European Thyroid Journal

Clinical Thyroidology / Systematic Review

Eur Thyroid J 2021;10:39–51
DOI: 10.1159/000511345

Received: February 14, 2020
Accepted: August 9, 2020
Published online: November 17, 2020

Thyroidectomy in Pediatric Patients with Graves' Disease: A Systematic Review of Postoperative Morbidity

Annabel S. Zaat[a] Joep P.M. Derikx[b] Nitash Zwaveling-Soonawala[a]
A.S. Paul van Trotsenburg[a] Christiaan F. Mooij[a]

[a]Department of Pediatric Endocrinology, Emma Children's Hospital, Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands; [b]Department of Pediatric Surgery, Emma Children's Hospital, Amsterdam UMC, University of Amsterdam and Vrije Universiteit, Amsterdam, The Netherlands

Key Words
Graves' disease · Thyroidectomy · Postoperative morbidity · Pediatric Graves' disease

Abstract
Background: Graves' disease (GD) is the most common cause of hyperthyroidism. In children, the overall relapse frequency after treatment with antithyroid drugs is high. Therefore, many pediatric GD patients eventually require thyroidectomy as definitive treatment. However, the postoperative complications of thyroidectomy in pediatric GD patients are poorly reported. ***Objective:*** To identify the frequency of short- and long-term postoperative morbidities after thyroidectomy in pediatric GD patients. ***Methods:*** A systematic review of the literature (PubMed and Embase) was performed to identify studies reporting short- and long-term postoperative morbidities after thyroidectomy in pediatric GD patients according to the PRISMA guidelines. ***Results:*** Twenty-two mainly retrospective cohort studies were included in this review evaluating short- and long-term morbidities in 1,424 children and adolescents. The frequency of transient hypocalcemia was 22.2% (269/1,210), with a range of 5.0–50.0%. The frequency of permanent hypocalcemia was 2.5% (36/1,424), with a range of 0–20.0%. Two studies reported high frequencies of permanent hypocalcemia, 20.0 (6/30) and 17.4% (9/52), respectively. The 20% frequency could be explained by low-volume surgeons in poorly controlled GD patients. Only 21 cases of permanent hypocalcemia were reported in the 1,342 patients included in the other 20 studies (1.6%). Transient and permanent recurrent laryngeal nerve injury were reported less frequently, with frequencies between 0–20.0 and 0–7.1%, respectively. Infection, hemorrhage/hematoma, and keloid development were only rarely reported as postoperative complications. ***Conclusion:*** The results of this systematic review suggest that thyroidectomy is a safe treatment option for pediatric GD patients. The minority of patients will experience transient and benign morbidities, with hypocalcemia being the most common transient postoperative morbidity. Permanent postoperative morbidities are relatively rare.

A.S. Paul van Trotsenburg and Christiaan F. Mooij contributed equally.

karger@karger.com
www.karger.com/etj

Karger
OPEN ACCESS

Christiaan F. Mooij
Department of Pediatric Endocrinology
Emma Children's Hospital, Amsterdam UMC, University of Amsterdam
Meibergdreef 9, NL–1105 AZ Amsterdam (The Netherlands)
c.mooij@amsterdamumc.nl

Introduction

Graves' disease (GD) is the most common cause of hyperthyroidism in both adults and children [1]. For patients with hyperthyroidism due to GD, there are 3 well-known and effective treatment options: antithyroid drugs (ATDs), radioactive iodine (RAI), and thyroidectomy. RAI and thyroidectomy aim to eradicate overactive thyroid tissue and subsequently achieve euthyroidism by thyroid hormone treatment. The preferred treatment method remains controversial, varies among institutions and physicians, and depends on patient characteristics and preferences. Yet, for newly diagnosed pediatric GD patients, ATDs are predominantly first-line treatment in Europe and are generally well tolerated [2, 3]. Unfortunately, the overall relapse frequency is high in children, and only a minority of pediatric GD patients (20–30%) experience a lasting remission [3–5]. Therefore, most pediatric GD patients eventually need definitive treatment.

RAI and thyroidectomy are both effective definitive treatment options for hyperthyroidism in pediatric GD patients [6]. Thyroidectomy is the only definitive treatment option for patients younger than 5 years and the preferred definitive treatment option for 5- to 10-year-old patients and patients with a large goiter and for patients with an increased cancer risk [5]. In addition, patients suffering from mechanical or cosmetic dysfunction due to an enlarged thyroid gland benefit from thyroidectomy. If thyroidectomy is proposed in pediatric GD patients, total thyroidectomy is the preferred surgical method, resulting in lower recurrence rates compared to subtotal or near-total thyroidectomy [2, 5]. Thyroidectomy in pediatric GD patients is considered a safe treatment option with a reported mortality rate below 0.1% [7]. Therefore, it is important to be well-informed about postoperative morbidity. Postoperative complications of thyroidectomy are predominantly transient and include hypocalcemia and recurrent laryngeal nerve (RLN) injury, although these complications may be permanent. To minimize these complications, it is recommended that thyroidectomy is performed by a high-volume thyroid surgeon who performs >30 thyroid surgeries annually [5]. Especially in pediatric patients, it is important to be informed about the risk of permanent postoperative morbidities, as they may require lifelong calcium or active vitamin D supplementation or long-lasting RLN neuropraxia. Data on postoperative morbidities in pediatric patients after thyroidectomy are relatively scarce, and high-quality research is lacking. In this study, we performed the first systematic literature search on this topic to identify the frequency of short- and long-term postoperative morbidities after thyroidectomy in pediatric GD. Presenting an overview of available data on postoperative morbidities of thyroidectomy in this patient group is not only helpful, but also imperative for preoperative counseling of the patients and their parents.

Methods

This systematic review was performed following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) 2009 guidelines [8] and was registered with PROSPERO (ID = CRD42020180889).

Literature Search

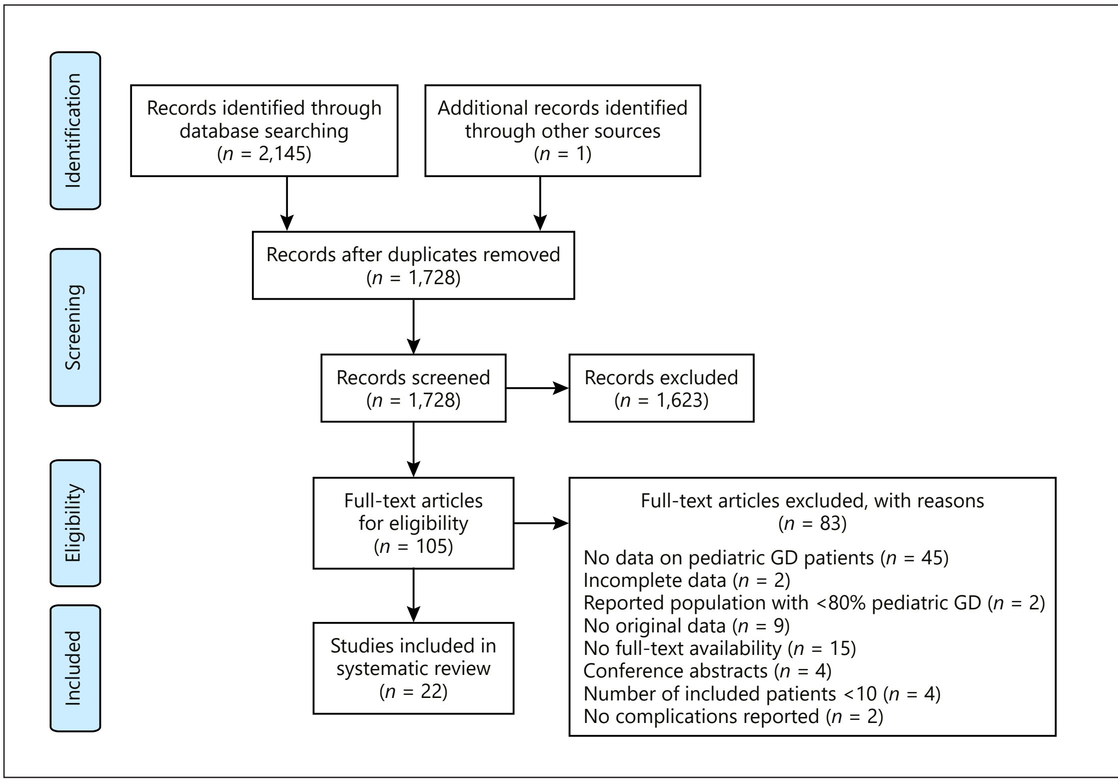
The literature search was performed using the electronic databases PubMed and Embase in April 2020 to identify studies evaluating short- and long-term postoperative morbidities in pediatric GD patients undergoing thyroidectomy. The following keywords were used: (Graves' Disease) AND (Child OR Adolescent OR Juvenile) AND (Thyroidectomy OR Thyroid surgery OR Surgery). The exact search strategy used for both the PubMed and Embase databases is available as supplemental data. No time frame was used for the literature search. The search was extended by scanning the references of relevant articles and using the "related article" function of the databases.

Study Selection and Quality Assessment

Title and abstract screening was performed independently and blinded by A.S.Z. and C.F.M. using the Rayyan web app for systemic reviews [9]. Full text screening was performed by A.S.Z. and discussed with C.F.M., and in case of discussion, a third reviewer (A.S.P.T.) was consulted. Original studies on pediatric and/or adolescent GD patients who underwent a thyroidectomy reporting on postoperative morbidities in a minimum of 10 GD patients were included. When a study reported data on postoperative morbidities in pediatric patients who underwent a thyroidectomy because of a benign thyroid disorder, and the studied cohort consisted of ≥80% GD patients but data were not specified for GD patients only, the study was included as well. Full text availability was the last inclusion criterion. Exclusion criteria were conference abstracts, review articles, and articles published in another language than English, Dutch, German, French, Italian, or Spanish. Part of the full text screening was a critical appraisal to evaluate the quality per study following the Newcastle-Ottawa Scale (NOS), a quality assessment form for cohort studies. As (almost) all studies had a retrospective and observational character without comparison to another cohort, we did not score for comparability of the cohort(s). Studies were rated as low, fair, or good quality based on the number of stars scored in the selection and outcome domain: 3 stars for good quality, 2 stars for fair quality, and 0 or 1 star for low quality. Only studies that scored 3 stars in both domains were rated as overall good quality.

Data Extraction

Data extraction was performed by A.S.Z. and was double-checked by C.F.M. Data on hypocalcemia (transient and perma-



Color version available online

Fig. 1. Flowchart illustrating the results of the literature search on studies evaluating postoperative morbidity in pediatric patients GD. GD, Graves' disease.

nent), RLN injury (transient and permanent), infection, hemorrhage/hematoma, and keloid development were collected. Furthermore, the used definitions and diagnostic criteria for the reported morbidities were collected from each included study. The differences herein will be discussed in the Results and Discussion sections. Although the diagnostic criteria and methods differed between the studies, we calculated the cumulative reported frequency of each postoperative morbidity to give an indication of the overall frequency of postoperative morbidity.

Results

Study Characteristics

The PubMed and Embase searches were performed on April 14, 2020, and yielded 1,728 unique articles. 1,623 articles were excluded after title and abstract screening, and an additional 83 articles were excluded after full text screening. Twenty-two mainly retrospective observational cohort studies were included in this review (Fig. 1). Based on the quality assessment, the quality of 4 of the included studies was rated as good [10–13], whereas the quality of the other 18 studies was rated as fair (see online suppl. Table 1; for all online suppl. material, see www.karger.com/doi/10.1159/000511345).

These 22 studies reported on the postoperative morbidity of 1,424 children and adolescents. The majority of the studied patients were female (Table 1). Thirteen studies focused mainly on total or near-total thyroidectomy (n = 705) [10, 11, 13–23]. In addition, Lobe and Wright [24] reported results in pediatric patients who underwent total thyroidectomy via a transaxillary endoscopic approach (n = 31). Subtotal thyroidectomy was performed in 5 studies (n = 550) [16, 25–28]. Four studies did not specify the surgical method used in the patients with GD (n = 110) [12, 29–31]. The mean duration of follow-up after surgery ranged widely among the studies (1–100 months). Cohen et al. [23] received additional follow-up data by calling patients who were not seen in the clinic over the previous 2 years. Table 1 also shows in which studies thyroidectomies were performed by a high-volume or a low-volume surgeon. Eight studies reported that the thyroidectomy was performed by a high-volume surgeon [10, 11, 13–15, 21, 29, 31]. In the study by Cohen et al. [23], surgery was performed by a low-volume surgeon.

Table 1. Characteristics of included studies evaluating postoperative morbidities of thyroidectomy in pediatric patients with GD

Study	Study period	Study design	Patients	Age, years	Performed surgery	High- versus low-volume surgeon	Follow-up, months, mean (range)
Akkari et al. [30]	2004–2012	Retrospective cohort study	*n* = 14[1]	<17	Not specified for patients with GD. Predominantly total thyroidectomy in entire study	Not reported	Minimum of 6 months in patients with postoperative hypoparathyroidism
Baumgarten et al. [21]	2009–2017	Retrospective cohort study	*n* = 123[1]	≤24 (range 2–24)	Total thyroidectomy	High (30/year)	Not reported
Bergman et al. [25]	1985–1999	Retrospective cohort study	*n* = 10 Girls: 9 Boys: 1	<19	Subtotal thyroidectomy	Not reported	20.4 [2.4–60]
Breuer et al. [14]	2002–2010	Case-control study	*n* = 32 Girls: 26 Boys: 6	<17.9	Total and near-total thyroidectomy	High (30/year)	Not reported
Chen et al. [29]	1992–2013	Retrospective cohort study	*n* = 22[1]	<19	Total and subtotal thyroidectomy; not specified for patients with GD	High (50/year)	36 [0–204]
Chiapponi et al. [15]	2000–2010	Retrospective matched case-control study	*n* = 21 Girls: 19 Boys: 2	<18	Total thyroidectomy	High (3,000/10 years)	Not reported
Cohen et al. [23]	2002–2014	Retrospective cohort study	*n* = 30 Girls: 24 Boys: 6	<18.9	Total thyroidectomy	Low (<7/year)	28.8
De Jong et al. [20]	1998–2018	Retrospective cohort study	*n* = 52[1]	≤18	Total thyroidectomy	Not reported	Not reported
Elfenbein et al. [31]	2009–2013	Retrospective cohort study	*n* = 31 Girls: 27 Boys: 4	<18	Unknown	High (100/year)	Not reported
Lobe and Wright [24]	2005–2009	Retrospective cohort study	*n* = 31[2] Girls: 26 Boys: 5	Mean age 12.7	Total thyroidectomy using TATE approach	Not reported	Not reported
Machens et al. [10]	1994–2018	Retrospective cohort study	*n* = 58 Girls: 51 Boys: 7	≤18	Total thyroidectomy	High	64.9 [4–227]
Nordenström et al. [13]	2004–2014	Retrospective cohort study	*n* = 214[1]	<18	Total thyroidectomy	High (100/year) in majority of reported patients	57.6 [15.6–82.8]
Peroni et al. [11]	1991–2009	Retrospective cohort study	*n* = 27 Girls: 22 Boys: 5	<18	Total thyroidectomy	High	48 [8–144]
Perzik [17]	1962–1972	Retrospective cohort study	*n* = 41 Girls: 32 Boys: 9	<19	Total thyroidectomy	Not reported	Not reported

Table 1 (continued)

Study	Study period	Study design	Patients	Age, years	Performed surgery	High- versus low-volume surgeon	Follow-up, months, mean (range)
Raval et al. [18]	1997–2007	Retrospective cohort study	$n = 15^3$	<14	Total thyroidectomy	Not reported	12.9 [6–34]
Sherman et al. [16]	1986–2003	Retrospective cohort study	$n = 78$ Girls: 68 Boys: 10	<18	Total and near-total (77%) and bilateral subtotal thyroidectomy (23%)	Not reported	47 [1–216]
Sinha et al. [12]	1987–2011	Retrospective cohort study	$n = 43^4$ Girls: 32 Boys: 11	<18	Total, near-total and subtotal thyroidectomy. Not specified for patients with GD	Not reported	16.8 [3.6–174]
Söreide et al. [27]	1979–1993	Retrospective cohort study	$n = 82$ Girls: 64 Boys: 18	≤18	Bilateral subtotal (86%), unilateral total combined with contralateral subtotal (7%) and total thyroidectomy (6%)	Not reported	99.6 [1–180]
Sugino et al. [26]	1989–1998	Retrospective cohort study	$n = 419^5$	≤20	Bilateral subtotal thyroidectomy	Not reported	62 [24–139]
Witte et al. [28]	1986–1997	Retrospective cohort study	$n = 21$ Girls: 18 Boys: 3	<18	Bilateral subtotal (71%), hemithyroidectomy (24%), and total thyroidectomy (5%)	Not reported	56.7
Yu et al. [22]	2002–2016	Retrospective cohort study	$n = 22^1$	≤21	Total thyroidectomy	Not reported	16.8 [0.5–128.4]
Zobel et al. [19]	2012–2019	Retrospective cohort study	$n = 38^{1,6}$	<21	Total thyroidectomy	Not reported	19

GD, Graves' disease; n = number of patients included with GD; TATE, transaxillary totally endoscopic. [1] Gender distribution within the studied population not specified for patients undergoing a thyroidectomy because of GD. [2] 87% ($n = 27/31$) of the patients included in this study with benign (para-)thyroid disorders underwent a thyroidectomy because of GD. [3] 80% ($n = 12/15$) of the patients included in this study with benign thyroid disorders underwent a thyroidectomy because of GD. [4] 84% ($n = 36/43$) of the patients included in this study with benign thyroid disorders underwent a thyroidectomy because of GD. [5] Age group: 15 years old or younger. $n = 74$: 61 girls and 13 boys. Gender distribution within the adolescents studied is not presented clearly. [6] Four of the patients who underwent a thyroidectomy because of GD were diagnosed with thyroid carcinoma based on pathology findings.

Table 2. The definitions and diagnostic methods used for postoperative morbidities in included studies on thyroidectomy in children with GD

Study	Transient hypocalcaemia	Permanent hypocalcaemia	Transient RLN injury	Permanent RLN injury	Infection	Hemorrhage	Keloid development
Akkari et al. [30]	Hypocalcemia resolved <6 months postoperatively. Diagnostic criteria not reported	Hypocalcemia >6 months postoperatively	–	Postoperative permanent RLN injury. Intraoperative RLN nerve monitoring was used. Not further specified	–	–	–
Baumgarten et al. [21]	Serum calcium <8.7 mg/dL or ionized calcium <1.1 mmol/L. Calcium supplementation required <6 months postoperatively	Persistently low calcium and PTH requiring calcium supplementation >6 months postoperatively	Vocal cord palsy confirmed with laryngoscopy in patients with intraoperative loss of signal (RLN monitor) and/or signs of neuropraxia. Symptoms resolve <6 months postoperatively	Vocal cord palsy confirmed with laryngoscopy lasting >6 months postoperatively	–	Bleeding requiring reoperation	–
Bergman et al. [25]	ns	ns	ns	ns	–	ns	ns
Breuer et al. [14]	Serum calcium <7.5 mg/dL without symptoms of hypocalcemia or serum calcium <8.0 mg/dL with clinical symptoms requiring (i.v.) calcium therapy	ns	RLN neuropraxia or hoarseness confirmed and followed up with laryngoscopy. Resolving <18 months postoperatively	ns	–	Hematoma requiring reoperation	–
Chen et al. [29]	Serum calcium <8.0 mg/dL requiring oral or i.v. calcium supplementation <6 months postoperatively	Requiring calcium supplementation >6 months postoperatively with serum calcium <8.0 mg/dL or PTH <15 pg/mL	Hoarseness and laryngoscopic confirmation of RLN palsy resolving <6 months postoperatively	Hoarseness and laryngoscopic RLN palsy lasting >6 months postoperatively	–	–	–
Chiapponi et al. [15]	Serum calcium <2.0 mmol/L or clinical symptoms requiring calcium supplementation	ns	Pre- and postoperative vocal cord function examination was performed by an independent ENT staff member. Diagnostic criteria not further specified	ns	–	ns	–
Cohen et al. [23]	Serum calcium <7.5 mg/dL requiring calcium and calcitriol supplementation <6 months postoperatively	Calcium and calcitriol supplementation required >6 months postoperatively	ns – hoarseness was not defined as transient RLN injury	ns	–	–	ns
de Jong et al. [20]	Serum calcium <2.15 mmol/L within 24 h postoperatively and calcium and alfacalcidol supplementation required on discharge up to 6 months postoperatively	Oral calcium and alfacalcidol supplementation required >6 months postoperatively	–	–	–	–	–
Elfenbein et al. [31]	Clinical signs of hypocalcemia that improved with oral or i.v. calcium supplementation. Supplementation required <6 months postoperatively	Clinical signs of hypocalcemia that require calcium carbonate treatment (>2,000 mg/day) to improve >6 months postoperatively	Visual damage to RLN or loss of signal of RLN during surgery and hoarseness resolving <6 months postoperatively	Hoarseness persisting >6 months postoperatively. Confirmed by laryngoscopy	–	–	–
Lobe and Wright [24]	ns	ns	ns	ns	–	ns	–
Machens et al. [10]	Signs and symptoms of postoperative hypoparathyroidism requiring calcium and vitamin D replacement <6 months	Calcium and vitamin D supplementation required >6 months postoperatively	Vocal fold palsy evaluated by pre- and postoperative laryngoscopy resolving within 6 months postoperatively	Vocal fold palsy >6 months postoperatively	Wound infection requiring reoperation	Wound hemorrhage requiring reoperation	–
Nordenström et al. [13]	–	Requiring active vitamin D treatment >6 months postoperatively	–	–	–	–	–
Peroni et al. [11]	Serum calcium <7.5 mg/dL requiring supplementation of calcium and calcitriol <6 months postoperatively	Requiring calcium and calcitriol supplementation >6 months postoperatively	ns	ns	ns	ns	ns
Perzik [17]	ns	ns	ns	ns	ns	ns	–
Raval et al. [18]	Duration: <6 months Ionized calcium <1.2 mmol/L and calcium supplementation at discharge up to 6 months postoperatively	Requiring calcium supplementation >6 months postoperatively	Postoperative hoarseness requiring laryngoscopic confirmation	ns	ns	ns	ns
Sherman et al. [16]	Hypocalcemia resolving <10 days	ns	ns	ns	ns	ns	–

Table 2 (continued)

Study	Transient hypocalcaemia	Permanent hypocalcaemia	Transient RLN injury	Permanent RLN injury	Infection	Hemorrhage	Keloid development
Sinha et al. [12]	Low calcium postoperatively requiring oral or i.v. calcium and vitamin D treatment postoperatively (not further specified)	Requiring oral calcium and vitamin D supplementation indefinitely	Temporary voice change	Permanent hoarseness or postoperative stridor with laryngoscopic confirmation	Wound infection requiring antibiotics	Bleeding requiring reoperation	–
Söreide et al. [27]	ns	ns	ns	ns	ns	ns	–
Sugino et al. [26]	Hypocalcemia based on serum calcium levels and physical examination the morning after surgery (not further specified)	ns	Hoarseness evaluated on the basis of objective and laryngoscopic findings, resolving <6 months postoperatively	ns	–	Bleeding requiring reoperation	–
Witte et al. [28]	ns	ns	ns	ns	–	–	–
Yu et al. [22]	Postoperative hypocalcemia with serum calcium <8 mg/dL or ionized calcium <1.0 mmol/L	Serum calcium <8.0 mg/dL requiring calcium supplementation for >1 year postoperatively and PTH <15 pg/mL without evidence of parathyroid recovery	–	–	–	–	–
Zobel et al. [19]	Serum calcium <8.0 mg/dL or symptoms of hypocalcemia requiring treatment with calcium and vitamin D <12 months postoperatively	Requiring supplementation with calcium and vitamin D >12 months postoperatively	–	–	–	–	–

RLN, recurrent laryngeal nerve; ns, not specified; –, morbidity not studied in this study; GD, Graves' disease.

The remaining 13 studies did not report whether thyroidectomies were performed by a low- or a high-volume surgeon [12, 16–20, 22, 24–26, 28, 30]. In 3 studies, thyroidectomies were performed by a pediatric surgeon [14, 21, 22], in 3 studies by an endocrine surgeon [11, 26, 29], and in 4 by both pediatric and adult surgeons [12, 18, 19, 31]. In the other studies, the surgeon's background was not specified.

In most studies, the majority of patients were initially treated with ATDs prior to thyroidectomy. Some studies specified the indication for thyroidectomy in their patients, including drug refractory hyperthyroidism, history of thyroid storm, noncompliance to ATD treatment, side effects of ATDs, compressive symptoms due to goiter, a coexisting suspicious thyroid nodule, concomitant germinoma, or the patient's choice. In the study by Sherman et al. [16], 3 patients underwent thyroidectomy after failure of RAI treatment to achieve euthyroidism. Preoperative thyroid hormone levels were reported by Cohen et al. [23] and indicated hyperthyroidism (mean free T4 3.2 ng/dL [41.19 pmol/L] and mean total T3 338.7 ng/dL [5.20 nmol/L]). Patients in the study of Peroni et al. [11] received preoperative preparation with Lugol's solution and were euthyroid or hypothyroid as assessed by TSH measurement. Sherman et al. and Breuer et al. [14, 16] did not report thyroid hormone concentrations before thyroidectomy, but their patients were preoperatively prepared with beta-blocker, Lugol's solution, or saturated solution of potassium, probably achieving euthyroidism or hypothyroidism at the moment of thyroidectomy. Söreide et al. [27] reported that medical treatment before surgery consisted of iodine (93% of the patients), beta-blocker (73%), and ATD treatment (62%), but they did not specify thyroid hormone concentrations at the time of surgery. Sugino et al. [26] reported all patients to be euthyroid at the time of surgery, without reporting the used preoperative treatment protocol. The other included studies did not report on preoperative preparation or preoperative thyroid hormone levels in their patients [10, 13, 15, 17–22, 24, 25, 28–31]. Further characteristics of the included studies are shown in Table 1. The definitions and diagnostic methods used for the individual postoperative morbidities varied widely between the studies or were not specified in some of the studies (Table 2). None of the studies reported cases of postoperative mortality.

Hypocalcemia

Transient Hypocalcemia

The reported frequency of transient hypocalcemia ranged from 5.0 to 50.0%, with a cumulative reported fre-

Table 3. The reported frequency of postoperative morbidities after thyroidectomy in pediatric patients with GD

Study	Transient hypocalcaemia, %	Permanent hypocalcaemia, %	Transient RLN injury, %	Permanent RLN injury, %	Infection, %	Hemorrhage/ hematoma, %	Keloid development, %
Akkari et al. (*n* = 14) [30]	21.4	7.1	–	7.1	–	–	–
Baumgarten et al. (*n* =123) [21]	38.2[2]	0.8	2.4	0	–	4.1	–
Bergman et al. (*n* = 10) [25]	50.0	0	20.0	0	–	0	0
Breuer et al. (*n* = 32) [14]	18.8	0	6.3	0	–	0	–
Chen et al. (*n* = 22) [29]	29.2	0	–	0	–	–	
Chiapponi et al. (*n* = 21) [15]	28.6	0	4.8	0	–	4.8	–
Cohen et al. (*n* = 30) [23]	26.7	20.0	0[3]	0	–	–	3.3
de Jong et al. (*n* = 52) [20]	48.1	17.4	–	–	–	–	–
Elfenbein et al. (*n* =31) [31]	35.5	3.2	9.7	3.2	–	–	–
Lobe and Wright (*n* = 31) [24]	9.7	0	9.7	0	–	3.2	–
Machens et al. (*n* = 58) [10]	29.3	0	3.4	0	3.4	3.4	–
Nordenström et al. (*n* = 214) [13]	–	7.0	–	–	–	–	–
Peroni et al. (*n* = 27) [11]	14.8	3.7	11.1	0	0	0	7.4
Perzik (*n* = 41) [17]	22.0	0	7.3	0	2.4	2.4	–
Raval et al. (*n* = 15) [18]	46.7	6.7	0	0	0	0	0
Sherman et al. (*n* = 78) [16]	6.4	0	1.3	0	0	0	–
Sinha et al. (*n* = 43) [12]	9.0	0	2.0	2.0	0	0	–
Söreide et al. (*n* = 82) [27]	5.0	0	4.0	0	0	1.2	–
Sugino et al. (*n* = 419) [26]	17.9	0	6.7	0	–	1.4	–
Witte et al. (*n* = 21) [28]	9.5	4.8	9.5	4.8	–	–	–
Yu et al. (*n* = 22) [22]	45.5	0	–	–		–	–
Zobel et al. (*n* = 38) [19]	14.7	0	–	–	–	–	–
All studies combined[1]	22.2 (*n* = 269/1,210)	2.5 (*n* = 36/1,424)	5.4 (*n* = 57/1,062)	0.4 (*n* = 4/1,098)	0.9 (*n* = 3/344)	1.7 (*n* = 17/980)	3.7 (*n* = 3/82)

n, number of patients included in the study; RLN, recurrent laryngeal nerve; GD, Graves' disease. [1] The reported frequency of the studies combined is calculated based on the reported frequencies in the individual studies regardless of the used diagnostic criteria for the postoperative morbidities. [2] Baumgarten et al. [21] reported transient hypocalcemia and transient hypoparathyroidism separately. The reported frequency of transient hypoparathyroidism was 22% (*n* = 22 out of 123). [3] Cohen et al. [23] reported that patients commonly experienced hoarseness that resolved by the subsequent clinical follow-up visit. The frequency was not quantified and hoarseness was not scored as transient RLN injury.

quency of 22.2% (269 out of 1,210 patients) (Table 3). Baumgarten et al. [21] reported transient hypocalcemia and transient hypoparathyroidism separately, with a reported frequency of transient hypoparathyroidism of 22% (*n* = 22 out of 123). De Jong et al. [20] reported both hypocalcemia at 24 h after thyroidectomy (48.1%) and hypoparathyroidism on discharge (46.2%; *n* = 24 out of 52). Zobel et al. [19] (*n* = 38) reported hypocalcemia immediately after surgery in 17 GD patients, with only 1 patient still being hypocalcemic after 6 months. This patient regained normal parathyroid function 1 year after surgery. This observation of regaining normal parathyroid function 1 year after surgery was also described in most children who underwent a total thyroidectomy because of another benign thyroid disorder or because of thyroid cancer [19]. Chen et al. [29] stated that GD was an independent risk factor to develop postoperative hypocalcemia in children undergoing a thyroidectomy (OR 3.99; $p = 0.02$).

Permanent Hypocalcemia

The frequency of permanent hypocalcemia ranged from 0 to 20.0%, with a cumulative reported frequency of 2.5% (36 out of 1,424 patients) (Table 3). The studies by Cohen et al. [23] and de Jong et al. [20] reported relatively high frequencies of permanent hypocalcemia of 20 and 17.4%, respectively. The other 20 studies reported (very) low frequencies of permanent hypocalcemia, with 13 studies reporting no cases of permanent hypocalcemia [10, 12, 14–17, 19, 22, 24–27, 29]. In these 20 studies, 1,342 patients were evaluated, and only 21 of them (1.6%) fulfilled the used criteria for permanent hypocalcemia.

RLN Injury

Transient RLN Injury

The reported frequency of transient RLN injury ranged from 0 to 20.0%, with a cumulative reported frequency of 5.4% (57 out of 1,062 patients) (Table 3). Cohen et al. [23] reported that patients commonly experienced hoarseness directly after surgery that had resolved at the next clinical follow-up visit. It was not specified if hoarseness was thought to be caused by RLN injury or intubation. Cohen et al. [23] did not quantify or score transient hoarseness as transient RLN injury.

Permanent RLN Injury

Four studies reported that one of their patients was diagnosed with permanent RLN injury (Table 3) [12, 28, 30, 31]. The other 14 studies evaluating RLN injury reported no cases of permanent RLN injury [10, 11, 14–16, 21, 23, 25, 26]. The cumulative reported frequency of permanent RLN injury was 0.4% (4 out of 1,098 patients). None of the studies reported on postoperative superior laryngeal nerve injury.

Infection

The frequencies of postoperative infections were reported in 7 studies [10–12, 16–18, 27]. Only 3 out of 344 evaluated patients were reported with a postoperative infection (cumulative reported frequency 0.9%) (Table 3). In 1 patient, the infection required reoperation [9]; in 1 patient, it required open drainage [16]; and 1 patient was treated with antibiotics [11].

Hemorrhage/Hematoma

Hemorrhage, postoperative bleeding, or a hematoma as a postoperative complication of thyroidectomy in pediatric GD patients was evaluated in 13 studies [10–12, 14–18, 21, 24–27]. The reported frequency of hemorrhage ranged from 0 to 4.8%, with a cumulative reported frequency of 1.7% (17 out of 980 patients) (Table 3). Despite the low reported frequency of hemorrhage after thyroidectomy, GD patients seem to have a higher risk of postoperative bleeding compared to patients who underwent a thyroidectomy for another cause (RR = 8.7 [95% CI: 1.06–71.85]; $p = 0.02$) [20]. A possible explanation for the higher risk of hemorrhage in GD patients may be the hypervascularity of the thyroid gland in these patients.

Keloid Development

Only 4 of the included studies evaluated the frequency of postoperative keloid development after thyroidectomy in pediatric GD patients [11, 18, 23, 25]. The reported frequency ranged from 0 to 7.4%, with a cumulative reported frequency of 3.7% (3 out of 82 patients) (Table 3).

Discussion

In this systematic review, we report the short- and long-term postoperative morbidities after thyroidectomy in pediatric patients with GD. Twenty-two studies evaluating 1,424 children and adolescents were included. The calculated cumulative frequencies of permanent hypocalcemia and RLN injury are low (2.5 and 0.4%, respectively). In contrast, transient hypocalcemia and transient RLN injury are more common, with reported complication rates of 6.5–50.0 and 0.0–20.0%, respectively. Fortunately, transient hypocalcemia and transient RLN injury are benign conditions. Transient hypocalcemia is well manageable with oral calcium and calcitriol administration [32]. In most cases, the function of the RLN will return spontaneously (median recovery time of 8 weeks), with speech therapy being the most common performed treatment [33]. These frequencies are comparable with those reported in adult GD patients after thyroidectomy (transient hypocalcemia in approximately 25% and permanent in 4%) [34]. The same applies to RLN palsy (in adults, permanent in <1%) [34]. Specific data on postoperative morbidities in pediatric GD patients who underwent a thyroidectomy are essential for adequate preoperative counseling of the patients and their parents.

Hypocalcemia

Hypocalcemia is the most common complication after thyroidectomy in pediatric GD. The primary cause of hypocalcemia is damage to or devascularization of the parathyroid glands during surgery. Therefore, in some studies, "hypoparathyroidism" and not "hypocalcemia" was reported as a postoperative morbidity. Transient hypocalcemia, which normally resolves within 6 months after thyroidectomy, can be distinguished from permanent hypocalcemia when calcium or active vitamin D supplementation (either oral or intravenous) is required for a longer time [32]. Although we calculated a cumulative frequency of hypocalcemia, it is important to realize that the definition of hypocalcemia was not uniform throughout the various included studies (Table 2). Cutoff serum levels for diagnosing hypocalcemia ranged from 1.87 to 2.15 mmol/L (equal to 7.5–8.7 mg/dL) in the included studies. In 10 studies, the diagnosis of hypocalcemia was solely based on serum calcium levels [10–12, 15, 18, 20–23, 29]. In contrast, in some studies, the presence of clinical symptoms (hand paresthesia, perioral numbness, muscle cramps, and Chvostek's sign) was combined with serum calcium levels to diagnose postoperative hypocalcemia [14, 19, 26]. Elfenbein et al. [31] diagnosed hypocalcemia solely based on the presence of clinical symptoms (numbness or tingling of the hands, feet, or mouth after surgery) that improved after calcium supplementation. Overall, uniformity considering diagnostic criteria and cutoff values of hypocalcemia was missing. Furthermore, 10 of the included studies considered hypocalcemia to be permanent if recovery has not occurred within 6 months [10, 11, 13, 18, 20, 21, 23, 29–31]. Yu et al. [22] discussed this cutoff of 6 months because in their cohort, recovery of hypocalcemia occurred as late as 33 months. In addition, Cohen et al. [23] reported cases of "permanent" hypocalcemia that restored after 24 months and 5.7 years. Yu et al. [22] recommended to prolong the follow-up to at least 1 year for determining the permanence of hypocalcemia. This recommendation is supported by the finding of Zobel et al. [19] that most patients regain normal parathyroid function within 1 year after surgery. Based on the results of this systematic review, we suggest considering hypocalcemia as permanent if recovery has not occurred within 6 months after surgery. However, one should realize that parathyroid function can normalize even several years after thyroidectomy [21, 22]. We recommend to use a uniform cutoff value to diagnose hypocalcemia after thyroidectomy. It is our clinical experience that postoperatively patients often experience a transient drop in serum calcium levels that resolves quickly and does not lead to clinical signs of hypocalcemia. We suggest maintaining different cutoff levels for defining hypocalcemia post-thyroidectomy depending on the presence or absence of symptoms; patients *with* clinical symptoms of hypocalcemia (serum calcium level <2.0 mmol/L [8.0 mg/dL]) versus patients *without* clinical signs of hypocalcemia (serum calcium level <1.9 mmol/L [7.5 mg/dL]). This will prevent unnecessary calcium supplementation and shorten postoperative hospitalization.

Transient hypocalcemia is the most frequently reported morbidity after thyroidectomy performed in pediatric GD. In contrast, permanent hypocalcemia is relatively rare. This finding may be explained by the fact that the damaged parathyroid glands heal in the first months after surgery. The studies by Cohen et al. and de Jong et al. [20, 23] reported remarkably high complication rates of permanent hypocalcemia: 20.0 and 17.4%. Cohen et al. [23] hypothesized that the relatively high complication rate of permanent hypocalcemia in their cohort may be explained by the fact that poorly controlled GD patients were studied, which may increase the risk of postoperative complications. Furthermore, a low number of annually performed thyroidectomies by the surgeons in this study were raised as an additional explanation for the high complication rate. None of the surgeons in the study of Cohen et al. [23] performed >7 thyroidectomies in any given year. According to the American Thyroid Association (ATA) guideline, it is not recommended to perform thyroidectomies if there is lack of access to a high-volume surgeon (>30 thyroidectomies per year) [5]. A study in adult patients reported that GD was a significant predictor of postoperative complications in surgeries performed by low- and intermediate-volume surgeons [35]. If there is no access to high-volume surgeons, the ATA favors RAI therapy above thyroidectomy as definitive treatment for GD [5]. In addition to the guidelines, research has demonstrated that thyroidectomies performed by high-volume surgeons have better outcomes with less morbidity [36, 37]. The results of the other included studies illustrate that the chance of permanent hypocalcemia after thyroidectomy by high-volume surgeons in pediatric GD patients indeed is low. One should realize that the size of the underlying population has to be large for a pediatric surgeon to be able to perform >30 pediatric thyroidectomies per year. The study by de Jong et al. [20] also reported a relatively high incidence of permanent hypocalcemia (17.4%). In their study, the number of parathyroid glands remaining in situ (PGRIS) during surgery was monitored. Patients with GD had the highest incidence of a PGRIS score below 4 (52%) compared to patients with other indications for thyroidectomy. A 2-fold increase of the risk of long-term hypoparathyroidism was seen in patients with a PGRIS <4 (OR = 2.61 [95% CI: 1.01–6.73]; p = 0.04) [20]. As PGRIS scores were not reported in the other included studies, we cannot further evaluate the hypothesis that the number of PGRIS is an important predictor for the development of permanent hypocalcemia after thyroidectomy.

RLN Injury

The second most frequently reported complication after thyroidectomy in pediatric GD patients is transient RLN injury. The RLNs are located dorsal of the thyroid gland and are easily harmed during thyroid surgery through a variety of mechanisms (i.e., stretching, crushing, or transection of the RLN) [38]. Nerve regrowth may occur slowly (up to 12 months) but may not always be sufficient to overcome damage [38]. The RLN innervates both abductors and adductors of the vocal cord. Because the simultaneous contraction of these antagonist muscles is important, even light damage may cause inappropriate coordination and result in deterioration of the voice.

Swallowing, coughing, and respiration may also be affected in RLN injury [38].

In the 18 included studies evaluating RLN injury, the methods to diagnose RLN injury varied or were not specified (Table 2) [10–12, 14–18, 21, 23–31]. Machens et al. [10] determined each patient's vocal cord function with a laryngoscopy before and after surgery and used intraoperative nerve monitoring. Some studies performed direct laryngoscopy to visualize normal or abnormal vocal cord movement in patients who were experiencing a soft voice after surgery or if transection of the RLN was immediately recognized during surgery [14, 18, 26, 29]. Sinha et al. [12] reported that laryngoscopic confirmation was only performed in those patients with permanent hoarseness or a postoperative stridor and not in those with a temporary change of their voice.

The reported frequency of transient RLN injury ranged between 0 and 11.1%, with 1 study reporting a higher frequency of 20.0% ($n = 2$) [25]. The true frequency of RLN injury in the included studies is debatable because of heterogeneity in, or absence of information on, the used diagnostic methods. To identify RLN injury, it is recommended to perform a laryngoscopy to visualize the function of the vocal cords in combination with clinical symptoms [33, 38]. A laryngoscopy is recommended due to the fact that RLN injuries can be subclinical [38]. However, some clinical RLN injuries after thyroidectomy occur in the absence of vocal cord paralysis proven with laryngoscopy [39]. Only Machens et al. [10] and Chiapponi et al. [15] performed a pre- and postoperative laryngoscopy or a vocal cord function test in the pediatric patients who underwent thyroidectomy for GD. Machens et al. [10] reported frequencies of transient and permanent RLN injury of 3.4 and 0.0%, whereas Chiapponi et al. [15] reported frequencies of 4.8 and 0.0%, respectively. These results are likely to accurately reflect the complication rates of RLN injury after thyroidectomy performed by a high-volume surgeon in pediatric GD, due to their reliable diagnostic methods. We would recommend standardized methods to identify RLN injury in future studies to get a better impression on the true complication rates after thyroidectomy and to gain insight into the relationship between clinical signs of RLN neuropraxia and findings at laryngoscopy. On the other hand, in light of the very low frequency, one may question the necessity of diagnostic methods like postoperative laryngoscopy to identify possible RLN injury. Since transient hoarseness may also be caused by intubation, we suggest to consider laryngoscopy only if patients suffer from long-lasting deterioration (>6 months) of the voice or other clinical signs of RLN neuropraxia, not resolving after speech therapy. The diagnosis of transient RLN injury in children should then solely be made on the basis of clinical signs of RLN neuropraxia, avoiding invasive diagnostic procedures like laryngoscopy in pediatric patients.

Due to the variable diagnostic criteria and definitions of the studied morbidities, variance in cutoff values for hypocalcemia in the included studies, and original data were missing or not available, it was not possible to report the pooled complication rates of all 1,424 studied patients. To give an indication of the real frequency of postoperative morbidity, we have calculated cumulative frequency rates, based on the diagnostic criteria used in each study. This is the major limitation of our review. Also, the inclusion of 3 studies containing a few patients without GD ($n = 14$) may have influenced the results. Therefore, we recommend that future prospective studies on morbidities of thyroidectomy in pediatric GD patients should use widely accepted standardized diagnostic criteria, as proposed in this review. We have decided only to include studies with a minimum of 10 pediatric GD patients to reduce the risk of publication bias of seldom seen morbidities in very small cohorts or individual cases. However, by doing this, we may have missed some data on postoperative morbidities after thyroidectomy for pediatric GD. The same applies to data on pediatric GD patients hidden in mainly adult series that were not included in this review. The quality of the vast majority of the included studies was scored as fair mainly based on their retrospective and observational character. Future well-designed prospective studies are needed to improve the quality of evidence reporting on postoperative morbidities in pediatric GD patients. Nevertheless, to our knowledge, this systematic review is the most elaborate review on short- and long-term postoperative morbidities after thyroidectomy in children with GD and therefore gives a good overview of both short- and long-term postoperative complications in pediatric GD patients.

In conclusion, based on the results of this review, thyroidectomy in pediatric patients with GD has low postoperative morbidity. The minority of pediatric patients had transient forms of hypocalcemia and RLN injury. Permanent postoperative morbidities are relatively rare. Therefore, we conclude that thyroidectomy in pediatric GD patients is a safe treatment option, especially if performed by high-volume surgeons.

Statement of Ethics

For this type of study (systematic review), formal consent is not required.

Conflict of Interest Statement

The authors report that they have no conflicts of interest to disclose.

Funding Sources

The authors did not receive any funding for the present work.

Author Contributions

All authors conceived the idea of evaluating postoperative morbidities after thyroidectomy in pediatric patients with Graves' disease. A.S.Z. and C.F.M., and if necessary A.S.P.T., performed the literature search including title and abstract screening, full text screening, and data abstraction. A.S.Z. and C.F.M. discussed the abstracted data and took the lead in writing this review. All authors discussed previous versions of the manuscript and agreed to the submission of the final version.

References

1 Rivkees SA. Controversies in the management of Graves' disease in children. J Endocrinol Invest. 2016;39(11):1247–57.
2 Kahaly GJ, Bartalena L, Hegedüs L, Leenhardt L, Poppe K, Pearce SH. 2018 European Thyroid Association guideline for the management of Graves' hyperthyroidism. Eur Thyroid J. 2018;7(4):167–86.
3 Léger J, Kaguelidou F, Alberti C, Carel JC. Graves' disease in children. Best Pract Res Clin Endocrinol Metab. 2014;28(2):233–43.
4 Rabon S, Burton AM, White PC. Graves' disease in children: long-term outcomes of medical therapy. Clin Endocrinol. 2016;85(4):632–5.
5 Ross DS, Burch HB, Cooper DS, Greenlee MC, Laurberg P, Maia AL, et al. 2016 American Thyroid Association guidelines for diagnosis and management of hyperthyroidism and other causes of thyrotoxicosis. Thyroid. 2016;26(10):1343–421.
6 The Committee on Pharmaceutical Affairs, Japanese Society for Pediatric Endocrinology, and the Pediatric Thyroid Disease Committee, Japan Thyroid Association; Minamitani K, Sato H, Ohye H, Harada S, Arisaka O. Guidelines for the treatment of childhood-onset Graves' disease in Japan, 2016. Clin Pediatr Endocrinol. 2017;26:29.
7 Segni M, Gorman CA. The aftermath of childhood hyperthyroidism. J Pediatr Endocrinol Metab. 2001;14(Suppl 5):1277–8.
8 Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4:1.
9 Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan – a web and mobile app for systematic reviews. Syst Rev. 2016;5(1):210.
10 Machens A, Elwerr M, Schneider R, Lorenz K, Dralle H. Disease impacts more than age on operative morbidity in children with Graves' disease after total thyroidectomy. Surgery. 2018;164(5):993–7.
11 Peroni E, Angiolini MR, Vigone MC, Mari G, Chiumello G, Beretta E, et al. Surgical management of pediatric Graves' disease: an effective definitive treatment. Pediatr Surg Int. 2012;28(6):609–14.
12 Sinha CK, Decoppi P, Pierro A, Brain C, Hindmarsh P, Butler G, et al. Thyroid surgery in children: clinical outcomes. Eur J Pediatr Surg. 2014;25(5):425–9.
13 Nordenström E, Bergenfelz A, Almquist M. Permanent hypoparathyroidism after total thyroidectomy in children: results from a National Registry. World J Surg. 2018;42(9):2858–63.
14 Breuer CK, Solomon D, Donovan P, Rivkees SA, Udelsman R. Effect of patient age on surgical outcomes for Graves' disease: a case–control study of 100 consecutive patients at a high volume thyroid surgical center. Int J Pediatr Endocrinol. 2013;2013:2–5.
15 Chiapponi C, Stocker U, Mussack T, Gallwas J, Hallfeldt K, Ladurner R. The surgical treatment of Graves' disease in children and adolescents. World J Surg. 2011;35(11):2428–31.
16 Sherman J, Thompson GB, Lteif A, Schwenk WF, van Heerden J, Farley DR, et al. Surgical management of Graves disease in childhood and adolescence: an institutional experience. Surgery. 2006;140(6):1056–2.
17 Perzik SL. Total thyroidectomy in Graves' disease in children. J Pediatr Surg. 1976; 11(2):191–4.
18 Raval MV, Browne M, Chin AC, Zimmerman D, Angelos P, Reynolds M. Total thyroidectomy for benign disease in the pediatric patient: feasible and safe. J Pediatr Surg. 2009;44(8):1529–33.
19 Zobel MJ, Long R, Gosnell J, Sosa JA, Padilla BE. Postoperative hypoparathyroidism after total thyroidectomy in children. J Surg Res. 2020;252:63–8.
20 de Jong M, Nounou H, Rozalén García V, Christakis I, Brain C, Abdel-Aziz TE, et al. Children are at a high risk of hypocalcaemia and hypoparathyroidism after total thyroidectomy. J Pediatr Surg. 2020;55(7):1260–4.
21 Baumgarten HD, Bauer AJ, Isaza A, Mostoufi-Moab S, Kazahaya K, Adzick NS. Surgical management of pediatric thyroid disease: complication rates after thyroidectomy at the Children's Hospital of Philadelphia high-volume Pediatric Thyroid Center. J Pediatr Surg. 2019;54(10):1969–75.
22 Yu YR, Fallon SC, Carpenter JL, Athanassaki I, Brandt ML, Wesson DE, et al. Perioperative determinants of transient hypocalcemia after pediatric total thyroidectomy. J Pediatr Surg. 2017;52(5):684–8.
23 Cohen RZ, Felner EI, Heiss KF, Wyly JB, Muir AB. Outcomes analysis of radioactive iodine and total thyroidectomy for pediatric Graves' disease. J Pediatr Endocrinol Metab. 2016;29(3):319–25.
24 Lobe TE, Wright SK. The transaxillary, totally endoscopic approach for head and neck endocrine surgery in children. J Laparoendosc Adv Surg Tech A. 2011;21(1):97–100.
25 Bergman P, Auldist AW, Cameron F. Review of the outcome of management of Graves' disease in children and adolescents. J Paediatr Child Health. 2001;37(2):176–82.
26 Sugino K, Ito K, Mimura T, Fukunari N, Nagahama M, Ito K. Surgical treatment of Graves' disease in children. Thyroid. 2004;14(6):447–52.
27 Söreide JA, van Heerden JA, Lo CY, Grant CS, Zimmerman D, Ilstrup DM. Surgical treatment of Graves' disease in patients younger than 18 years. World J Surg. 1996;20(7):794–800.
28 Witte J, Goretzki PE, Röher HD. Surgery for Graves disease in childhood and adolescence. Exp Clin Endocrinol Diabetes. 1997;105(Suppl 4):58–60.
29 Chen Y, Masiakos PT, Gaz RD, Hodin RA, Parangi S, Randolph GW, et al. Pediatric thyroidectomy in a high volume thyroid surgery center: risk factors for postoperative hypocalcemia. J Pediatr Surg. 2015;50(8):1316–9.

30 Akkari M, Makeieff M, Jeandel C, Raingeard I, Cartier C, Garrel R, et al. Thyroid surgery in children and adolescents: a series of 65 cases. Eur Ann Otorhinolaryngol Head Neck Dis. 2014;131(5):293–7.
31 Elfenbein DM, Katz M, Schneider DF, Chen H, Sippel RS. Thyroidectomy for Graves' disease in children: indications and complications. J Pediatr Surg. 2016;51(10):1680–3.
32 Orloff LA, Wiseman SM, Bernet VJ, Fahey TJ, Shaha AR, Shindo ML, et al. American Thyroid Association statement on postoperative hypoparathyroidism: diagnosis, prevention, and management in adults. Thyroid. 2018;28(7):830–41.
33 Joliat GR, Guarnero V, Demartines N, Schweizer V, Matter M. Recurrent laryngeal nerve injury after thyroid and parathyroid surgery: incidence and postoperative evolution assessment. Medicine. 2017;96(17):e6674.
34 Burch HB, Cooper DS. Management of Graves disease: a review. JAMA. 2015;314(23):2544–54.
35 Kandil E, Noureldine SI, Abbas A, Tufano RP. The impact of surgical volume on patient outcomes following thyroid surgery. Surgery. 2013;154(6):1346–3.
36 Sosa JA, Bowman HM, Tielsch JM, Powe NR, Gordon TA, Udelsman R. The importance of surgeon experience for clinical and economic outcomes from thyroidectomy. Ann Surg. 1998;228(3):320–30.
37 Tuggle CT, Roman SA, Wang TS, Boudourakis L, Thomas DC, Udelsman R, et al. Pediatric endocrine surgery: who is operating on our children? Surgery. 2008;144(6):869–77.
38 Lynch J, Parameswaran R. Management of unilateral recurrent laryngeal nerve injury after thyroid surgery: a review. Head Neck. 2017;39(7):1470–8.
39 Kletzien H, Macdonald CL, Orne J, Francis DO, Leverson G, Wendt E, et al. Comparison between patient-perceived voice changes and quantitative voice measures in the first postoperative year after thyroidectomy: a secondary analysis of a randomized clinical trial. JAMA Otolaryngol Head Neck Surg. 2018;144(11):995–1003.