published comparing complete Nissen to partial Thal fundoplication. Our systematic review and meta-analysis of these studies found similar short- and long-term reflux controls after both complete and partial fundoplication, whereas partial fundoplication required significantly fewer dilatations to treat severe postoperative dysphagia than did complete fundoplication.

In this meta-analysis the relative risk of postoperative dysphagia in patients who underwent complete fundoplication was 2.6 compared to those who underwent partial fundoplication. This was, however, not statistically significant (p=0.13), which was probably due to excessive heterogeneity between study results. This heterogeneity was caused by the only RCT that was included in our meta-analysis. Exclusion of this RCT would result in less heterogeneity and a significant difference (p=0.04) in favor of partial fundoplication. However, the RCT by Kubiak et al. [10,19] was well-designed and it is therefore not justifiable to exclude this study from meta-analysis. Severe postoperative dysphagia requiring endoscopic dilatation occurred significantly less frequently after partial fundoplication than after complete fundoplication. This statistically significant relative risk observed after meta-analysis is further strengthened by uniformity in reported study results (I^2=11 %).

In order to evaluate whether an anterior Thal or posterior Toupet fundoplication had different outcomes when compared to the posterior, complete Nissen fundoplication, subgroup analysis was performed. This analysis showed similar reflux control after Toupet compared to Nissen fundoplication. Comparing Thal to Nissen fundoplication demonstrated that short-term reflux control was slightly less effective (<3 %) after Thal fundoplication, but studies with long-term follow-up showed similar reflux control after both techniques. Postoperative dysphagia occurred less frequently after both Toupet and Thal compared to Nissen fundoplication, although these differences were not significant. These subgroup analyses are restricted by a small number of studies. Also with regard to reflux control, a limited number of patients, especially in the Toupet group, were included in the studies. Finally, we did not find studies that directly compared Toupet to Thal fundoplication, therefore differences in

efficacy and adverse events between these two techniques cannot be directly evaluated. Meta-analysis of revisional surgery showed a non-significant trend in favor of complete fundoplication (RR 0.58; p=0.08). Subgroup analysis suggested that this was mainly based on a large number of reinterventions in the Thal group, whereas Toupet fundoplication required a similar number of reinterventions as Nissen fundoplication. In-hospital complication rates were comparable in both complete and partial fundoplication. Unfortunately, only one study [10,19] specified in-hospital complications, therefore the severity of these complications in both groups is unknown.

Only two retrospective studies used objective gastroesophageal function tests. Basewicz et al. [31] demonstrated a higher total acid exposure time after Thal fundoplication than after both Nissen and Toupet fundoplication in a small group of patients. However, this difference was not statistically significant. Goessler et al. [29] measured a higher LES pressure after complete fundoplication. Nonetheless, as is known from the adult literature, a high LES pressure is not associated with more effective reflux control or more postoperative dysphagia after antireflux surgery [35,36]. The role of manometry in children requires further study.

A number of issues need to be considered regarding the conclusions of this systematic review on complete versus partial fundoplication in pediatric GERD patients. Firstly, the majority of the included studies in this review were retrospective in design, which resulted in limited access to study outcomes and various forms of bias. Second, in five [9,31–34] of the eight included studies, significantly more patients had undergone a complete fundoplication. Third, several studies have shown that individual experience in performing antireflux surgery may influence the outcome [37,38], however, none of the studies reported on differences in experience or learning curves between the two techniques. There was also a lack in data on randomization with regard to individual surgeons, as only one study reported if the procedures were (randomly) allocated to a surgeon. Therefore, at this moment, we cannot draw any conclusion on effects of individual practice and expertise. Fourth, patient populations among the different studies were heterogeneous. Some authors have suggested that the efficacy of antireflux surgery is lower in neurologically impaired (NI) children than in normally (NN) developed children, because of concurrent gastrointestinal dysmotility in NI children [4,39–41]. In our systematic review, two studies reported only on NI children [30,31]. These studies compared Nissen fundoplication to mainly Thal (Toupet n=4) fundoplication, demonstrating an overall long-term reflux control of approximately 60 % after both procedures. Recently, a retrospective study reporting on long-term follow-up of only NN children after antireflux surgery showed reflux control in up to 80 % of patients after 10 years follow-up [42]. Contradictory to these results, the only published systematic review that included merely prospective studies on pediatric antireflux surgery could not distinguish a difference in reflux control between NI and NN children [5]. Furthermore, the eight studies in this review included patients who were treated between 1974 and 2007. Indications for

antireflux surgery varied over the years and despite recent guidelines of the NESPHGAN [2] an unequivocal definition of therapy-resistant GERD in children does not exist. This results in a large variety of patients included in this systematic review. Finally, both conventional and laparoscopic surgical approaches were included in this review and meta-analysis. Currently, a laparoscopic approach is the gold standard, since reflux control and postoperative dysphagia [43] are similar in both procedures and laparoscopic surgery may result in less postoperative pain, faster recovery, shorter hospital stay, and better cosmesis [43–46].

This systematic review and meta-analysis showed that reflux control is similar after both complete and partial fundoplication, while partial fundoplication significantly reduces the number of dilatations to treat severe dysphagia. However, because of the lack of a well-designed study, we have to be cautious in making definitive conclusions. To decide which type of fundoplication is the best practice in pediatric GERD patients, more randomized controlled trials comparing complete to partial fundoplication in children with GERD are warranted. Finally, considering the trend shown in this systematic review in favor of Toupet fundoplication compared to Thal fundoplication, perhaps future research should particularly focus on investigating this specific type of fundoplication.

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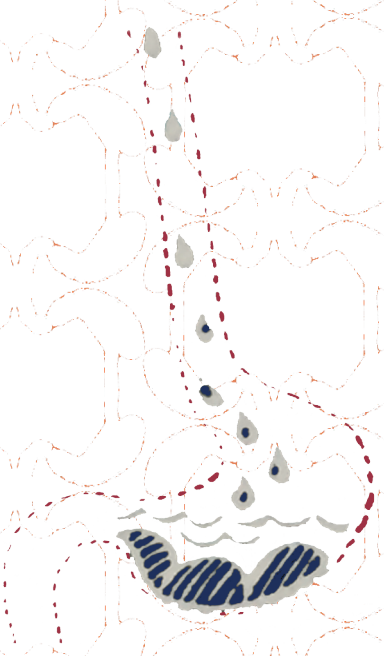
Appendices

Part Four

8. Summary and general discussion



Gastroesophageal reflux disease (GERD) frequently occurs in the pediatric population [1;2]. In severe GERD resistant to medical treatment, (laparoscopic) antireflux surgery (ARS) may be indicated [2-4]. Laparoscopic ARS is one of the most frequently performed major surgical procedure in the pediatric population. The studies presented in this thesis reported on the efficacy (short- and long-term and effects of laparoscopic fundoplication in pediatric GERD patients.

In chapter one a general introduction of the clinical presentation, pathophysiology, diagnosis and (surgical) treatment of GERD in children were presented. Furthermore, at the end of the chapter the aims of the different studies in this thesis were summarized.

EFFICACY OF ANTIREFLUX SURGERY

Although many studies have reported a high success rates of ARS [5-7], the efficacy of ARS and the association between ARS and gastroesophageal function in children are difficult to deduce from these publications as most studies are underpowered, retrospective and have a heterogeneous study design as well as study populations.

In **chapter two** we performed a systematic review of all prospective trials reporting on the efficacy of ARS in children. In total, 17 prospective trials on ARS in the pediatric population were identified. The median success rate, defined as complete relief of symptoms, was 86% with a remarkably wide range of 57–100%. Efficacy comparing children with impaired neurodevelopment (NI) to children with normal neurodevelopment (NN) was inconsistent between studies. Different surgical techniques (total versus partial fundoplication, or laparoscopic versus open approach) showed similar reflux recurrence rates. However, less postoperative dysphagia was observed after partial fundoplication and laparoscopic ARS was associated with less pain medication and a shorter hospital stay. Complications of ARS were not consistently reported and varied widely. Postoperative complications, such as esophageal perforation, pneumonia and wound infections, were seen in 0-54%, and severe dysphagia in 0-33%. Twenty-four-hour pH monitoring was performed routinely in almost all studies before performing ARS, however only 8 studies also performed objective monitoring after ARS. In all these studies total acid exposure time decreased after ARS. Effects on motility were rarely or not investigated. In the only 3 studies that performed manometry and gastric emptying no increase in lower esophageal sphincter pressure and an either unchanged or accelerated gastric emptying after ARS were found. No studies were identified that assessed gastroesophageal function by barium swallow, endoscopy, or MII-pH monitoring before and after ARS. It can be concluded from this systematic review that there is a lack of high-quality prospective studies on the (objective) results of ARS in the pediatric population. Similarly, results on the effects of pediatric ARS on gastroesophageal function are also very limited.

In **chapter three** we investigated the efficacy of laparoscopic ARS (LARS) in a prospective, multicenter study in 25 pediatric GERD patients. Furthermore, we aimed to identify predictors of LARS failure. After LARS 12% of patients had persistent or recurrent reflux symptoms and one third of these patients had persistent pathological acid exposure on MII-pH monitoring. New-onset postoperative dysphagia was found in 12% of patients after LARS. Twenty-four-hour MII-pH monitoring showed a significant decrease in total acid exposure time from 8.5% to 0.8% and in total number of reflux episodes (91 to 14) as well as in acid and weakly acidic reflux. Lower esophageal sphincter (LES) resting pressure significantly increased after LARS from 10 mmHg to 24 mmHg, but complete LES relaxation, peristaltic contractions and gastric emptying time were not different after LARS.

Subgroups analysis comparing children with NI to NN patients showed that the presence of reflux symptoms before and after LARS was similar. Acid exposure time and number of reflux episodes measured by MII-pH monitoring were higher in NI children before LARS, although reflux reduction by LARS was similar. Comparing laparoscopic Thal with Nissen fundoplication showed that the presence of reflux symptoms before and after LARS was also similar. There was a trend towards more frequent dysphagia after Nissen compared to Thal. Finally, before LARS, LES resting pressure, total acid exposure time and number of reflux episodes measured by MII-pH monitoring were higher in the Thal group, however after LARS this difference was no longer present.

Due to the success of LARS in this cohort we were not able to identify predictors of LARS failure. However, we concluded that the total number of reflux episodes on MII-pH monitoring before operation was a significant predictor for the effect of LARS on reflux reduction.

Long-term efficacy of LARS was investigated in **chapter four**. A prospective cohort study was performed including 57 patients that underwent laparoscopic Thal fundoplication. At 3 to 4 months, at 1 to 5 years, and at 10 to 15 years after ARS, 81%, 80%, and 73% of patients, respectively, were completely free of reflux symptoms. Disease-free survival analysis however demonstrated that only 57% of patients were symptom free at 10 to 15 years after ARS. Total acid exposure time significantly decreased from 13.4% before ARS to 0.7% at 3 to 4 months after ARS; however, at 3 to 4 months after ARS, pH monitoring was still pathological in 18% of patients. At 10 to 15 years after ARS, the number of patients with pathological reflux had significantly increased to 43%. No significant differences were found comparing NI and NN patients.

EFFECTS OF ANTIREFLUX SURGERY

MII-pH monitoring is a well-established method used to diagnose GERD. One of the newer applications of MII-pH monitoring is the assessment of mucosal integrity by calculating the baseline impedance [8]. Recovery of impaired mucosal integrity, as reflected by an increased baseline impedance, may relief symptoms in GERD patients and be a marker for the clinical outcome of therapy [9;10]. **Chapter five** evaluates the effect of LARS on the mucosa integrity. We found that distal baseline impedance increased after LARS from 2445 Ω to 3792 Ω. This increase in baseline impedance is likely to reflect recovery of mucosal integrity and thereby mucosal healing after LARS. Preoperative baseline impedance strongly correlated with acid exposure time (r:-0.76, $p<0.001$); however no association between symptomatic outcome and baseline impedance was identified. Therefore, it seems likely that other factors may contribute to symptom perception in children with GERD. Finally, determinants, such as age, type of fundoplication or change in acid exposure time did not influence the effect of LARS on baseline impedance.

To better assess the impact of pediatric diseases and treatments from the perspective of the pediatric patient and their caregivers health-related quality of life (HRQoL) assessment has been increasingly recognized as an essential part of treatment- outcome [11]. In **chapter six** we studied the effect of LARS on HRQoL and identified predictors that may affect HRQoL outcome after LARS. This is one of the few studies investigating HRQoL prospectively in pediatric GERD patients undergoing LARS. Moreover, it is the first study investigating HRQoL both by parental proxy-report as well as children's self-reports.

HRQoL total score improved significantly after LARS, both from a parental and child's perspective. The psychosocial health summary and physical health summary scores also improved significantly after LARS. HRQoL before and after LARS was significantly lower in NI children. However, neurodevelopment itself did not influence the effect of LARS on HRQoL. Furthermore, reflux symptoms were also associated with a lower HRQoL. The only significant predictor for improvement in HRQoL after LARS was age at the time of operation, showing that in older children LARS results in more improved HRQoL.

SURGICAL TECHNIQUES

As mentioned in the introduction various types of fundoplication (i.e. complete Nissen or partial Thal and Toupet fundoplication) can be performed in pediatric GERD patients. However, up to now no consensus on which type is the preferred type in pediatric GERD patients is available. In **chapter seven** a systematic review of the literature and meta-analysis comparing complete fundoplication to partial fundoplication in children with

GERD was presented. Eight original trials comparing complete to partial fundoplication in pediatric GERD patients were identified. Seven of the eight studies had a retrospective study design. Short-term (RR 0.64; p=0.28) and long-term (RR 0.85; p=0.42) postoperative reflux control, and postoperative dysphagia (RR 2.56, p=0.13) were similar for complete and partial fundoplication. Complete fundoplication required significantly more endoscopic dilatations for severe dysphagia (RR 7.26; p=0.007) than partial fundoplication. Subgroup analysis comparing Nissen to Toupet or Thal fundoplication separately showed that reflux control was similar after Nissen, Toupet and Thal, however a trend was shown to less effective short-term reflux control after Thal fundoplication. Furthermore, both Thal and Toupet fundoplication resulted in less postoperative dysphagia, although these differences were not significant. It is however important to be cautious in making definitive conclusions because up to now no well-designed studies have been performed.

GENERAL DISCUSSION

In the literature short-term complete relief of symptoms after (laparoscopic) ARS is demonstrated in 86% of patients [12-14], which was also found in our prospective, multicenter study (88%). However, long-term efficacy of LARS is disappointingly lower as GERD persists or recurs in 43% of children. This high recurrence rate is in contrast to the majority of previously published studies [12;15-17], and in particular to the only published study on follow-up 10 years after ARS by Esposito et al. [18]. They showed long-term reflux control in up to 87% of patients. A possible factor causing this difference is that all previous studies on long-term efficacy of pediatric ARS had a retrospective cohort design. This may have introduced selection bias by including only patients that were alive and available for evaluation in the analysis. Furthermore, most studies defined only redo-surgery as failure of therapy, whereas in our current study all patients with recurrent GERD symptoms were included in analysis. In adult studies, it has been shown that fundic capacity increases during the years after ARS [19]. Apart from wrap failure, this could provide a potential explanation for the decrease in efficacy of ARS over time. Another contributing factor could be that a child may outgrow the fundoplication over time. Patients with untreated GERD are at risk of developing Barrett's esophagus and ultimately esophageal adenocarcinoma. The development of Barrett's esophagus and esophageal adenocarcinoma is not limited to older age groups but is also seen in children [20]. This risk depends on the duration and severity of gastroesophageal reflux [21;22]. Therefore, it is crucial to implement routine long-term follow-up after ARS in pediatric patients with gastroesophageal reflux disease.

Apart from the above-mentioned improvement in reflux symptoms, LARS also reduces both acid as well as weakly acidic gastroesophageal reflux. The additional use of MII-pH allows us to identify weakly acidic reflux episodes. Acid suppressive therapy is often not fully successful

in treating weakly acidic reflux since it decreases the acidity of the refluxate by reducing gastric acid production, but does not treat the actual reflux of gastric content [23]. In young children gastric content is buffered by frequent feeds and is therefore often not acidic. Therefore, in (young) children that suffer from predominantly weakly acidic GERD LARS may be the only therapeutic option.
In most studies persistent or recurrent reflux symptoms were more prevalent than objective acid exposure on MII-pH monitoring. In adults a lack of correlation between reflux symptoms and objective assessment of the presence of (acid) refluxate in the esophagus has been reported as well [24;25]. It is thought that recurrent or persistent symptoms may be caused by concomitant functional disease such as functional dyspepsia or hypersensitivity of the esophagus to gastroesophageal reflux [25].

Several studies have postulated that NI patients may insufficiently benefit from LARS [26;27], however up to now no study had been able to show significant differences. In **chapters three** and **four** short-term and long-term efficacy of LARS showed similar results comparing NI to NN children. In **chapter six** it is shown that HRQoL is significant lower in NI children compared to NN children. It is presumably not surprising that NI children with, more (co-) morbidity than NN children, scored lower in overall HRQoL. More importantly, however; after regression analysis we identified that the neurodevelopment itself did not influence the effect of LARS on HRQoL improvement, which underscores the fact that LARS has similar beneficial effect on both NN as well as NI children.

This thesis had aimed to identify the type of fundoplication that would be the preferred technique in pediatric GERD patients. In **chapter two**, **three**, **four** and **seven** we describe the outcome of the comparison of partial to complete fundoplication. Overall both complete (Nissen) and partial (Thal or Toupet) fundoplication both have similar reflux control by means of complete relief of symptoms, while partial fundoplication significantly reduces the number of dilatations to treat severe postoperative dysphagia. A recent meta-analysis in adults also reported no differences in reflux control between partial and complete fundoplication and similarly showed more frequent severe dysphagia after Nissen fundoplication. However, it is still important to be cautious in drawing definitive conclusions as none of the performed studies in this thesis were powered to identify differences between the techniques. Moreover, the current literature still lacks well-designed studies. Therefore, before one can decide on the preferred technique of fundoplication to treat pediatric GERD patients, adequately powered randomized controlled trials comparing complete (Nissen) to partial (Thal and/or Toupet) fundoplication in children with GERD are warranted.

LES resting and nadir pressure were shown to significantly increase after LARS, which is in accordance to previous studies on pediatric antireflux surgery [6;13;28]. An increase in the esophagogastric junction competence is expected, as it is one of the mechanisms in which

LARS prevents GERD [29-31]. It has been reported that LARS may affect LES relaxations and esophageal motility and thereby inducing postoperative dysphagia [28]. Our prospective study however showed that LARS had no effect on LES relaxations and esophageal motility. In this cohort new-onset dysphagia was observed in 12% of patients after LARS and was significantly more prevalent in NI children. New-onset dysphagia is thought to be caused by fundoplication-induced restriction and postoperative swelling at the esophagogastric junction [29-31]. LES pressure testing in our cohort showed a significant increase in LES resting and nadir pressure, which may reflect this restriction. Previous studies on pediatric and adult ARS showed similar results on LES function after LARS [6;13;32].

LARS aims to prevent gastroesophageal reflux events and to protect the esophageal mucosa from potential stressors in the refluxate. Previous studies have shown a strong inverse correlation between baseline impedance and acid exposure in pediatric GERD patients [23;33;34]. **Chapter five** presents the effect of LARS on baseline impedance as a reflection of mucosal integrity in pediatric patients with GERD. Our main findings were that LARS resulted in improved baseline impedance and a decrease in reflux symptoms. This result corresponds to previous studies attempting to identify a similar association after PPI treatment in children or after endoscopic fundoplication in adults [23;35], which indicates that LARS successfully eliminates (acid) reflux resulting in an increase in baseline impedance and is likely to reflect recovery of mucosal integrity due to mucosal healing. Although both baseline impedance increased and symptomatic reflux control improved these two parameters were not significantly correlated. This suggests that in addition to the mucosal integrity, also content, proximal extent and volume of the refluxate, as well as peripheral and central mediated sensitivity have an effect on GERD symptom perception [36].

HRQoL total score improved significantly after LARS, both from a parental and child's perspective. In **chapter six** we identified predictors that influence HRQoL and the effect of LARS on HRQoL. As discussed above children with NI scored lower on overall HRQoL, but had similar increase in HRQoL as a result of LARS compared to NN children. Only age at the time of operation was a statistically significant predictor of improvement in HRQoL after LARS. This indicates that older children have a more favorable HRQoL outcome after LARS compared to younger children, which may suggest caution when younger children are referred for therapy-resistant GERD. It has been suggested that recurrence of GERD and even the necessity for redo-fundoplication are more frequent in younger patients. These suggestions were based on two retrospective studies both using regression analysis to identify risk factors, showing the need for more redo-fundoplication and higher recurrence of GERD in younger children [37;38]. Furthermore, it has been hypothesized that younger children are able to outgrow a fundoplication [7]. Nonetheless, age was not a significant predictor of reflux episode reduction by LARS, as is measured by a more objective assessment test, i.e. 24-hour MII-pH monitoring.

An analysis to identify predictors for the effect of LARS on reflux reduction showed that the number of preoperative reflux episodes on MII-pH monitoring is a significant predictor of reflux reduction after LARS. This indicates that patients with a higher number of reflux episodes on MII-pH monitoring had significantly more reflux reduction after LARS. Neurodevelopment, type of fundoplication, age and gastric emptying were not found to have a significant effect.

In this thesis we were not able to identify predictors of failure of LARS as the failure rate was fairly low in the studied patient groups. Up to now only one study has tried to identify predictors of failure [39]. This study was however underpowered and therefore not able to identify any significant predictor of LARS failure. Future studies should be designed as, randomized, multicenter trials with an adequate powered patient population and long-term follow-up in order to identify parameters predicting success of therapy and to compare different patient groups as well as different surgical techniques. Furthermore, the prospective, multicenter trial discussed in this thesis shall be followed-up in time as failures may develop after longer follow-up. This long-term follow up may allow us to identify predictors of LARS failure in time.

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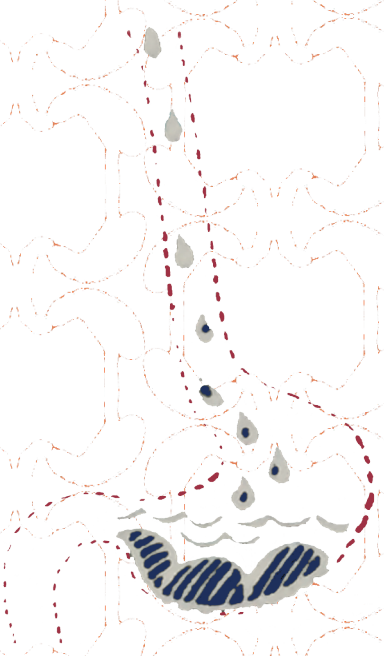
9. Nederlandse samenvatting en discussie



Gastro-oesofageale reflux ziekte (GORZ) komt veel voor bij kinderen [1;2]. Bij ernstige GORZ, die niet onder controle te krijgen is met medicamenteuze behandeling, kan (laparoscopische) antirefluxchirurgie (ARC) aangewezen zijn [2-4]. ARC wordt uitgevoerd door de fundus van de maag om de slokdarm te wikkelen (fundoplicatie) en is een van de meest uitgevoerde grotere operaties binnen de kinderchirurgie. De studies in dit proefschrift beschrijven de korte en lange termijn effectiviteit en de effecten van laparoscopische ARC (LARC) in kinderen met GORZ.

Het proefschrift is uit drie delen opgebouwd: 1. Effectiviteit van antirefluxchirurgie; 2. Effecten van antirefluxchirurgie en 3. Chirurgische technieken. Daarnaast geeft **hoofdstuk één** als eerste een algemene introductie van de klinische presentatie, pathofysiologie, diagnose en (chirurgische) behandeling van GORZ bij kinderen.

EFFECTIVITEIT VAN ANTIREFLUXCHIRURGIE

In de huidige literatuur zijn verscheidene studies die een hoog succes percentages beschrijven na ARC [5-7], desondanks blijft het nog steeds moeilijk om de effectiviteit en het verband tussen ARC en gastro-oesofageale functie uit deze stukken hard te maken. Dit is voornamelijk doordat de meeste studies weinig patiënten includeerden, retrospectief uitkomsten rapporteren en vaak een heterogene studieopzet en populatie hebben.

In **hoofdstuk twee** beschrijven we de resultaten van een systematisch review van alle prospectieve studies die uitkomsten rapporteren van ARC bij kinderen. In totaal hebben we 17 prospectieve studies kunnen identificeren die over ARC bij kinderen rapporteerden. De mediane kans op succes, gedefinieerd als volledige verlichting van de symptomen, was 86%. De spreiding in het gerapporteerde succes tussen studies was echter opvallend groot (57-100%). De verschillende studies rapporteerden tegenstrijdige uitkomsten wanneer effectiviteit werd vergeleken tussen kinderen met normale neurologische ontwikkeling en kinderen met psychomotore retardatie. Er werden verschillende ARC-technieken (complete versus partiële fundoplicatie, of laparoscopisch versus open) gebruikt. Recidief refluxklachten kwamen even vaak voor bij alle technieken. Er was echter wel sprake van significant minder dysfagie bij kinderen die een partiële fundoplicatie ondergingen. Een LARC gaat bovendien gepaard met minder pijnmedicatie gebruik na operatie en een kortere ziekenhuisopname. Complicaties na ARC werden niet consequent gerapporteerd en varieerden behoorlijk. Postoperatieve complicaties zoals oesofagusperforatie, pneumonie en wondinfecties werden gezien bij 0 - 54% van de kinderen. Dysfagie na ARC werd bij 0 - 33% van de kinderen gezien. In bijna alle studies werd voor ARC een routine 24-uurs pH-metrie verricht, maar slechts 8 studies onderzochten de zuurexpositie in de slokdarm ook na de operatie. In al deze 8 studies nam de hoeveelheid zuurexpositie in de slokdarm af na antirefluxchirurgie. Het effect van

ARC op de gastro-oesofageale motiliteit werd zelden onderzocht. In slechts 3 studies werd routinematig een manometrie of maagledigingsonderzoek verricht. Deze studies lieten zien dat de onderste slokdarmspierrustdruk (LES-rustdruk) voor en na ARC gelijk bleef en dat maaglediging gelijk bleef of versnelde na ARC. In geen van de studies is gebruik gemaakt van slikfoto's, endoscopie of multichannel intraluminale impedantie pH-metrie (MII-pH-metrie) om de gastro-oesofageale functie te onderzoeken. Uit deze systematische review concluderen we dat er dat er een gebrek is aan kwalitatief hoogwaardige prospectieve studies naar de (objectieve) resultaten van ARC bij kinderen. De effecten van pediatrische ARC op gastro-oesofageale functie zijn dan ook zeer beperkt bekend.

In **hoofdstuk drie** beschrijven we de effectiviteit van laparoscopische ARC (LARC) in een prospectieve, multicenterstudie bij 25 pediatrische GERD patiënten. Deze studie is verder ook gericht op het identificeren van voorspellers van het falen van LARC. Na LARC hadden 12% van de patiënten refluxsymptomen en één derde van deze patiënten had aanhoudende pathologisch zuurexpositie op de MII-pH-metrie. Ook zagen we dat na LARC 3 kinderen (12%) dysfagie ontwikkelden. Vierentwintig-uurs MII-pH-metrie toonde een significante daling van de totale zuurexpositie van 8,5% naar 0,8%. Daarnaast namen het totale aantal refluxepisodes (zowel zure als zwak zure) af van 91 naar 14. Ook de LES-rustdruk nam aanzienlijk toe van 10 mmHg naar 24 mmHg. Complete LES-relaxatie, peristaltische contracties en maagledigingstijd bleven na LARC echter onveranderd.

Subgroepenanalyse, waarbij we kinderen met psychomotore retardatie vergeleken met kinderen met normale neurologische ontwikkeling, liet zien dat refluxsymptomen voor en na LARC vergelijkbaar waren. Bij kinderen met psychomotore retardatie waren de zuurexpostie en het aantal refluxepisodes - gemeten met MII-pH-metrie - vóór LARC hoger, maar de refluxreductie na het verrichten van LARC was vergelijkbaar. Wanneer we laparoscopische Thal-fundoplicatie vergeleken met de Nissen-fundoplicatie bleek dat de aanwezigheid van refluxsymptomen voor en na LARC eveneens vergelijkbaar was. Er was wel te zien dat dysfagie frequenter voorkomt na Nissen-fundoplicatie dan na Thal-fundoplicatie. Tot slot zagen we dat de LES-rustdruk, de totale zuurexpositie en het aantal refluxepisoden hoger was na Thal-fundoplicatie, maar dat dit verschil na LARC volledig was verdwenen.

Door het succes van LARC in dit cohort waren we niet in staat om voorspellers van het falen van LARC te identificeren. Wel konden we vaststellen dat het totale aantal refluxepisoden voor LARC een belangrijke voorspeller voor het effect van LARC op refluxreductie is.

Hoofdstuk vier rapporteert over de lange termijn effectiviteit van LARC. Dit is onderzocht in een prospectieve cohortstudie onder 57 patiënten die laparoscopische Thal-fundoplicatie ondergingen. Na 3-4 maanden, 1-5 jaar en 10-15 jaar na LARC waren respectievelijk 81%, 80% en 73% van de patiënten volledig vrij van refluxsymptomen. Ziektevrij overlevings-

analyse liet zien dat na 10-15 jaar na LARC slechts 57% van de patiënten klachtenvrij was. De totale zuurexpositie daalde aanzienlijk van 13,4% voor LARC tot 0,7% 3-4 maanden na LARC. Bij 18% van de kinderen was de pH-metrie echter nog wel pathologisch verhoogd en dit percentage steeg na 10-15 jaar significant tot zelfs bij 43% van de kinderen. Er werden geen significante verschillen gevonden als we kinderen met psychomotore retardatie vergeleken met kinderen met normale neurologische ontwikkeling.

EFFECTEN VAN ANTIREFLUXCHIRURGIE

MII-pH-metrie is op dit moment de meest gebruikte methode om GORZ te diagnosticeren. Een van de recent ontdekte toepassingen van MII-pH-metrie is de beoordeling van mucosale integriteit door de baseline impedantie van de mucosa te berekenen [8]. Een verbetering/verhoging van de baseline impedantie, die herstel van verstoorde mucosale integriteit reflecteert, zou potentieel een marker voor de klinische uitkomst van de behandeling kunnen zijn [9; 10].

Hoofdstuk vijf evalueert het effect van LARC op de mucosale integriteit, waarbij we zagen dat de distale baseline impedantie toegenomen was na LARC van 2445 Ω tot 3792 Ω. Deze verbetering van de baseline impedantie betekent dat er herstel optreedt van de mucosale integriteit, wat uiteindelijk de genezing van de mucosa na LARC weerspiegelt.

Baseline impedantie correleert sterk met de hoeveelheid zuurexpositie aan de slokdarm (r: -0,76; p <0,001). Er werd echter geen verband gevonden tussen baseline impedantie en symptomatische uitkomst. Het lijkt daarom meer waarschijnlijk dat ook andere factoren kunnen bijdragen aan symptoomperceptie bij kinderen met GORZ. We konden geen determinanten, zoals leeftijd, type fundoplicatie of verandering in de expositie identificeren die het effect van LARC op de baseline impedantie beïnvloeden.

Kwaliteit van leven vragenlijsten worden in toenemende mate erkend als een essentieel onderdeel van de analyse naar uitkomsten van behandeling [11]. Dit komt vooral doordat met vragenlijsten de impact van pediatrische ziekten en behandelingen vanuit het perspectief van de patiënten zelf, en hun verzorgers, bepaald kan worden. In **hoofdstuk zes** beschrijven we het effect van LARC op de kwaliteit van leven en proberen we voorspellers te identificeren die kwaliteit van leven kunnen beïnvloeden na LARC. Dit is één van de weinige studies die de kwaliteit van leven bij kinderen met GORZ die LARC ondergaan prospectief onderzoekt. Het is bovendien het eerste onderzoek naar kwaliteit van leven dat zowel proxy-rapportage door ouders/verzorgers, als zelfrapportage door de kinderen zelf gebruikt.

Na LARC verbeterde de kwaliteit van leven significant, zowel vanuit het perspectief van de ouders/verzorgers als van het kind. Subanalyses naar specifiek psychosociale en fysieke kwaliteit van leven lieten eenzelfde effect zien na LARC. Kwaliteit van leven voor en na LARC was significant lager bij kinderen met psychomotore retardatie, maar de neurologische ontwikkeling heeft geen effect op de verbetering van kwaliteit van leven na LARC. Refluxsymptomen waren daarnaast ook geassocieerd met een lagere kwaliteit van leven. De enige significante voorspeller voor verbetering in kwaliteit van leven na LARC was de leeftijd op het moment van operatie. LARC resulteert bij oudere kinderen in meer verbetering van kwaliteit van leven.

CHIRURGISCHE TECHNIEKEN

Bij kinderen met GORZ kunnen drie verschillende fundoplicatietechnieken gebruikt worden: Nissen-fundoplicatie (360 graden posterieur / complete), Thal-fundoplicatie (270 graden anterieur / partiele) of Toupet-fundoplicatie (270 graden posterieur / partiele). Echter, tot op heden is er nog geen consensus over welk type de beste techniek is bij kinderen met GORZ.

In **hoofdstuk zeven** presenteren we een systematische review van de literatuur en een meta-analyse ter vergelijking van complete (Nissen) fundoplicatie met de partiele varianten (Thal en Nissen) bij kinderen met GORZ. Acht originele studies werden er gevonden waarvan er 7 een retrospectieve studieopzet hadden. Korte termijn (RR 0,64; p = 0,28) en lange termijn (RR 0,85; p = 0,42) postoperatieve refluxcontrole en postoperatieve dysfagie (RR 2,56; p = 0,13) waren vergelijkbaar na complete en partiële fundoplicatie. Wel vereist complete fundoplicatie aanzienlijk meer endoscopische dilataties ter behandeling van ernstige dysfagie (RR 7,26; p = 0,007) vergeleken met partiële fundoplicatie. Subgroep-analyse, waarbij Nissen- met Toupet- of Thal-fundoplicatie afzonderlijk werd vergeleken, liet zien dat refluxcontrole vergelijkbaar was na Nissen-, Toupet- en Thal-fundoplicatie. Thal lijkt op korte termijn echter wel minder effectief. Bovendien resulteerde zowel Thal- als Toupet-fundoplicatie in minder postoperatieve dysfagie vergeleken met Nissen-fundoplicatie, maar deze verschillen waren niet significant. Deze resultaten laten zien dat een partiële fundoplicatie mogelijk gunstiger is voor kinderen met GORZ. Het is echter belangrijk voorzichtig te zijn bij het maken van definitieve conclusies, omdat tot nu toe alle studies die verschillen tussen de verschillende technieken vergelijken van lage methodologische kwaliteit zijn.

DISCUSSIE

In de literatuur wordt op korte termijn volledige verlichting van symptomen na LARC gerapporteerd tot bij 86% van de patiënten [12-14]. Korte termijn effectiviteit in onze prospectieve, multicenterstudie was vergelijkbaar goed (88%). Op de lange termijn is de effectiviteit echter teleurstellend veel lager, omdat GORZ bij 43% van de kinderen recidiveert. Dit hoge recidief percentage is tegenstrijdig met de lange termijn effectiviteit gerapporteerd in eerder gepubliceerde studies [12; 15-17]. In de enige andere gepubliceerde studie met follow-up langer dan 10 jaar na ARC, uitgevoerd door Esposito et al. [18], werd een effectiviteit van 87% gezien.

Eén van de mogelijke factoren die dit verschil kunnen verklaren is dat alle eerdere studies die lange termijn effectiviteit van pediatrische ARC hebben onderzocht een retrospectief studiedesign hebben. Dit kan resulteren in selectiebias doordat alleen patiënten die nog levend zijn en bereikbaar waren voor evaluatie in de analyse zijn meegenomen. Daarnaast beschouwen de meeste studies alleen redo-chirurgie als falen van de therapie, terwijl in onze huidige studie alle patiënten met recidief van refluxsymptomen werden geclassificeerd als niet succesvol, doordat er een ziektevrije overlevingsanalyse werd uitgevoerd. In studies onder volwassenen is te zien dat de capaciteit van de fundus van de maag in de jaren na ARC weer toeneemt [19]. Naast het loslaten van de fundoplicatie, kan toename van de capaciteit ook een mogelijke verklaring zijn voor afname van de werkzaamheid van ARC over langere tijd. Een andere verklaring zou kunnen zijn dat kinderen in de loop van de tijd uit hun fundoplicatie groeien.

Patiënten met onbehandelde GORZ lopen op lange termijn het risico op het ontwikkelen van Barrett's slokdarm en uiteindelijk adenocarcinoom van slokdarmkanker. De ontwikkeling van Barrett's slokdarm en adenocarcinoom is niet beperkt tot oudere leeftijdsgroepen maar komt ook voor bij kinderen [20], en is afhankelijk van de duur en ernst van de gastro-oesofageale reflux [21; 22]. Daarom is het van cruciaal belang om routinematige follow-up te verrichten na ARC bij kinderen met GORZ.

Naast de hierboven genoemde verbetering van refluxsymptomen vermindert LARC ook zowel zure als zwak zure gastro-oesofageale reflux. Door middel van het aanvullend gebruik van MII naast pH-metrie kunnen we zwak zure reflux identificeren. Zuur onderdrukkende therapie is vaak niet volledig succesvol bij het behandelen van zwak zure reflux aangezien het enkel de zuurgraad van het refluxaat vermindert en daarom niet het eigenlijke reflux van maaginhoud richting de slokdarm behandelt [23]. Bij jonge kinderen wordt de maaginhoud vaak gebufferd door kleinere intervallen tussen de voedingen. Maaginhoud is om die reden vaak niet zuur. LARC zou bij (jongere) kinderen daarom dan ook mogelijk de enige therapeutische optie zijn.

In de meeste studies waren postoperatieve refluxsymptomen meer prevalent dan pathologische zuurexpositie gemeten met MII-pH-metrie. Deze discrepantie tussen refluxsymptomen en objectieve beoordeling van de aanwezigheid van (zuur) refluxaat in de slokdarm wordt ook bij volwassenen gezien [24; 25]. Een verklaring van aanhoudende klachten ondanks objectief vermindering van reflux zou kunnen zijn dat patiënten gelijktijdig meer functionele ziekten hebben, zoals functionele dyspepsie of overgevoeligheid van de slokdarm [25].

Verschillende eerder gepubliceerde studies veronderstelden dat kinderen met psychomotore retardatie onvoldoende kunnen profiteren van LARC [26; 27]. Tot nu toe is er echter geen enkele studie in staat om ook daadwerkelijk significante verschillen te laten zien. In de **hoofdstukken drie** en **vier** laten we zien dat op korte en lange termijn effectiviteit van LARC gelijk is zowel bij kinderen met psychomotore retardatie als kinderen met normale neurologische ontwikkeling. Verder zien we in **hoofdstuk zes** wel dat de kwaliteit van leven significant lager is bij kinderen met psychomotore retardatie in vergelijking tot kinderen met normale neurologische ontwikkeling. Het is niet verwonderlijk dat kinderen met psychomotore retardatie, die meer (co-)morbiditeiten hebben dan normaal ontwikkelde kinderen, lager scoorden in kwaliteit van leven. Veel belangrijker echter is dat we na regressieanalyse konden vaststellen dat de neurologische ontwikkeling zelf niet van invloed is op het effect van LARC ter verbetering van kwaliteit van leven. Dit onderstreept wat eerder beschreven is dat LARC, bij zowel kinderen met normale neurologische ontwikkeling als kinderen met psychomotore retardatie, een even gunstig effect heeft op kwaliteit van leven en dus even effectief is.

Eén van de doelstellingen van dit proefschrift was om uit te zoeken welke type fundoplicatietechniek bij kinderen met GORZ het beste is. In **hoofdstuk twee**, **drie**, **vier** en **zeven** beschrijven we de resultaten van analyses waarbij we de verschillende fundoplicatietechnieken vergeleken. Complete (Nissen) en partiële (Thal of Toupet) fundoplicatie waren even effectief in het behandelen van refluxsymptomen en totale zuurexpositie aan de slokdarm, terwijl kinderen na partiële fundoplicatie significant minder vaak endoscopische interventies nodig hadden om ernstige dysfagie te behandelen. Een recente meta-analyse bij volwassenen liet precies dezelfde uitkomsten zien. In het maken van definitieve conclusies moeten we echter nog voorzichtig zijn, omdat in geen van de uitgevoerde studies in dit proefschrift de studiepopulatie zodanig berekend was op het aantonen van een verschil tussen de fundoplicatietechnieken. Bovendien is nog nooit een methodologisch goede studie verricht om dit verschil aan te tonen. Voordat men kan beslissen wat de meest geschikte techniek van fundoplicatie is ter behandeling van GORZ bij kinderen moeten eerst gerandomiseerde gecontroleerde studies verricht worden. Verder moeten deze studies een adequate steekproefomvang hebben

die berekend is op het aantonen van een verschil tussen complete (Nissen) en partiële (Thal en/of Toupet) fundoplicatie bij kinderen met GORZ.

LES-rust- en -nadirdruk namen significant toe na LARC, hetgeen in overeenstemming is met eerdere studies naar LARC bij kinderen [6; 13; 28]. Eén van de mechanismen waardoor LARC gastro-oesofageale reflux voorkomt, is een verhoging van de competentie van de gastro-oesofageale overgang, en daarmee is dus een verhoging van de LES-drukken te verwachten na LARC [29-31]. Ook wordt er beschreven dat LARC invloed kan hebben op LES-relaxaties en slokdarmmotiliteit en daardoor postoperatieve dysfagie kan veroorzaken [28]. Onze prospectieve studie liet zien dat LARC geen effect op LES-relaxaties en slokdarmmotiliteit had. In dit cohort ontwikkelde 12% van de kinderen dysfagie na LARC en kwam dysfagie vaker voor bij kinderen met psychomotore retardatie zowel voor als na LARC. Er wordt gedacht dat dysfagie na LARC wordt veroorzaakt door de door fundoplicatie geïnduceerde beperking en postoperatieve zwelling van de gastro-oesofageale overgang [29-31]. De toename in LES rust- en nadirdrukken in het huidige cohort weerspiegelen dit. Eerdere studies naar pediatrische en volwassen ARC toonden vergelijkbare LES-functie na LARC [6; 13; 32].

LARC wordt verricht ter voorkoming van gastro-oesofageale reflux en daarmee het slokdarmslijmvlies te beschermen tegen mogelijke stressoren in het refluxaat. Eerdere studies bij kinderen met GORZ hebben aangetoond dat er sterke negatieve correlatie bestaat tussen de baseline impedantie en blootstelling van zuur aan de slokdarm [23; 33; 34]. **Hoofdstuk vijf** laat het effect van LARC op de baseline impedantie bij kinderen zien als weerspiegeling van de mucosale integriteit. Onze bevindingen waren dat LARC resulteerde in een verhoogde baseline impedantie en een afname van refluxsymptomen. Dit resultaat komt overeen met eerdere studies die een soortgelijke associatie lieten zien tussen PPI behandeling bij kinderen of na endoscopische fundoplicatie volwassenen [23; 35]. Hieruit kan je concluderen dat LARC succesvol is in het elimineren van (zure) reflux en hiermee de baseline impedantie verhoogt. Een verhoging in de baseline impedantie betekent dat de mucosale integriteit herstelt. Hoewel LARC baseline impedantie en refluxsymptomen beiden verbetert, waren deze uitkomsten niet significant met elkaar gecorreleerd. Dit suggereert dat naast de mucosale integriteit, ook inhoud, hoogte tot waar het refluxaat de slokdarm in komt en het volume van de refluxaat, alsmede perifeer en centraal gemedieerde sensitiviteit effect hebben op GERD symptoomperceptie [36].

Na LARC verbeterde de kwaliteit van leven, zowel vanuit het perspectief van de ouders/verzorgers als vanuit kind zelf. In **hoofdstuk zes** probeerden we verder voorspellers die de kwaliteit van leven en het effect van LARC op deze kwaliteit van leven beïnvloeden te identificeren. Kinderen met psychomotore retardatie hadden een lagere kwaliteit van leven, maar het effect van LARC op de verbetering van de kwaliteit van leven was gelijk aan het effect bij kinderen met normale neurologische ontwikkeling.

Alleen leeftijd op het moment van operatie was een statistisch significante voorspeller van verbetering in kwaliteit van leven na LARC. Dit geeft aan dat de oudere kinderen een sterkere verbetering van kwaliteit van leven hebben na LARC dan jongere kinderen. Wanneer jongere kinderen doorverwezen worden in verband met therapieresistente GORZ moeten we voorzichtig zijn in het beslissen tot chirurgische interventies over te gaan. In eerdere literatuur is al eens gesuggereerd dat jongere kinderen meer kans hebben of recidief van GORZ en zelfs vaker een re-fundoplicatie nodig hebben. Dit is gebaseerd op twee retrospectieve studies waarin een regressieanalyse verricht is om risicofactoren van LARC-falen te identificeren [37, 38]. Bovendien zou je kunnen hypothetiseren dat de jongere kinderen in de tijd hun fundoplicatie ontgroeien [7]. Desalniettemin was leeftijd geen belangrijke voorspeller van refluxreductie na LARC wat gemeten werd met een meer objectieve 24-uurs MII-pH-metrie.

Verdere analyse naar voorspellers van het effect van LARC op refluxreductie liet zien dat het aantal preoperatieve refluxepisodes gemeten met MII-pH-metrie een significante voorspeller was. Hieruit kun je concluderen dat hoe meer refluxepisodes op de MII-pH-metrie analyse hoe meer reductie na LARC. Neurologische ontwikkeling, type fundoplicatie, leeftijd en maaglediging hadden geen significant effect op de refluxreductie.

In dit proefschrift waren we uiteindelijk niet in staat om voorspellers van het falen van LARC te identificeren omdat het aantal patiënten dat uiteindelijk faalde na LARC zeer laag was. Tot nu toe is er slechts één onderzoek dat eerder heeft getracht voorspellers van falen te identificeren [39]. Deze studie had echter te weinig patiënten geïncludeerd en was dus niet in staat om een belangrijke voorspeller voor het falen van LARC te identificeren. In de toekomst moeten we dan dus alleen nog maar gerandomiseerde multicenterstudies verrichten die afdoende patiënten includeren en die verschillende technieken en patiënten groepen vergelijken. Daarnaast is het belangrijk dat er een langdurige follow-up plaatsvindt zodat voorspellers van succes geïdentificeerd kunnen worden. Bovendien wordt de prospectieve, multicenterstudie beschreven in dit proefschrift, op de langere termijn vervolgd waarbij de verwachting is dat meer kinderen recidief klachten zullen ontwikkelen. Met een langdurige follow-up kunnen mogelijk wel voorspellers van het falen van LARC op de lange termijn geïdentificeerd worden.

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Fedde Rinsma, ik ben blij dat ik jouw op het motiliteitslab in Maastricht tegenkwam! Ik vond het altijd prettig om samen te filosoferen over de effecten van (chirurgische) interventies in de behandeling van refluxziekte. Uiteindelijk heeft dat geleid tot een paar mooie samen geschreven stukken. Ik hoop dat we dit kunnen voortzetten in de toekomst en ik wens je veel succes in je verdere carrière.

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11. List of publications

Systematic review and meta-analysis of laparoscopic Nissen (posterior total) versus Toupet (posterior partial) fundoplication for gastro-oesophageal reflux disease.
J.A.J.L. Broeders, F.A. Mauritz, U. Ahmed Ali, W.A. Draaisma, J.P. Ruurda, H.G. Gooszen, A.J.P.M. Smout, I.A.M.J. Broeders, E.J. Hazebroek. *British Journal of Surgery 2010; 97: 1318–1330*

Systematische review en meta-analyse van laparoscopische Nissen (posterieure totale) versus Toupet (posterieure partiële) fundoplicatie voor gastro-oesofageale refluxziekte.
F. A. Mauritz, U. Ahmed Ali, W. A. Draaisma, J. P. Ruurda, H. G. Gooszen, A. J. P. M. Smout, I. A. M. J. Broeders, E. J. Hazebroek. *Nederlands Tijdschrift van Heelkunde 2011; jaargang 20, nummer 3: 108-113*

The effects and efficacy of antireflux surgery in children with gastroesophageal reflux disease: a systematic review.
F.A. Mauritz, M.Y.A. van Herwaarden-Lindeboom, W. Stomp , S. Zwaveling, K. Fischer, R.H.J. Houwen, P.D. Siersema, D.C. van der Zee. *Journal of Gastrointestinal Surgery 2011; 15: 1872-1878*

Clinical Outcome in Relation to Timing of Surgery in Chronic Pancreatitis. A Nomogram to Predict Pain Relief.
U. Ahmed Ali, V.B. Nieuwenhuijs, C.H. van Eijck, H.G. Gooszen, R.M. van Dam, O.R. Busch, M.G.W. Dijkgraaf, F.A. Mauritz, S. Jens, J. Mast, H. van Goor, M.A. Boermeester, for the Dutch Pancreatitis Study Group. *Archives of Surgery 2012; 147; 10: 925-932*

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Laparoscopic thal fundoplication in children: A prospective 10- to 15-year follow-up study.
F.A. Mauritz, M.Y.A. van Herwaarden-Lindeboom, S. Zwaveling, R.H.J. Houwen, P.D. Siersema, D.C. van der Zee. *Annals of Surgery 2014; feb; 259(2):388-93*

Efficacy and adverse events of laparoscopic gastrostomy placement in children: results of a large cohort study.
J. Franken, F.A. Mauritz, N. Suksamanapun, C.C. Hulsker, D.C. van der Zee, M.Y.A. van Herwaarden-Lindeboom. *Surgical Endoscopy 2015, June; 29(6): 1545-1552*

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Validation of a Novel 3D Ultrasound Method for assessing Gastric Accommodation.
W. Buisman, M.Y.A. van Herwaarden-Lindeboom, F.A. Mauritz, M. El Ouamari, T. Hausken E.J. Olafsdottir, D.C. van der Zee, O.H. Gilja. *Under revision at Ultrasound in Medicine*

Laparoscopic gastrostomy versus percutaneous endoscopic gastrostomy placement in children: Results of a systematic review and meta-analysis.
N. Suksamanapun, F.A. Mauritz, J. Franken, D.C. van der Zee, M.Y.A. van Herwaarden-Lindeboom. *Submitted*

Evaluation of gastric accommodation: a comparison study of 3D-ultrasound versus dynamic magnetic resonance imaging of gastric volume.
W.J. Buisman, F.A. Mauritz, W.E. Westerhuis, O.H. Gilja, D.C. van der Zee, M.Y.A. van Herwaarden-Lindeboom. *Submitted*

Effects and efficacy of laparoscopic fundoplication in children with GERD: The Dutch prospective, multicenter study.
F.A. Mauritz, J.M. Conchillo, L.W.E. van Heurn, P.D. Siersema, C.E.J. Sloots, R.H.J. Houwen, D.C. van der Zee, M.Y.A. van Herwaarden-Lindeboom. *Submitted*

Quality of life increases after laparoscopic fundoplication in children with GERD: results of a prospective, multicenter study.
F.A. Mauritz, R.K. Stellato, L.W.E. van Heurn, P.D. Siersema, C.E.J. Sloots, R.H.J. Houwen, D.C. van der Zee, M.Y.A. van Herwaarden-Lindeboom. *Submitted*

Esophageal mucosal integrity recovers after laparoscopic antireflux surgery in children with gastroesophageal reflux disease (GERD).
F.A. Mauritz*, N.F. Rinsma*, L.W.E. van Heurn, P.D. Siersema, C.E.J. Sloots, D.C. van der Zee, A.A.M. Masclee, J. M. Conchillo , M.Y.A. Van Herwaarden-Lindeboom. * both authors contributed equally. *Submitted*

Impact of laparoscopic antireflux surgery on belching in pediatric GERD patients.
F.A. Mauritz*, N.F. Rinsma*, L.W.E. van Heurn, P.D. Siersema, C.E.J. Sloots, D.C. van der Zee, A.A.M Masclee, J. M. Conchillo, M.Y.A. Van Herwaarden-Lindeboom. * both authors contributed equally. *Submitted*

Gastrostomy placement affects gastric function in children: a prospective study with the 13c-octanoic acid breath test.
J. Franken*, F.A. Mauritz*, R.K. Stellato, D.C. Van der Zee, M.Y.A. Van Herwaarden-Lindeboom. * both authors contributed equally. *Submitted*

12. Curriculum vitae

Femke Mauritz werd geboren op 4 december 1984 te Nijmegen en groeide op in Wageningen. Na haar middelbare school periode ('t Pantarijn, Wageningen) begon zij in 2003 met de studie Geneeskunde aan de Universiteit van Utrecht. Tijdens haar studie deed zij onderzoek op de afdeling chirurgie onder begeleiding van onder andere dr. U. Ahmed Ali, dr. J.A.J.L. Broeders en prof. dr. H.G. Gooszen. Ook liep zij het co-schap Gynaecologie in het 's Lands Hopitaal te Paramaribo (Suriname), een extra-curriculair co-schap chirurgie in het Hospital Nacional Arzobispo Loayza te Lima (Peru) en haar oudste co-schap chirurgie in het Universitair Medisch Centrum Utrecht. Na het afstuderen volgde een korte periode als arts-assistent chirurgie in het Erasmus Medisch Centrum te Rotterdam. Al spoedig kreeg ze de mogelijkheid om een promotietraject van 3 jaar te starten op de afdeling kinderchirurgie van het Wilhelmina Kinderziekenhuis onder begeleiding van prof. dr. D.C. van der Zee, prof. dr. P.D. Siersema en dr. M.Y.A. van Herwaarden-Lindeboom. Het wetenschappelijk onderzoek naar de effecten en effectiviteit van antirefluxchirurgie bij kinderen heeft uiteindelijk geleid tot dit proefschrift. Na haar tijd als onderzoeker is Femke weer begonnen in de kliniek als arts-assistent chirurgie. Initieel in het Amphia Ziekenhuis te Breda (opleider dr. L. van der Laan) en momenteel is zij werkzaam in het Sint Franciscus Gasthuis te Rotterdam (opleider T.M.A.L. Klem). Femke woont samen met Renz in Den Haag.