Outcomes of pediatric laparoscopic fundoplication: A critical review of the literature

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BACKGROUND/OBJECTIVE: Laparoscopic fundoplication for gastroesophageal reflux disease (GERD) is one of the most common procedures performed in children. A critical literature review was performed to evaluate the level and quality of evidence supporting the efficacy of this procedure.

METHODS: Systematic reviews of the EMBASE, PubMed and CENTRAL databases were conducted to retrieve all articles published over a 15-year period (1996 to 2010) reporting medium- to long-term outcomes (minimum six months follow-up) of laparoscopic fundoplication for the treatment of pediatric GERD. Articles were critically appraised using the Newcastle-Ottawa quality assessment scale and the Cochrane risk of bias assessment tool. Extracted outcomes included GERD recurrence, need for reoperation, postoperative morbidity and mortality.

RESULTS: A total of 5302 articles were retrieved. Thirty-six studies met inclusion and exclusion criteria, including five prospective (level 2b), four retrospective comparative (level 3b) and 27 case series (level 4). No studies compared laparoscopic fundoplication with medical treatment. Thirty-six per cent of studies did not describe the symptoms used to suspect GERD; 11% did not disclose the diagnostic modalities used; and 41% did not report the findings of diagnostic modalities. Only 17% of studies provided a definition of recurrence, and only 14% attempted to control for confounding variables. The follow-up intervals were inconsistently reported, ranging between two months and nine years. Significant heterogeneity among studies limited the ability to pool outcomes. Mean (± SD) recurrence rates varied between 0% and 48±19.6% of patients. Reoperation was required in 0.69±0.95% to 17.7±8.4% of patients. Mortality ranged between 0% and 24±16.7%.

CONCLUSION: The level and quality of the evidence supporting laparoscopic fundoplication are extremely poor. Higher-quality data are required before the procedure can be considered to be an effective intervention in the treatment of pediatric GERD.

Key Words: *Fundoplication; Gastroesophageal reflux disease; Laparoscopic; Pediatric*

Les résultats de la fundoplication laparoscopique en pédiatrie : une analyse bibliographique critique

HISTORIQUE ET OBJECTIF : La fundoplication laparoscopique pour traiter le reflux gastro-œsophagien pathologique (RGOP) est l'une des interventions les plus effectuées chez les enfants. Les chercheurs ont procédé à une analyse bibliographique critique pour évaluer la qualité et la catégorie des preuves en corroborant l'efficacité.

MÉTHODOLOGIE : Les chercheurs ont procédé à l'analyse systématique des bases de données EMBASE, PubMedet CENTRAL pour en extraire tous les articles publiés sur une période de 15 ans (1996 à 2010) rendant compte des résultats à moyen et long terme (minimum de six mois de suivi) de la fundoplication laparoscopique pour traiter le RGOP en pédiatrie. Ils ont effectué l'évaluation critique des articles au moyen de l'échelle d'évaluation de la qualité de Newcastle-Ottawa et de l'outil d'évaluation du risque de biais de Cochrane. Les résultats obtenus incluaient la récurrence du RGOP, le besoin de réopérer, la morbidité postopératoire et la mortalité.

RÉSULTATS : Au total, les chercheurs ont extrait 5 302 articles. Trente-six études respectaient les critères d'inclusion et d'exclusion, soit cinq études prospectives (catégorie 2b), quatre études comparatives prospectives (catégorie 3b) et 27 séries de cas (catégorie 4). Aucune étude ne comparait la fundoplication laparoscopique avec le traitement médical. Trente-six pour cent des études ne décrivaient pas les symptômes retenus pour présumer un RGOP, 11 % ne révélaient pas les modalités diagnostiques utilisées et 41 % ne précisaient pas les résultats des modalités diagnostiques. Seulement 17 % des études incluaient une définition de la récurrence et seulement 14 % cherchaient à contrôler les variables confusionnelles. Les intervalles de suivi, qui n'étaient pas transmis de façon uniforme, variaient entre deux mois et neuf ans. En raison de l'hétérogénéité importante des études, la possibilité de regrouper les résultats était limitée. Le taux de récurrence moyen (± ÉT) variait entre 0 % et 48±19,6 % des patients. Il a fallu réopérer de 0,69±0,95 % à 17,7±8,4 % des patients. Le taux de mortalité se situait entre 0 % et 24±16,7 %.

CONCLUSION : La qualité et la catégorie des preuves en appui à la fundoplication laparoscopique sont extrêmement faibles. Il faudra des données de meilleure qualité avant que l'intervention puisse être considérée comme efficace pour traiter le RGOP en pédiatrie.

The treatment of gastroesophageal reflux disease (GERD) in infants and children presents an ongoing challenge to physicians and surgeons. A step-up approach is recommended beginning with conservative therapies and progressing to acid suppression if symptoms persist (1,2). Laparoscopic fundoplication (LF) is considered when medical treatments have failed (1,2). However, the definition of failure is largely subjective and clinician dependent. Currently, there are no studies comparing medical therapies with LF for the treatment of pediatric GERD. While complications of LF are well documented, the indications are often vague and objective documentation of refractory reflux is often missing (2-4). Despite this, LF remains one of the most common operations performed by pediatric surgeons in the United States.

Published reviews of LF have simply analyzed the data from individual studies without assessment of their quality (5-7). Position papers and treatment guidelines have been formulated by national and international surgical organizations based on the same data, typically without comment on the level of the evidence (6,8). To fill this gap, we conducted a critical review of all articles published from 1996 to 2010 that reported the medium- to long-term outcomes of LF. Our primary goal was to assess the quality of the literature. Our secondary goal was to evaluate reported outcomes.

METHODS

Systematic searches of the EMBASE, PubMed and CENTRAL databases from 1996 to 2010 were conducted in conjunction with

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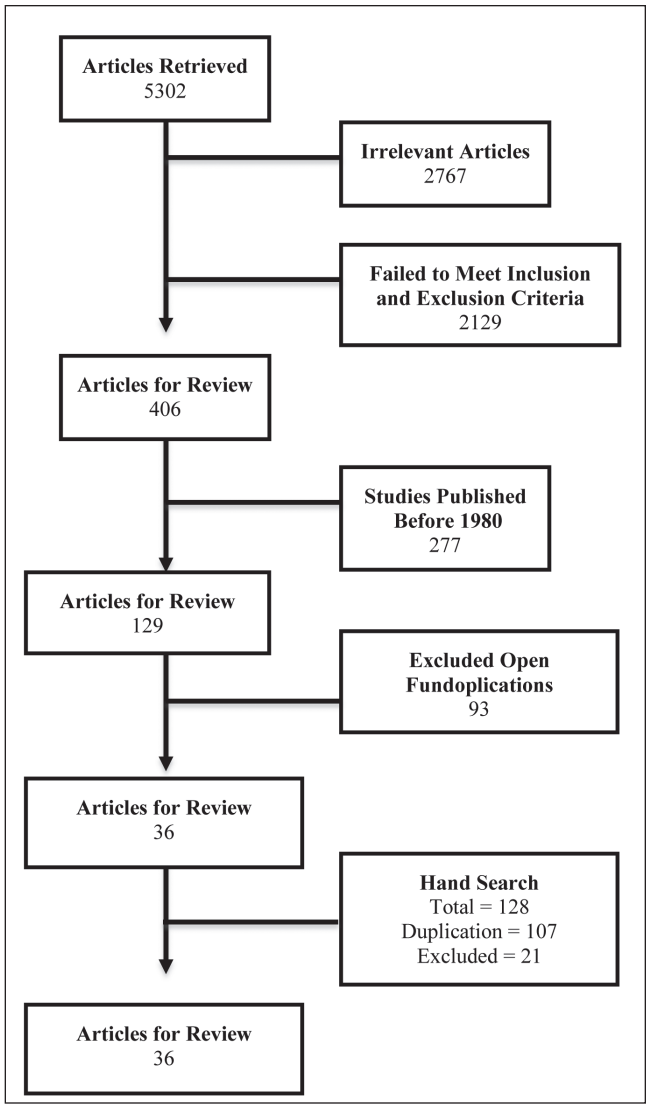

Figure 1) *Article selection*

librarians at the Montreal Children's Hospital, McGill University Health Centre (Montreal, Quebec). All studies reporting the medium- to long-term outcomes of LF in the treatment of pediatric GERD were retrieved. No language limitations were placed. Separate search strategies were formulated for each database using database-specific subject terms, syntax and free-text forms. Queries included a combination of exploded and nonexploded subject headings including the following: "gastroesophageal reflux disease", "GERD", "fundoplication", "anti-reflux surgery" and "pediatrics". Review articles, case series involving <20 patients, editorials and letters were excluded. Articles reporting <50% follow-up at six months were also excluded.

A single investigator reviewed all retrieved citations' titles and abstracts to eliminate those that clearly did not meet inclusion and exclusion criteria. Two independent reviewers reviewed the remaining articles in their entirety for final selection based on the standardized eligibility criteria. Any disagreements in the selection process were resolved through discussion between reviewers. The references of the selected articles were manually searched to identify any additional relevant articles.

The articles were reviewed in detail for quality assessment and data extraction. Data were then pooled and discrepancies dealt with through re-review until consensus was reached. Article quality was determined by study design, a standardized quality assessment form based on the Newcastle-Ottawa quality assessment scale and the Cochrane risk-of-bias assessment tool. Data were extracted using a standardized data extraction form. Extracted data included baseline demographics, diagnostic criteria, study intervention, follow-up details and outcomes, including postoperative mortality, GERD recurrence and need for reoperation.

Quality assessments are reported qualitatively with special attention devoted to study design, confounders, biases and length of follow-up reporting. Outcomes are reported as proportions with 95% CIs. Pooled estimates are presented where appropriate, based on χ^2 testing for heterogeneity.

RESULTS

The literature search retrieved a total of 5302 articles, 36 of which met inclusion and exclusion criteria (Figure 1). A summary of the selected articles is presented in Table 1.

Quality assessment

The retrieved studies all constituted low-level evidence: five prospective comparative studies (level 2b) (9-13), four retrospective comparative studies (level 3b) (14-17) and 27 case series (level 4) (18-44). Three of the prospective studies compared LF in neurologically impaired versus neurologically intact patients. There were no randomized controlled trials of LF versus medical therapy. All nonrandomized comparative studies compared LF with open fundoplication or minor technical modifications in the laparoscopic technique; none compared LF with medical therapy. There were three before-and-after studies (11-13). However, none of these studies clearly described the treatments, if any, that patients received before LF. Thus, the preoperative disease status was largely unknown, making the outcomes difficult to interpret (11-13).

Table 2 outlines the quality features of the selected articles. Only five studies attempted to control for confounders in their analysis. The factors controlled for varied among studies and included age, sex, comorbidities, respiratory status and surgical technique. The percentage of neurological impairment was reported in 78% of studies; however, the majority did not control for this factor in their analysis. Similarly, the rates of esophageal atresia were reported in 22% of studies, none of which controlled for its presence during analysis. No studies controlled for the confounding effects of the learning curve associated with LF.

Bias was present throughout, with only two studies clearly attempting to reduce bias (10,33). The first was a prospective study involving a cohort of institutionalized patients (10). To reduce detection bias, this study used universal pH testing at 12 months postoperatively to detect recurrence and had no patients lost to follow-up. However, the authors did not describe how patients were assigned to LF, raising the possibility of a significant selection bias (10). The second study (33) was a case series that used clear selection criteria for LF, routine pH testing at 12 months to detect recurrence and had no loss to follow-up.

The remaining studies were prone to selection, detection, reporting and attrition bias. With regard to selection bias, the studies failed to adequately describe why patients were selected for LF over other surgical or medical treatments. They also failed to describe the background population from which the reported samples were derived. Detection bias was prevalent due to the lack of a definition of recurrence, which was only present in 17% of studies, as well as the reliance on patient- and caregiver-reported symptoms to trigger further investigations. Only two studies used a standardized follow-up interview with blinded assessors (12,13). Reporting bias was prevalent because studies failed to indicate which outcomes were being investigated a priori. Furthermore, studies failed to report the absence of many common complications, making it unclear whether these did not occur, were not investigated or were omitted. Finally, attrition bias was a common problem because patients were lost to follow-up over time, particularly in studies reporting extended follow-up periods. All studies failed to indicate the features of participants lost to follow-up compared with those remaining in the sample. Follow-up protocols were rarely reported.

TABLE 1
Summary of articles

Author (reference), year	n	Study design	Population	Fundoplication technique
Esposito et al (9), 2001	36	Prospective cohort	<1 year of age	Nissen; Toupet
Cheung et al (10), 2006	20	Prospective cohort	Neurologically impaired	Nissen
Capito et al (11), 2008	127	Prospective cohort	Mixed	Nissen-Rossetti
Engelmann et al (12), 2010	40	Prospective cohort	Mixed	Thal
Engelmann et al (13), 2010	26	Prospective cohort	Mixed	Thal
Somme et al (14), 2002	53	Retrospective cohort	<1 year of age	Nissen
Diaz et al (15), 2005	456	Retrospective cohort	Mixed	Nissen
Barsness et al (16), 2007	26	Retrospective cohort	<1 year of age	Nissen
Curtis et al (17), 2010	384	Retrospective cohort	Mixed	Nissen
Longis et al (18), 1996	30	Case series	Mixed	Nissen-Rossetti; Toupet
Thompson et al (19), 1996	25	Case series	<1 year of age	Nissen
Rothenberg et al (20), 1997	56	Case series	Respiratory disease	Nissen; Nissen-Rossetti
Tovar et al (21), 1998	27	Case series	Mixed	Nissen
Hopkins and Stringel (22), 1999	25	Case series	Mixed	Nissen
Dick and Potts (23), 1999	50	Case series	Mixed	Modified Nissen
Esposito et al (24), 2000	289	Case series	Mixed	Nissen-Rossetti; Toupet
Schleef et al (25), 2000	30	Case series	Mixed	Thal
Liu et al (26), 2001	117	Case series	Mixed	Nissen-Rossetti
Allal et al (27), 2001	142	Case series	Mixed	Nissen; Toupet
Mattioli et al (28), 2002	70	Case series	Mixed	Nissen-Rossetti
Van der Zee et al (29), 2002	149	Case series	Mixed	Nissen; Thal
Pimpalwar et al (30), 2002	54	Case series	Neurologically impaired	Nissen
Mattioli et al (31), 2002	288	Case series	Mixed	Nissen; Toupet; Thal
Esposito et al (32), 2003	80	Case series	Neurologically impaired	Nissen; Thal
Mattioli et al (33), 2004	48	Case series	Neurologically normal	Nissen-Rossetti
Kwiecien et al (34), 2004	132	Case series	Mixed	Toupet
Lima et al (35), 2004	47	Case series	Neurologically impaired	Nissen; Toupet; Dor
Kawahara et al (36), 2004	56	Case series	Neurologically impaired	Nissen; Thal
Okuyama et al (37), 2004	42	Case series	Neurologically impaired	Nissen
Liu et al (38), 2006	368	Case series	Mixed	Nissen-Rossetti
Esposito et al (39), 2006	238	Case series	Neurologically normal	Nissen; Toupet; Thal
Boesch and Acton (40), 2007	25	Case series	Respiratory disease	Nissen
Tannuri et al (41), 2008	151	Case series	Mixed	Nissen
Perger et al (42), 2008	44	Case series	Mixed	Nissen
Mathei et al (43), 2008	106	Case series	Mixed	Nissen
Shariff et al (44), 2008	79	Case series	<1 year of age	Nissen

Outcomes

Mortality was reported by 58% of the studies. All mortalities were attributed to progression of the patients' underlying cardiac, neurological or respiratory disorders. Figure 2 illustrates the reported mortality rates with 95% CIs. The mean (± SD) pooled mortality rate in neurologically impaired children was found to be 17.9±4.9% (χ^2 for heterogeneity P=0.549).

Recurrence rates following LF were reported by 83% of studies. However, only six studies used an explicit definition of recurrence. The reported recurrence rates ranged between 0% and 48±19.6% (Figure 3). Significant heterogeneity existed among the studies, preventing pooling of data (χ^2 for heterogeneity P<0.001).

The need for reoperation following LF was reported in 50% of the studies. A consistent definition of indications for reoperation was absent. Some studies reported the percentage of re-do fundoplications due to recurrent GERD, while others included reoperation for wrap stenosis, pyloroplasty and recurrent hiatal hernia. The rate of reoperation was reported to be between 0.69±0.95% and 17.7±8.4% (Figure 4). Studies reporting neurologically impaired and neurologically normal populations were sufficiently homogenous to allow pooling (χ^2 for heterogeneity P=0.16 and P=0.528, respectively). The pooled estimate for reoperation in neurologically impaired patients was 15.4±4.2%. The pooled estimate for reoperation in neurologically normal patients was 7.0±3.3%. The neurologically impaired group underwent significantly more reoperations than the neurologically normal group (χ^2 P=0.003).

TABLE 2
Summary of quality features

Quality feature	Percentage of studies
Description of % of population with neurological impairment	78
Description of % of population with history of esophageal atresia	22
Description of patient symptoms	64
Description of diagnostic tests	89
Results of diagnostic tests	52
Description of surgical techniques	75
Median and range of follow-up provided	33
Relevant outcomes reported (recurrence, reoperation or death)	100
Clear definition of recurrence given	17
Details regarding complications	92
Attempts to control for confounders	14
Attempts to reduce bias	6

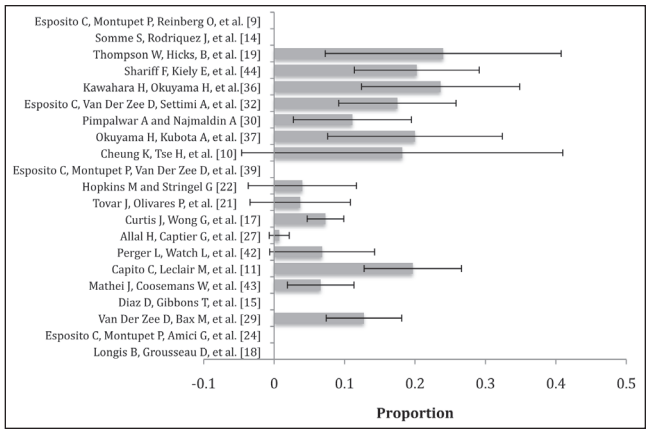

Figure 2) *Mortality rates. Bars represent 95% CIs*

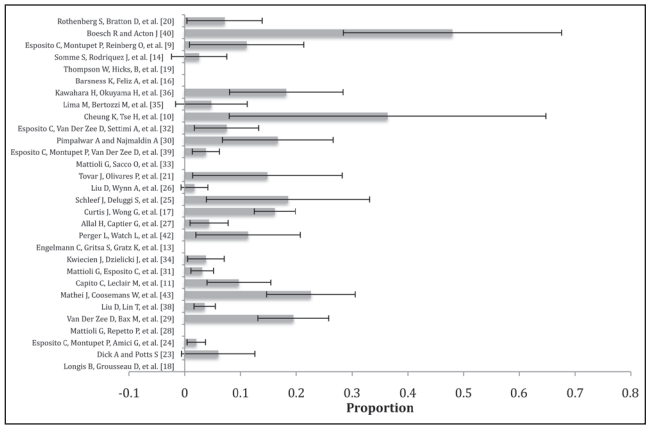

Figure 3) *Recurrence rates. Bars represent 95% CIs*

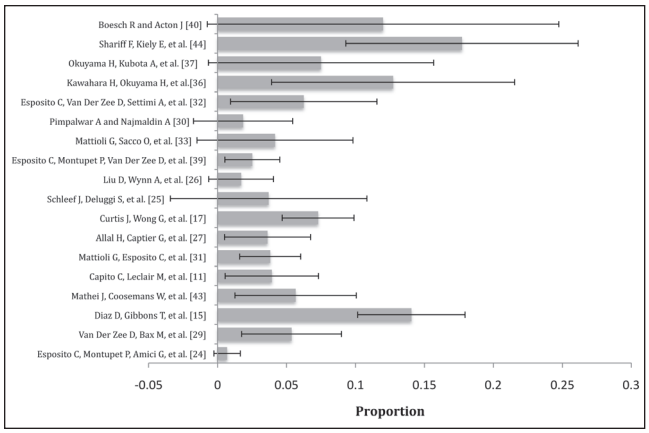

Figure 4) *Reoperation rates. Bars represent 95% CIs*

DISCUSSION

LF is the current standard surgical treatment for refractory pediatric GERD. However, little is known about the long-term outcomes of this procedure and its true effectiveness. The available literature is of extremely poor quality according to evidence-based standards. Presently, there are no randomized trials or prospective cohort studies comparing LF with medical therapy. Thus, there is no conclusive evidence that surgery is superior to medical therapy (4).

In our review, 75% of studies were case series, which are known to favour the described intervention. They lead to false inferences up to 50% of the time (45). Multiple innovative treatments, once believed to be effective based on case series, were subsequently found to be no better than standard treatments when rigorously studied (45). Although nine of the included studies were comparative, none were randomized and three used historical controls. The use of historical controls is often confounded by changes in management, separate from the intervention in question, leading to false inferences in 40% to 60% of cases (45).

Studies frequently failed to adequately describe their study populations, diagnostic criteria, follow-up protocols and outcome measures. The majority of studies indicated the proportion of the study population that was neurologically impaired. However, most failed to analyze this population separately, despite its association with worse outcomes (46). We found a statistically significant difference in reoperation rates between these two groups in our study. Similar concerns exist over studies including patients with esophageal atresia (3). Mixed populations were reported by 57% of reviewed studies. The failure to report and control for underlying comorbidities makes it difficult to apply results to a given patient population (3).

There was also a consistent failure to explicitly outline the diagnostic criteria of GERD, the selection criteria for intervention and the outcome measures used. The lack of criteria for diagnosis and treatment likely relates to the lack of a standard definition of GERD in the pediatric population. An international panel of experts created guidelines in 2009 (1); however, most studies were published before 2009. Furthermore, these guidelines have yet to be universally adopted; therefore, recent studies fail to apply them (1,47). Comparing studies was further hindered by the lack of clear, a priori outcomes and standardized follow-up protocols. Many have called for the use of standardized outcome measures when reporting the efficacy of GERD treatments (3,47-49). However, as noted by Gold et al (49), validated outcome measures do not currently exist. Finally, patient- and parent-reported outcomes were heavily used in this body of literature, increasing the risk of a placebo effect, especially given the subjective nature of many of the reported outcomes. This is compounded by a potential second placebo response due to the natural history of GERD in children, the efficacy of nonpharmacological methods and expectation bias (50). All of these factors likely overestimate the true effectiveness of LF.

The biases present in the analyzed studies further limit the conclusions that can be drawn from them. Selection bias was present because clear inclusion and exclusion criteria were lacking from the majority of the studies. Thus, surgeons were likely to include patients they believed would benefit most from LF, and exclude those considered to be at increased risk of complications. The lack of clear a priori follow-up protocols means that many complications were likely not detected, not reported or both. Significant attrition bias existed due to the failure to account for patients lost to follow-up. The proportion lost to follow-up, as well as the reasons for that loss, was not reported by any of the reviewed studies.

Recurrence rates varied widely. The largest study of open fundoplication, a multicentre retrospective series of 7467 cases (51), reported a recurrence rate of 7%. However, this was probably a gross underestimation because the study was poorly designed to detect recurrence. Objective testing for GERD using esophagogastroduodenoscopy or pH probe was only performed in 54% and 26%, respectively, and the results of this objective testing were not reported (51). The study presented no standard follow-up, no standard assessment of outcomes and no quality of life measures (51). The wide range of recurrences in the current review are likely due to variations in the definition of recurrence and generally poor follow-up data. Studies with very high recurrence rates may have erroneously implicated GERD as the reason for the patient's symptoms (5,52). For example, a recurrence rate of 48±19.6% was found in a population with respiratory disease attributed to GERD (40). The link between respiratory disease and GERD is not firmly established, and several studies have shown no benefit to LF when performed for respiratory indications (48,53,54).

Reoperation was required in all 18 studies reporting this outcome. The indications for reoperation varied among studies and included recurrence, wrap failure, esophageal stenosis, recurrent hiatal hernia and pyloroplasty for postoperative delayed gastric emptying. The pooled estimate of reoperation rate in neurologically impaired patients was 15.4±4.2% versus 7.0±3.3% in neurologically normal patients. Neurologically impaired patients also had the highest mortality rates, along with patients undergoing fundoplication before their first birthday (19,36). These differences support the notion that neurologically impaired patients experience worse outcomes after LF (55). LF should be considered a palliative procedure for many of these patients and the surgeon should openly share the outcome information to provide the family with realistic expectations.

Prospective studies comparing LF with medical therapies are needed. Although, a randomized controlled trial would be optimal, it is unlikely to occur due to the wide adoption of LF by surgeons and parents alike as a common treatment option for pediatric GERD. A well-designed multicentre prospective cohort study using matched controls is a more realistic option. Such a study should aim to provide long-term follow-up and provide subgroup analysis to determine the long-term effects of LF in different populations. In the meantime, adoption of a universal definition of GERD may allow more objective selection of patients for LF (47). The use of standard outcome measures, as suggested by Gold et al (49), can create uniformity in the literature, allowing meaningful comparisons among studies. The enthusiasm for LF in children should be tempered until higher-quality evidence is available to support its long-term efficacy.

SUMMARY

Pediatric LF is one of the most common operative procedures performed in children. Multiple case series and several reviews of pediatric LF have been published over the past 15 years. However, none of the reviews critically evaluated the quality of the literature from an evidence-based perspective. We performed a critical review of the literature on pediatric LF outcomes over a 15-year period. Our results indicate that the level and quality of the evidence supporting LF are extremely poor. Higher-quality data are required before the procedure can be considered to be an effective intervention for the treatment of pediatric GERD.

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