

Laparoscopic Nissen fundoplication for gastro-oesophageal reflux disease in infants

Ling Leung · Carol Wing Yan Wong ·
Patrick Ho Yu Chung · Kenneth Kak Yuen Wong ·
Paul Kwong Hang Tam

Accepted: 14 October 2014 / Published online: 28 October 2014
© Springer-Verlag Berlin Heidelberg 2014

Abstract

Introduction Data on laparoscopic Nissen fundoplication for gastro-oesophageal reflux disease (GERD) in infants remain limited. We describe our experience with this operation in children and in particular, infants younger than 12 months old.

Materials and methods Medical records of all paediatric patients who had laparoscopic fundoplication done for GERD from 1998 to 2013 were reviewed. Patients were divided into two groups based on age: group I: 0–12 months, and group II >12 months. Data on indications, patient's demographics, operative time, blood loss, conversions, complications, recurrences and duration of hospitalization were studied.

Results A total of 86 patients were reviewed (group I, $n = 21$; group II, $n = 65$). While the mean age and body weight for group I were 8 ± 2.99 months and 6 ± 1.96 kg, the values for group II were 98 ± 65 months and 18 ± 9.6 kg, respectively. All patients had concurrent laparoscopic gastrostomy for feeding difficulties. The mean operative time was shorter in group I (157 ± 55 vs 169 ± 52 min, $p = 0.66$). Both groups had minimal blood loss only. The surgical outcomes in both groups were comparable in terms of recurrence (0 vs 3 %, $p = 0.105$) and complications (9.5 vs 6 %, $p = 0.275$). The median follow-up duration for group I and group II was 23 and 40 months, respectively. Sixteen (76 %) patients in group I and 45 (67 %) patients in group II did not develop pneumonia post fundoplication.

Conclusion Laparoscopic Nissen fundoplication can be safely performed in infants with outcomes comparable to older patients and a shorter operative duration. Low recurrence rate (up to 3 %) is shown by our long term follow-up data. We recommend laparoscopic Nissen fundoplication to be considered in managing infants with GERD.

Keywords Children · Fundoplication · Gastro-oesophageal reflux · Laparoscopy

Introduction

Laparoscopic Nissen fundoplication in children to treat gastroesophageal reflux disease (GERD) was first reported in 1991 by Dallemagne et al. [1]. Subsequent large scale studies by Rothenberg et al. has shown laparoscopic fundoplication to be a safe and effective treatment [2–4]. Recent meta-analysis reported laparoscopic Nissen fundoplication had better outcomes when compared with the open technique, with a shorter hospital stay, earlier full feeding, less morbidity and no difference in recurrence [5]. Data on laparoscopic Nissen fundoplication for GERD in infants remain limited. Some studies demonstrated its safety and efficacy in infants, [6–8] whereas other showed a higher incidence of intra-operative complications in infants weighing less than 5 kg [9]. We describe our experience with this operation in children and in particular, infants younger than 12 months old.

Materials and methods

Medical records of all paediatric patients who had laparoscopic fundoplication from 1998 to 2013 in our centre were

L. Leung · C. W. Y. Wong · P. H. Y. Chung ·
K. K. Y. Wong (✉) · P. K. H. Tam
Division of Paediatric Surgery, Department of Surgery,
The University of Hong Kong, Queen Mary Hospital,
Pokfulam Road, Hong Kong
e-mail: kkywong@hkucc.hku.hk

reviewed. The data collected included patient age, body weight at operation, diagnosis, associated anomalies, pre-operative investigations, operating time, blood loss, conversion, complications, recurrence, hospital stay and duration of follow-up. Patients were divided into two groups based on age: group I (0–12 months) and group II (>12 months). All paediatric surgical patients who underwent laparoscopic fundoplication for symptomatic GERD with objective evidence as shown by investigations were included. All patients had undergone one or more of the following investigations: 24 h pH study, impedance, contrast study, oesophagogastrroduodenoscopy and milk scan. Exclusion criteria are patients with malrotation, hiatal hernia with gastric volvulus, oesophageal atresia and tracheoesophageal fistula or congenital diaphragmatic hernia. Recurrence was defined as GERD demonstrated by 24 h pH below 4 for >5 % of the time of the study or by contrast study.

Operative technique

All operations were done under general anesthesia with the patient in supine position. A large bore Ryle's tube was inserted into the stomach as a temporary oesophageal stent. A 5 mm sub-umbilical camera port was inserted; three more 5 mm working ports were inserted at left and right flanks, left upper quadrant (stomach retractor). The pressure of pneumoperitoneum was limited to 8–10 mmHg of carbon dioxide. A Nathanson liver retractor was inserted below the xyphisternum to expose the oesophagogastric junction. The oesophagogastric and phreno-oesophageal ligaments were divided. The right and left diaphragmatic crus were identified. We did not routinely divide the short gastric vessels. We usually found that the fundus in most cases were floppy enough without the need to divide short gastric vessels. Nissen fundoplication was completed by creating a tension free wrap with four interrupted 2/0 Ethibond sutures. Gastrostomy was performed in the same operative session for patients having feeding difficulties. Outcome measures included the following: recurrence, conversion, complication, operative time, blood loss and duration of hospitalization. All patients were followed up in our outpatient clinic in 1 week, 6 weeks, 2, 3 and then 6 months intervals. Contrast follow-through and/or 24 h pH study was arranged for those who were symptomatic to detect recurrence. Statistical analysis was performed using unpaired *t* test and Pearson test, a *p* value of <0.05 was considered to be statistically significant.

Results

A total of 121 patients underwent laparoscopic fundoplication from 1998 to 2003. Thirty-five patients were

Table 1 The demographics of the patients recruited in this study

Patient demographics	Age <12 months (<i>N</i> = 21)	Age >12 months (<i>N</i> = 65)
Sex		
Male	10 (48 %)	34 (52 %)
Female	11 (52 %)	31 (48 %)
Symptoms		
Failure to thrive	3 (14 %)	4 (6 %)
Feeding intolerance	9 (43 %)	23 (35 %)
Aspiration pneumonia	11 (52 %)	33 (51 %)
Oesophagitis	0	4 (6 %)
Epigastric pain	0	1 (2 %)
Neurologically impaired	16 (76 %)	59 (91 %)
Ventilator dependence	4 (19 %)	1 (2 %)
Other major congenital anomalies	11 (52 %)	30 (46 %)

excluded. Twenty were due to prolonged hospitalization for medical problems, 7 due to oesophageal atresia and tracheo-oesophageal fistula, 6 due to hiatal hernia and gastric volvulus, 1 due to malrotation and 1 due to congenital diaphragmatic hernia. Twenty-one patients were included in group I and 65 in group II. The demographic data of patients were summarized in Table 1. Eleven (52 %) of group I and 30 (46 %) of group II patients had other major congenital anomalies. Four (24 %) in group I and 9 (13 %) in group II had metabolic disease, 3 (14 %) of group I had myopathy, 5 (7 %) had brain malformation and 3 (4 %) had cleft lip and palate in group II. Sixteen (76 %) of group I and 59 (91 %) of group II were neurologically impaired. All patients underwent pre-operative investigations to diagnose GERD. Twenty-four hour pH monitoring or impedance was done in 16 (76 %) of group I and 46 (71 %) of group II. Other investigations performed included contrast meal, videofluoroscopic swallowing study, milk scan and oesophagoduodenogastroscopy. All patients had feeding difficulties and had gastrostomy performed in the same operative session.

The mean age and weight at operation, operative time (including time for laparoscopic gastrostomy in the same operative session), blood loss, average hospital stay, number of conversion and recurrence were presented in Table 2. The blood loss was 0 ml for group I and 6 ± 22.2 for group II and it was statistically significant ($p = 0.01$). There was no conversion in group I whereas there was 1 (1.5 %) conversion in group II ($p = 0.261$). The procedure was converted open due to bleeding from short gastric artery. Post operative course was uneventful and the patient was discharged on day 9. No recurrence occurred in group I. Two (3 %) patients had recurrence in group II ($p = 0.105$). Three (4.5 %) patients in group II underwent

Table 2 The clinical data of the two groups of patients

	Age <12 months (N = 21)		Age >12 months (N = 65)		p value
	Range		Range		
Mean age (months)	7.7 ± 2.99	(2.6–12)	98 ± 65	(17–228)	<0.001
Mean weight (kg)	6.4 ± 1.96	(3.6–11)	18 ± 9.6	(6.2–64.5)	<0.001
Average operative time (min)*	157 ± 54.7	(74–315)	169 ± 51.5	(95–352)	0.66
Average blood loss (ml)	0	0	6 ± 22.2	(0–100)	0.01
Average hospital stay (days)	10 ± 11.69	(4.0–45)	9 ± 11.7	(2.0–72)	0.42
Conversion to open (N)	0		1 (1.5 %)		0.261
Recurrences (N)	0		2 (3 %)		0.105
Redo-fundoplication (N)	0		3 (4.5 %)		0.043

* Including laparoscopic gastrostomy

Table 3 Complications of fundoplication in the two groups of patients

	Age <12 months (N = 21)	Age >12 months (N = 65)
Major complications	2 (9.5 %)	4 (6 %)
Gastrostomy leakage	1	2
Fundal perforation	1	0
Pyloric stenosis	0	1
Gastrocolic fistula	0	1
Other complications	1 (4.7 %)	14 (22 %)
Gastrostomy infection	1	10
Gastroparesis/ileus	0	3
Liver laceration	0	1

laparoscopic redo-fundoplication ($p = 0.043$). All recurrences were due to wrap disruption and redo-fundoplication was performed at 2, 6 and 8 years after the first fundoplication, respectively. Two out of three of these patients were neurologically impaired. One of the three redo-fundoplication was a complication from another hospital and therefore was not counted as recurrence in our series.

The complications in both groups were included in Table 3. Two (9.5 %) major complications occurred in group I and 4 (6 %) in group II ($p = 0.275$). In group I, one patient had gastrostomy site infection and leakage requiring revision of gastrostomy. The other patient in group I was 5.87 kg at operation, had fundal perforation during gastrostomy procedure and required insertion of gastroduodenal tube. The hospital stay for the two patients was 10 and 28 days, respectively. There were two gastrostomy leakages in group II, and both required revision of gastrostomy. One of the two patients later developed gastric outlet obstruction after revision and required pyloroplasty. One patient presented with gastrocolic fistula 11 years after the operation and it was repaired.

One (4.7 %) in group I and 14 (22 %) in group II developed other complications ($p = <0.001$). The most common was gastrostomy infection; it occurred in 1

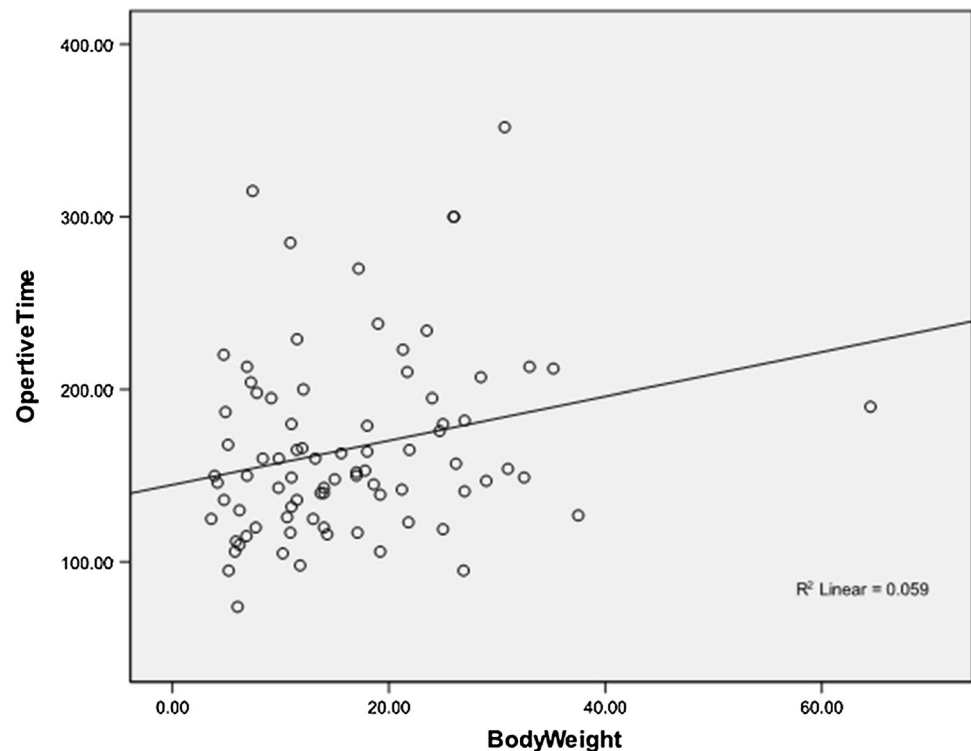
(4.7 %) patient in group I and 14 (22 %) in group II. All gastrostomy infections were treated conservatively by daily dressing, topical or oral antibiotics. In group II, 3 patients had gastroparesis and 1 had intra-operative liver laceration. All patients who had gastroparesis were neurologically impaired; they were discharged on post operative days 9–22. The patient who had minor liver laceration resulting from retractor placement did not have significant bleeding and was discharged on day 7.

A statistically significant correlation was identified between the operative time and body weight of patient at operation (Pearson correlation = 0.243, $p = 0.028$), as shown in Fig. 1. When the first 15 cases were excluded from data analysis for consideration of learning curve, the correlation was still found to be significant with Pearson correlation = 0.256, $p < 0.05$. No other statistically significant correlation was found between recurrence, conversion, complication, blood loss and body weight of patient at operation. All patients were seen in our outpatient clinic after the operation. The median follow-up duration for group I and group II were 23 and 40 months, respectively. Sixteen (76 %) patients in group I and 45 (67 %) patients in group II did not develop pneumonia post fundoplication.

Discussion

GERD is a result of persistent gastric reflux causing complications such as failure to thrive, aspiration pneumonia, oesophagitis, oesophageal stricture and sudden infant death syndrome. Neurologically impaired children are particularly at risk due to oesophageal dysmotility, increased muscle spasticity and gag reflex [10]. GERD requires treatment to avoid the potential complications. In our series, majority of the patients who underwent laparoscopic fundoplication were neurologically impaired (76 % of group I and 91 % of group II). In contrast to adult patients, lifestyle modification is not a first-line treatment since neonates and infants have

Fig. 1 Plot graph showing the correlation between operative time and body weight of patients



shorter intra-abdominal oesophagus and their diet is predominantly fluid [11, 12]. Regarding medical treatment options, the efficacy for proton pump inhibitor or prokinetics in neonates and infants remained unproven [13, 14]. Therefore, fundoplication is indicated to correct GERD in neonates and infants.

Laparoscopic Nissen fundoplication in children was first reported in the early 1990s [1]. Since then, laparoscopic fundoplication have been shown to decrease the length of stay, time to full enteral feeds and analgesic requirement when compared with the open technique [15, 16]. Some studies also demonstrated improvement in pulmonary status in patients with respiratory compromise [17–19]. It has become the standard treatment of GERD in most tertiary centers. Rothenberg et al. [3, 19, 20] described the outcome of the largest series of laparoscopic Nissen fundoplication. The recurrence rate was reported to be 3.2 % and a significant decrease in morbidity and hospitalization was found. No conversions to open surgery occurred after the first 3 years of the study, and all major complications occurred in the first 5 years of the study. The reported intra-operative and postoperative complication rates were 0.13 and 4.0 %, respectively. The recurrence rate and the need for redo procedure in patients younger than a year of age are higher (6.4 %). Comparison of open and laparoscopic fundoplication in the neonatal intensive care unit population had been reported by Thatch et al. [21]. Laparoscopic group showed a

significantly shorter time to goal feed and a lower 24-hour postoperative narcotic requirement compared to open group. No acute complication was reported in the laparoscopic group. However, data on recurrence, conversion and other complications were not mentioned. A meta-analysis by Siddiqui et al. [5] analyzed six comparative studies which found patients in the laparoscopic group have shorter hospital stay, earlier feeding and less morbidity. There was no significance difference in recurrence at 12 months. A combined conversion rate of 2 % was found. However, the studies were all non-randomized and were heterogeneous in which there were differences in the age of patients and their neurological status. The authors suggested laparoscopic fundoplication should be considered as a first-line operative technique when expertise is available.

Whilst fundoplication has been performed in children, its safety and efficacy in neonates and infants are still debated. The major advantage of laparoscopic fundoplication in neonates and infants is to avoid the potential complications of GERD. It had been suggested that in children with neurological impairment or other systemic conditions, erosive oesophagitis could occur when the child reaches 2 years of age [22]. However, the operation can be more technically demanding in neonates and infants due to a narrow surgical field. This group of patients also has a higher anesthetic risk, intolerance of pneumoperitoneum and hypothermia.

Table 4 Table showing results of our study with other studies

	Esposito et al.	Shah et al.	Shariff et al.	Our centre
No of patients	36	122	79	21
Median age (months)	7	7	6	8
Median weight (kg)	4.7	3.7	5.6	6.0
Neurologically impaired (%)	28	29	61	76
Associated anomalies (%)	42	41	19	52
Conversion	1 (3 %)	8 (7 %)	2 (2.5 %)	0
Recurrences	4 (11 %)	3 (3 %)	22 (28 %)	0
Complications	3 (8 %)	6 (5 %)	16 (20 %)	2 (9.5 %)
Redo-fundoplication	4 (11 %)	2 (2 %)	14 (18 %)	0

Published outcomes of laparoscopic Nissen fundoplication in infants and neonate age group were limited. Several studies advocated safety and feasibility of laparoscopic fundoplication in infants [6–8]. Other studies argued against the safety of this operation in neonates. Iwanaka et al. [9] reported significantly increased intra-operative complications in infants weighing less than 5 kg compared with those weighing greater than 10 kg (33 vs 4.3 %). However, their findings could be affected by the small number of cases and the learning curve of surgeon.

A comparison of our results and those of the published series was shown in Table 4. Esposito et al. [6] reported favorable results in 36 infants with GERD who underwent laparoscopic fundoplication. Three (8.3 %) had an intra-operative complication of bleeding from a diaphragmatic vessel, pneumothorax and severe hiatal hernia. Four (11.1 %) redo procedures were performed, 2 were due to wrap disruption or migration. One major drawback of this study is that the operative technique was not standardized. Shah et al. [7] reported 8 (7 %) conversions in patients weighing less than 5 kg, which were all due to dense intraperitoneal adhesions. Three (2.5 %) patients had recurrence, one of which required laparoscopic redo-fundoplication. Reported intra-operative complications included gastric fundus perforation, intra-operative bleeding from an accessory hepatic artery at the time of liver retractor placement. In their study, the operations were done by different attending surgeons. Late complications and follow-up duration were not mentioned. Shariff et al. [8] studied patients who were under 1 years old. They reported three intra-operative complications, one bleeding from liver edge, one pneumothorax and one intolerance of pneumoperitoneum. Two (2.5 %) needed conversion to open. No factors that predict recurrence or complications were identified. Late mortality of 20 % was reported; none was related to the operation.

Our recurrence rate of 3 % in the 12 months or older group is comparable to previously published rates in other series. Hiatal hernia and wrap disruption are the leading causes for recurrence requiring redo-fundoplication. Similar to the published series, no mortality related to surgery was reported. Complications were mostly gastrostomy related, similar complications were also reported by Shah et al. [7] and Shariff et al. [8]. One limitation of our study is the small sample size of patients in group I.

Our series demonstrated a shorter operative duration, zero conversion, mortality and recurrence rates in infants. A low recurrence rate (up to 3 %) in older children was also shown. We recommend laparoscopic Nissen fundoplication to be safe and feasible in managing GERD even in small infants. Most of the complications in our series were gastrostomy related, we would like to make the following recommendations. Firstly, to minimize gastrostomy wound infection, antibiotic prophylaxis should be prescribed and the wound should be reviewed early in the postoperative course. Should infection occurs, it should be treated promptly with daily dressing. Wound swab should be taken and antibiotic to be adjusted accordingly. Secondly, potential liver injury can be avoided by careful placement of retractor and its position can be adjusted periodically for optimal exposure. Thirdly, methylene blue injection via the gastrostomy under direct laparoscopic vision is a useful method in detecting iatrogenic perforation.

In conclusion, laparoscopic Nissen fundoplication can be safely performed in infants with outcomes comparable to older patients and a shorter operative duration. Low recurrence rate (up to 3 %) is shown by our long term follow-up data. We recommend laparoscopic Nissen fundoplication to be considered in managing infants with GERD.

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Dallemagne B, Weerts JM, Jehaes C, Markiewicz S, Lombard R (1991) Laparoscopic Nissen fundoplication: preliminary report. *Surg Laparosc Endosc* 1(3):138–143
2. Zaninotto G, Molena D, Ancona E (2000) A prospective multicenter study on laparoscopic treatment of gastroesophageal reflux disease in Italy: type of surgery, conversions, complications, and early results. Study Group for the Laparoscopic Treatment of Gastroesophageal Reflux Disease of the Italian Society of Endoscopic Surgery (SICE). *Surg Endosc* 14(3):282–288
3. Rothenberg SS (2013) Two decades of experience with laparoscopic nissen fundoplication in infants and children: a critical evaluation of indications, technique, and results. *J Laparoendosc Adv Surg Tech Part A* 23(9):791–794. doi:10.1089/lap.2013.0299

4. Rothenberg SS (2005) The first decade's experience with laparoscopic Nissen fundoplication in infants and children. *J Pediatr Surg* 40(1):142–146. doi:[10.1016/j.jpedsurg.2004.09.031](https://doi.org/10.1016/j.jpedsurg.2004.09.031) discussion 147
5. Siddiqui MR, Abdulaal Y, Nisar A, Ali H, Hasan F (2011) A meta-analysis of outcomes after open and laparoscopic Nissen's fundoplication for gastro-oesophageal reflux disease in children. *Pediatr Surg Int* 27(4):359–366. doi:[10.1007/s00383-010-2698-y](https://doi.org/10.1007/s00383-010-2698-y)
6. Esposito C, Montupet P, Reinberg O (2001) Laparoscopic surgery for gastroesophageal reflux disease during the first year of life. *J Pediatr Surg* 36(5):715–717. doi:[10.1053/jpsu.2001.22943](https://doi.org/10.1053/jpsu.2001.22943)
7. Shah SR, Jegapragasan M, Fox MD, Prince JM, Segura BJ, Kane TD (2010) A review of laparoscopic Nissen fundoplication in children weighing less than 5 kg. *J Pediatr Surg* 45(6):1165–1168. doi:[10.1016/j.jpedsurg.2010.02.078](https://doi.org/10.1016/j.jpedsurg.2010.02.078)
8. Shariff F, Kiely E, Curry J, Drake D, Pierro A, McHoney M (2010) Outcome after laparoscopic fundoplication in children under 1 year. *J Laparoendosc Adv Surg Tech Part A* 20(7):661–664. doi:[10.1089/lap.2010.0213](https://doi.org/10.1089/lap.2010.0213)
9. Iwanaka T, Uchida H, Kawashima H, Nishi A, Kudou S, Satake R (2004) Complications of laparoscopic surgery in neonates and small infants. *J Pediatr Surg* 39(12):1838–1841. doi:[10.1016/j.jpedsurg.2004.08.011](https://doi.org/10.1016/j.jpedsurg.2004.08.011)
10. Pensabene L, Miele E, Del Giudice E, Strisciuglio C, Staiano A (2008) Mechanisms of gastroesophageal reflux in children with sequelae of birth asphyxia. *Brain Dev* 30(9):563–571. doi:[10.1016/j.braindev.2008.01.009](https://doi.org/10.1016/j.braindev.2008.01.009)
11. Boix-Ochoa J, Canals J (1976) Maturation of the lower esophagus. *J Pediatr Surg* 11(5):749–756
12. Omari TI, Barnett CP, Benninga MA, Lontis R, Goodchild L, Haslam RR, Dent J, Davidson GP (2002) Mechanisms of gastro-oesophageal reflux in preterm and term infants with reflux disease. *Gut* 51(4):475–479
13. van der Pol RJ, Smits MJ, van Wijk MP, Omari TI, Tabbers MM, Benninga MA (2011) Efficacy of proton-pump inhibitors in children with gastroesophageal reflux disease: a systematic review. *Pediatrics* 127(5):925–935. doi:[10.1542/peds.2010-2719](https://doi.org/10.1542/peds.2010-2719)
14. Vadlamudi NB, Hitch MC, Dimmitt RA, Thame KA (2013) Baclofen for the treatment of pediatric GERD. *J Pediatr Gastroenterol Nutr* 57(6):808–812. doi:[10.1097/MPG.0b013e3182a2747b](https://doi.org/10.1097/MPG.0b013e3182a2747b)
15. Collins JB, Georgeson KE, Vicente Y, Hardin WD, Jr (1995) Comparison of open and laparoscopic gastrostomy and fundoplication in 120 patients. *J Pediatr Surg* 30(7):1065–1070 discussion 1070–1061
16. Meehan JJ, Georgeson KE (1996) Laparoscopic fundoplication in infants and children. *Surg Endosc* 10(12):1154–1157
17. Rothenberg SS, Bratton D, Larsen G, Deterding R, Milgrom H, Brugman S, Boguniewicz M, Copenhaver S, White C, Wagener J, Fan L, Chang J, Stathos T (1997) Laparoscopic fundoplication to enhance pulmonary function in children with severe reactive airway disease and gastroesophageal reflux disease. *Surg Endosc* 11(11):1088–1090
18. Diaz DM, Gibbons TE, Heiss K, Wulkan ML, Ricketts RR, Gold BD (2005) Antireflux surgery outcomes in pediatric gastroesophageal reflux disease. *Am J Gastroenterol* 100(8):1844–1852. doi:[10.1111/j.1572-0241.2005.41763.x](https://doi.org/10.1111/j.1572-0241.2005.41763.x)
19. Rothenberg S, Cowles R (2012) The effects of laparoscopic Nissen fundoplication on patients with severe gastroesophageal reflux disease and steroid-dependent asthma. *J Pediatr Surg* 47(6):1101–1104. doi:[10.1016/j.jpedsurg.2012.03.013](https://doi.org/10.1016/j.jpedsurg.2012.03.013)
20. Rothenberg SS (1998) Experience with 220 consecutive laparoscopic Nissen fundoplications in infants and children. *J Pediatr Surg* 33(2):274–278
21. Thatch KA, Yoo EY, Arthur LG, Finck C, Katz D, Moront M, Prasad R, Vinocur C, Schwartz MZ (2010) A comparison of laparoscopic and open Nissen fundoplication and gastrostomy placement in the neonatal intensive care unit population. *J Pediatr Surg* 45(2):346–349. doi:[10.1016/j.jpedsurg.2009.10.073](https://doi.org/10.1016/j.jpedsurg.2009.10.073)
22. Rudolph CD, Mazur LJ, Liptak GS, Baker RD, Boyle JT, Colletti RB, Gerson WT, Werlin SL, North American Society for Pediatric G, Nutrition (2001) Guidelines for evaluation and treatment of gastroesophageal reflux in infants and children: recommendations of the North American Society for Pediatric Gastroenterology and Nutrition. *J Pediatr Gastroenterol Nutr* 32(Suppl 2):S1–S31