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This chapter reviews the pathophysiology, clinical manifestations, diagnosis and treatment of hyperthyroidism. Hyperthyroidism has multiple and often dramatic clinical manifestations because thyroid hormones control the basal metabolic rate, affect cardiovascular function by increasing the sensitivity of beta-receptors to catecholamines, and profoundly influence growth, sexual maturation, and neurological and cognitive development [1, 2]. “Hyperthyroidism” refers to excessive activity of the thyroid gland resulting in overproduction of thyroid hormones while “thyrotoxicosis” describes the clinical features of the hypermetabolic state associated with excess levels of circulating free thyroid hormones. In practice, the two terms are often used less precisely and interchangeably. There are several challenges in the diagnosis and management of hyperthyroidism in children

including biological, psychosocial, and environmental issues [3, 4]. However, despite these challenges the vast majority of pediatric patients with hyperthyroidism have an excellent prognosis.

Pathophysiology

A brief review of the normal mechanisms of thyroid hormone production, control and action is necessary before considering the abnormal state of hyperthyroidism. Please see Chap. 1 for further details.

Thyroid hormone production depends on an adequate supply of iodine. Dietary inorganic iodide is absorbed by the intestine into the circulation and then actively transported into follicular cells by an iodide transporter, the iodide pump (sodium iodide symporter or NIS, a transmembrane glycoprotein), that efficiently concentrates iodine in the thyroid gland. Then via a process called organification, thyroid peroxidase converts iodide into reactive iodine that is incorporated into tyrosine residues in the thyroglobulin molecule forming either monoiodothyronine (MIT) or diiodothyronine (DIT). These iodinated tyrosines are then coupled. MIT may combine with DIT to form triiodothyronine (T3) or its isomer, reverse T3, or two DITs can combine to form tetraiodothyronine (T4 or thyroxine). T3, reverse T3, and T4 remain attached to thyroglobulin that is stored in the follicular lumen. Thyroglobulin returns to the follicular cell by endocytosis and in the follicular

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cell free T3 (fT3) and free T4 (fT4) are cleaved from thyroglobulin by hydrolysis and released into the circulation. T3 is the active form of thyroid hormone and is 3 or 4 times more potent than T4 [1].

The synthesis of T4 and T3 is controlled by a complex feedback mechanism influenced by stimulatory and inhibitory factors via the hypothalamic–pituitary–thyroid axis. Thyrotrophin-releasing hormone (TRH) is secreted by the hypothalamus and stimulates the anterior pituitary gland to secrete thyroid stimulating hormone (TSH). Circulating TSH binds to specific TSH receptors on thyroid follicular cells. The TSH receptor is a G-protein coupled receptor and activates thyroid hormone production via a second messenger system, ultimately leading to the release of T4 and a lesser amount of T3. Raised circulating levels of T3 act as a negative feedback stimulus for the hypothalamus and anterior pituitary, resulting in decreased TSH production [5].

All T4 is produced by the thyroid gland but 85% of T3 is derived from peripheral conversion of T4 to T3 by deiodination. Most of the T3 and T4 circulating in the blood is bound to transport proteins such as thyroxine binding globulin (TBG) and albumin and only a small amount is unbound and biologically active. T3 and T4 act

by binding to receptors in peripheral tissues. T3 acts by binding to nuclear receptors and regulates the transcription of various cellular proteins that affect metabolism. Any process that causes an increase in the peripheral circulation of unbound thyroid hormone can cause signs and symptoms of hyperthyroidism. Disturbances of the normal homeostatic mechanism can occur at the level of the pituitary gland, the thyroid gland, or in the periphery. Regardless of aetiology, the result is an increase in transcription in cellular proteins causing an increase in the basal metabolic rate and the other effects of hyperthyroidism.

Aetiology and Incidence

More than 95% of children and adolescents with thyrotoxicosis suffer from Graves’ disease [6]. The aetiology is still unclear but a likely combination of hereditary, immunological and environmental factors. Other rare conditions that cause hyperthyroidism in childhood are listed in Table 2.1 [5, 7–9].

Graves’ disease is caused by thyroid stimulating immunoglobulins that activate TSH receptors on thyroid follicular cells resulting in thyroid hormone overproduction. Note that the clinical aspects of this syndrome, including the

Table 2.1 Causes of hyperthyroidism in children

• Graves’ disease (95% of cases)
• Thyroiditis
– Chronic lymphocytic thyroiditis (Hashimoto’s thyroiditis)—transient
– Subacute thyroiditis
• Autoimmune neonatal thyrotoxicosis (placental passage of maternal thyroid hormone receptor antibodies)—transient
• Autonomous functioning lesions
– Toxic thyroid adenoma
– Activating mutation of the TSH receptor gene
– Activating mutation of Gsα (McCune–Albright syndrome)
– Hyperfunctioning papillary or follicular carcinoma
• Isolated pituitary resistance to thyroid hormone
• TSH secreting pituitary adenoma
• Exogenous causes
– Excessive thyroid hormone replacement therapy
– Iodine induced hyperthyroidism

goitre, ophthalmopathy, and palpitations were described in the late eighteenth and early nineteenth centuries independently by several physicians from Great Britain and continental Europe including Parry, Graves, Basedow and Flajani. All of their names, either singly or in various combinations, have been attached to this common clinical condition. We will use the name “Graves’ disease” because it is commonly recognised in the English medical literature.

Although Graves’ disease is common in adults it is uncommon in children with a frequency of 0.1–3 per 100,000 children [10]. The incidence increases throughout childhood, with the peak incidence in children aged 10–15 years. The majority (60%) of patients being postpubertal [11]. As with most autoimmune diseases, Graves’ disease in children is more common in girls than boys, at a ratio of 5–6:1 [12]. Other causes of hyperthyroidism do not show a male or female preponderance. For example, the hyperthyroidism of McCune–Albright syndrome is not more common in girls even though the associated precocious puberty is more common in girls than in boys [13].

Graves’ disease is often associated with other autoimmune diseases and there is often a strong family history of thyroid and non-thyroid autoimmune problems [14] such as systemic lupus erythematosus, rheumatoid arthritis, myasthenia gravis, vitiligo, immune thrombocytopenic purpura, and pernicious anaemia. In addition, there are several lines of evidence suggesting a genetic component or predisposition to the disease. Some studies suggest that up to 80% of the susceptibility to Graves’ is determined by genetic factors [9]. Graves’ disease has been linked with human leukocyte antigen (HLA)-B8 and (HLA)-DR3 and with abnormalities in chromosomes 6p21 and 2q33 [15]. It is also more common in children with Trisomy 21 [16]. Overall, genetic susceptibility is thought to have a polygenic inheritance, although monozygotic twin studies suggest interplay between environmental and genetic factors.

Evaluation

The diagnosis of hyperthyroidism is often challenging due to the large spectrum of physical and psychological complaints [17]. However, a focused history and physical examination can usually select patients for lab tests and imaging studies that will confirm the diagnosis. The following discussion of the evaluation of patients with hyperthyroidism will focus on Graves’ disease and only briefly mention the other rare causes of hyperthyroidism in children.

History

The symptoms of Graves’ disease in children and adolescents can develop insidiously over months but can also have an abrupt onset. The most common symptoms are behaviour changes such as increased anxiety and hyperactivity. These symptoms are often similar to those of attention deficit hyperactivity disorder (ADHD), [18] and a high degree of clinical suspicion is necessary to pursue the diagnosis of Graves’ disease in this situation. Individuals with Graves’ disease invariably have an altered mental status with increased irritability, emotional lability, and outbursts which understandably create distress for themselves and their families. Other early symptoms of hyperthyroidism in children include deterioration of school performance and changes in handwriting.

Children with hyperthyroidism may fatigue easily and this usually manifests as exercise intolerance. In severe cases they may have difficulty climbing up stairs as a result of muscle weakness. Sleep disturbances are common as is weight loss despite a good appetite. Hyperthyroidism can also cause idiopathic intracranial hypertension (also known as benign intracranial hypertension or pseudotumor cerebri) in children and present with headache and even nausea and vomiting [19]. Symptoms of hyperthyroidism caused by autonomic nervous system

disturbances include tremor, heat intolerance, sweating, diarrhoea and palpitations. In girls, menstrual cycle irregularities, including amenorrhoea, are common symptoms. Finally, parents may report that the child has a growth spurt that results from the increased height velocity associated with hyperthyroidism [20].

In addition to hyperthyroidism, Graves' disease may be associated with eye abnormalities that are the result of autoimmune attack of soft tissue in the orbit. The full array of signs and symptoms in Graves' ophthalmopathy describes the triad of exophthalmos, chemosis and diplopia. Patients may complain of persistent visual blurring secondary to optic neuropathy or severe eye pain secondary to corneal ulceration. When these symptoms of congestive ophthalmopathy are present then urgent referral to an ophthalmologist for an eye assessment is necessary. Compared to adults, thyroid eye disease is usually mild in children.

Physical Examination

Vital signs of children with hyperthyroidism usually reveal tachycardia and less commonly hypertension. Height and weight are important to evaluate because hyperthyroidism may cause increased linear growth velocity and weight loss. General examination may reveal sweatiness, facial flushing, a tremor or, rarely, choreiform movements [21]. Further to the symptoms described above the eye signs such as eyelid retraction, proptosis, periorbital oedema, optic neuropathy, corneal ulceration, and rarely ophthalmoplegia may be present in Graves' disease (Fig. 2.1). Importantly, the eye changes sometimes present before signs of thyrotoxicosis. All children with Graves' disease should be referred to ophthalmology for formal assessment since the eye findings may be subtle but potentially serious.

Pubertal stage should be assessed as part of the evaluation of associated menstrual irregularity and to evaluate the uncommon possibility of McCune–Albright syndrome which could present with precocious puberty and cafe au lait pigmentation. Additional skin signs of Graves'



Fig. 2.1 A 14-year-old girl with Graves' disease who had diffuse goitre and asymmetrical proptosis (From Bhansali et al. [47], with permission.)

disease include the uncommon finding of pretibial myxoedema which represents an unusual autoimmune dermatopathy.

The examination of the neck for thyroid abnormalities is essential in the assessment of hyperthyroidism. A goitre or diffuse enlargement of the thyroid is almost always present in Graves' disease even though it may not have been noticed by the patient or family. Thyroid nodules are less commonly present. Examination of the thyroid is usually done with the neck slightly extended. Swallowing will elicit movement of the thyroid and potentially clarify the identity of a midline neck swelling. Examination of the thyroid is often best performed by standing behind the patient. As with any swelling or mass, evaluation and description of a thyroid goitre or nodule's size, site, symmetry, consistency and tenderness is essential. The increased blood flow to a hyperfunctioning thyroid sometimes results in a thyroid bruit.

Laboratory Tests

In the evaluation of hyperthyroidism the pivotal investigation is to measure thyroid function tests

—particularly the TSH, fT4 and fT3. In primary hyperthyroidism, when the thyroid gland is producing excessive thyroid hormones, TSH is suppressed and fT4 and fT3 are elevated. In addition, there is preferential conversion of fT4 to fT3 so usually the fT3 will be relatively more elevated. In contrast to the low TSH in primary or thyroid hyperthyroidism, the TSH is elevated in secondary or pituitary hyperthyroidism when there is production of TSH from the pituitary that is not responsive to the normal control mechanisms. When evaluating and managing hyperthyroidism fT3 and fT4 are usually better tests than total T3 and total T4 because total T3 and total T4 measure the much larger pool of protein-bound thyroid hormones in addition to the unbound, free forms. Therefore measurement of total T3 and T4 may be misleading in situations with abnormal serum protein levels or when there are changes in protein binding. Free T3 is relatively more important than free T4 in the diagnosis of hyperthyroidism since fT3 rises before fT4 in thyrotoxicosis. Rarely the fT4 levels can be normal but the fT3 is raised in “T3-toxicosis”.

Other thyroid tests can confirm the aetiology of hyperthyroidism. The diagnosis of Graves’ disease can be confirmed by the detection of stimulatory TSH receptor antibodies. Thyroid peroxidase antibodies are elevated in autoimmune thyroiditis that may present with hyperthyroidism as well as the more common presentation of hypothyroidism. Graves’ disease may also have thyroid ophthalmological immunoglobulin associated with eye signs and thyroid growth immunoglobulins associated with thyroid enlargement.

Other Investigations

Although history, physical examination and thyroid function tests are the critical components of the evaluation of hyperthyroidism other imaging investigations are occasionally useful. Thyroid ultrasound can be useful to confirm the suspicion of a diffuse thyroid goitre and screen for thyroid nodules. See Chap. 3 for further

discussion of the evaluation and management of thyroid nodules.

Radioactive iodine (RAI) uptake and scanning may be used when the aetiology of hyperthyroidism is still unclear after laboratory evaluation. In Graves’ disease, RAI uptake is elevated and the scan shows diffuse uptake.

Management

Current treatment options include antithyroid medications that block thyroid hormone production and radioactive iodine and thyroidectomy that eliminate thyroid hormone producing follicular cells. None of the current treatment options are ideal and there is controversy regarding the best therapy for children with hyperthyroidism. In view of the lack of clinical trials to guide treatment decisions, our current opinion is to tailor treatment based on the individual patient’s needs while considering the risks and benefits of each treatment [22]. Medical treatment is the first option for treating hyperthyroidism and maybe the only treatment necessary. It is rare that children require hospital admission at diagnosis, however, if there are marked hyperdynamic cardiovascular symptoms then admission maybe necessary until beta-blockers have controlled these symptoms. Two-thirds of patients relapse following medical treatment and in these individuals, radioiodine or surgery are the second-line options [21]. The outcome from both is excellent. Although the patient will be hypothyroid and need lifelong thyroxine treatment this is easy to manage and results in clinically euthyroid individuals. The risk of relapse decreases with a longer primary course of antithyroid medication [9].

Despite the management challenges, prognosis in the majority of children with hyperthyroidism is good when treatment is timely and appropriate [23]. It is important to remember that long-term consequences of hyperthyroidism can result from both the disease and the treatment used [2]. Stratifying patients according to risk of relapse after medical management with antithyroid medication by identifying predictive factors

early has led to improvement in overall management. Factors include young age, severity of hyperthyroidism at diagnosis and the presence or absence of other autoimmune conditions are important to consider.

Medical Management

If the individual is very symptomatic then propranolol (or another beta blocker) is used to control the symptoms of sympathetic overdrive, such as tremor and tachycardia, until definitive therapy. Propranolol is usually begun orally at 0.25–0.5 mg/kg/dose, two to four times daily and the dose is titrated for symptom relief. Propranolol can be stopped when the thyroid hormone levels fall into the normal range. Propranolol should be avoided in patients with asthma but a more selective beta-blocker can be used in this circumstance.

Antithyroid drugs are usually considered first-line treatment of hyperthyroidism in children [24]. Antithyroid drugs are known as thionamides and include propylthiouracil (PTU), carbimazole and the active metabolite methimazole. They inhibit thyroid hormone synthesis by interfering with the organification process by which iodine attaches to the tyrosine moieties in thyroglobulin, i.e. the thyroid peroxidase mediated iodination. PTU and methimazole are available in the United States and much of the rest of the world. Methimazole is preferred to PTU because PTU is associated with a risk of severe liver damage (PTU induced hepatitis) and production of cytoplasmic anti-neutrophil autoantibodies. Antibody-positive vasculitis is exceptionally rare. PTU can block the conversion of T4 to T3 whereas methimazole cannot [9, 25]. The United States Food and Drug Administration (FDA) recommend that PTU should be used in children only if other treatment options are unavailable. Another antithyroid drug is carbimazole. Carbimazole is metabolised by the patient into methimazole. Carbimazole is widely used in the United Kingdom, Europe, and the countries of the former British Commonwealth. Carbimazole, methimazole and propylthiouracil

have side effects that range in severity from a transient rash to agranulocytosis and neutropenia. Allergic-type reactions with fever, rash, urticaria, gastrointestinal symptoms and arthralgia occur in 1–5% of patients. These reactions are usually transient and can be treated with antihistamines without discontinuing therapy. Agranulocytosis and neutropenia is a rare but serious side effect. Although it is not necessary to check regular complete blood counts it is important to communicate to the family and child that they should immediately report symptoms of easy bruising, sore throat, mouth ulcers, or fever and a complete blood count performed urgently to ensure immunocompetency. It is important to provide the family with verbal and written instructions that specify what symptoms mandate urgent reporting and the need to stop medications. Clear documentation of these discussions and instructions is essential. Even when the patient suffers a serious side effect of an antithyroid drug it is often possible to switch to an alternative antithyroid drug with careful monitoring.

The recommended dose of carbimazole for children less than 12 years is 0.25 mg/kg/dose three times per day. For children between 12 and 18 years the dose is 10 mg three times per day. The dose for propylthiouracil is 25 mg three times per day for children 1–5 years, 50 mg three times per day for children 5–12 years and 100 mg three times per day for adolescents 12–18 years. The conversion between these two antithyroid drugs is 1 mg of carbimazole equates to approximately 10 mg of propylthiouracil.

There are two main antithyroid drug treatment strategies, (1) block and replacement or (2) dose titration. In block and replacement the thyroid gland is first “blocked” or “switched off” with antithyroid drugs, suppressing T4 and T3 and rendering the patient virtually hypothyroid. The “block” is accomplished using relatively higher doses of any of the antithyroid drugs. With this strategy it usually takes 2 weeks or more of treatment before the patient becomes euthyroid. When T4 and T3 levels have fallen and stimulate the patient’s TSH into the normal range then “replacement” with exogenous thyroxine commences. Some of the possible advantages of the

“block and replace” regimen include having less blood tests, improved stability and possibly higher remission rates [5, 26–28]. The higher doses of antithyroid drugs used in “block and replacement therapy” provides better control of thyroid hyperfunction and may be responsible for a higher remission rate. Compliance with taking the needed thyroxine replacement can be increased by direct observation of treatment by parents or providing a pill box. The best routine with the most effective pharmacokinetic action is to take thyroxine in the morning on an empty stomach.

The second antithyroid drug strategy is “dose titration therapy” which uses lower doses of antithyroid drugs so that within 1–2 months of starting antithyroid treatment the fT4 and fT3 fall and the TSH remains suppressed. When fT3 and fT4 are within the lower half of the normal range, which can take up to 3 months with this option, the antithyroid drug dose is reduced and “titrated” to keep the fT3 and fT4 in the normal range without the need for exogenous thyroxine treatment. A potential advantage of the “dose titration” strategy may be better compliance with the monotherapy of an antithyroid drug alone rather than an antithyroid drug and thyroid hormone replacement. In addition, the lower doses of antithyroid drugs may result in fewer side effects. More blood tests may be necessary in the “titration” phase and this is a disadvantage of the dose titration therapy, especially in children.

It is not clear which treatment strategy is superior. Part of the controversy exists due to the variability of patient response to antithyroid drugs and the limited data available about definitive therapy in prepubertal children [29]. A recent study reports that the relapse risk was higher for children of nonwhite ethnic origin with high serum levels of TSH receptor autoantibodies and T4 at diagnosis. However, children who were older at disease onset and had a longer duration of antithyroid treatment had a lower relapse risk [29, 30]. Ongoing trials by the British Society of Paediatric Endocrinology and Diabetes may provide information as to the ideal method of antithyroid drug treatment of Graves’s disease in children.

Antithyroid drugs have been associated with a lower remission rate in children with Graves’ disease compared to adults and a longer duration of therapy is required in prepubertal patients [11]. Treatment with antithyroid drugs should be for a minimum of 2 years as this has been shown to decrease the risk of relapse [9, 31]. Most clinicians report a remission rate of less than 25%, with approximately two-thirds of patients relapsing either on treatment or after stopping treatment. The decision to stop antithyroid drug treatment is planned around the age and particular circumstances of a patient. It should not be stopped in adolescents going through puberty or during important exam times in their life. A cautious reduction of treatment and close monitoring over summer holidays is recommended. Once relapsed, individuals will need further medical management to regain control before definitive treatment is undertaken with radioactive iodine or surgery [24].

Methods identifying the likelihood of remission would greatly improve patient management [9, 32]. There are very few studies evaluating the long-term outcome of the relationship between duration of antithyroid treatment and remission rates. Some studies have evaluated age, goitre size, severity of hyperthyroidism at onset measured by thyroid hormone receptor antibodies (TRAb) levels at onset and at end of antithyroid treatment as well as duration of treatment as predictive markers of Graves’ relapse. Absence of goitre at diagnosis is associated with better outcome. TRAb levels which normalise within a year are also predictive of positive outcome as well as levels that are less than 2.5 times the upper reference limit at diagnosis [33]. A recent multicentre study has shown that serum TRAb levels are a sensitive, specific and reproducible biomarker for pediatric Graves’ and that is correlates well with disease severity [34]. Furthermore, recent studies have concluded that antithyroid medication could be offered up to 10 years before definitive management in cases with good compliance and with no major adverse effects secondary to antithyroid medication. [9] Regardless of the mode of treatment it does not seem to impact on the health associated quality

of life. However, this would be important to study specifically in children in order to evaluate the emotional, behavioural and neuropsychological long-term outcomes. Certainly large prospective randomised trials in children would address these management dilemmas.

Radioactive Iodine Treatment

Radioactive iodine therapy is increasingly viewed as a safe and effective treatment in the management of hyperthyroidism in children [6, 28, 35–37]. The goal of radioiodine treatment is to ablate thyroid follicular cells to the extent that results in the patient becoming hypothyroid [15]. There have always been concerns around giving radioiodine therapy to children due to the long-term risk of thyroid cancer and certainly there are rare cases. However, thyroid cancer is also more common in patients with untreated Graves' disease so the magnitude of risk after radioiodine treatment is unclear. Radioiodine is not considered first-line treatment in paediatrics but reserved for children who either relapse while being treated with antithyroid drugs or following discontinuation of antithyroid drugs. It is also indicated for individuals who cannot tolerate antithyroid drugs or who will not comply with the prescribed treatment. The cure rate for radioiodine is up to 50% and the incidence of hypothyroidism around 40% [35]. The efficacy of radioiodine therapy is dose related. High cure rates without an associated higher risk of thyroid cancer are reported when using appropriate doses of radioiodine. Due to the theoretical risk of thyroid cancer in children treated with radioiodine, it is considered best to use a high dose of radioiodine in order to minimise the thyroid tissue that remains and is at long-term risk of neoplastic change. It has been shown that at least 300 microCi/g are needed in order to ensure ablation of thyroid tissue [2, 37]. In 85–90% of patients, a single dose of radioiodine is sufficient to cure hyperthyroidism but even when a moderately high initial dose of radioiodine is used a second dose maybe necessary [36]. Of 48 patients treated with radioiodine, 89% became

hypothyroid after the initial dose, whilst the remaining 11% needed a second dose. [15].

In the United Kingdom, only patients over 10 years of age are generally offered radioiodine treatment. In circumstances of significant eye involvement radioiodine is not recommended because it may cause marked deterioration although this is not a universal observation [36]. Long-term follow-up studies have been reassuring so far but more are required.

Surgical Management of Hyperthyroidism

Indications for Operative Management of Hyperthyroidism

Thyroidectomy as treatment for hyperthyroidism is generally indicated when there is failure of medical therapy, intolerance of medical treatment (such as adverse drug reactions), severe thyrotoxicosis, severe ophthalmopathy, large glands producing obstructive or compressive symptoms, coexistence of a thyroid nodule, or patient preference. As mentioned previously, radioactive iodine is not indicated in children younger than 10 years of age so those patients should be referred for surgical treatment. An important additional benefit of surgical treatment is that it can allow for detection and treatment of clinically occult malignancies that may coexist in up to 5% of children [38].

Access to thyroid surgery for children is limited because of a vicious cycle. Most surgeons have limited experience since few children are referred for thyroidectomy and physicians are reluctant to refer children for thyroidectomy because they unlikely to have access to a surgical unit with sufficient experience. For example, the national audit maintained by the British Association of Endocrine and Thyroid Surgeons (<http://www.baets.org.uk>) showed that 52 surgeons performed 151 thyroid operations in children <17 years, with only 6 surgeons performing more than five such operations over the lifetime of the database. In the financial year 2009 only seven thyroidectomies for Graves' disease in

children were recorded. Though these data might be incomplete, it is undoubted that most surgeons rarely perform thyroidectomy for Graves' disease in children. This has a negative impact on availability of this service and partially explains the reticence to recommend surgery in these patients.

Preoperative Preparation

All patients undergoing thyroidectomy for hyperthyroidism have to be fully controlled on medication and biochemically euthyroid at the time of the operation. Those who do not tolerate antithyroid drugs (e.g. those with agranulocytosis induced by carbimazole) can be controlled acutely using high dose iodine (either from Lugol solution or from potassium iodine) for 7–10 days before proceeding with the operation. Beta-blockers (e.g. propranolol) can also be added to control the heart rate and decrease the peripheral conversion of T3 in T4. The operation must be done in a narrow time-window because the acute inhibition of the thyroid with iodine fails after 10–14 days and a severe, rebound thyrotoxicosis can ensue.

Perioperative Anaesthesia Considerations

The current medical practice of good preoperative medical control of thyrotoxicosis has eliminated the much feared perioperative complication of "thyroid storm". Routine monitoring of cardiac rhythm is maintained during the perioperative period but it is unlikely to demonstrate severe changes during the procedure.

There is increasing evidence that the use of an endotracheal tube with electrodes touching the vocal cords may be beneficial. Such tubes allow the use of intraoperative nerve monitoring (IONM), whereby during the operation the surgeon has the possibility of using a stimulating electrode to demonstrate normal conductivity of the current through the recurrent laryngeal nerve (RLN). Guidelines and standards for the use of

IONM have been published and can easily be adopted in children. In short, the vagus nerve is identified at the beginning of the procedure and successful stimulation of the vagus nerve demonstrates that the circuit is functional. Thereafter, any anatomical structure thought to be the RLN during the dissection may be stimulated to test for RLN function. At the end of the procedure, the vagus is stimulated once more to check whether the latency or amplitude of the current has changed (i.e. whether there is any electrophysiological evidence of injury to the nerve).

Choice of Operation for Hyperthyroidism

There is an on-going debate on which surgical procedure provides best outcomes for children with Graves' disease. Total thyroidectomy is the preferred surgical treatment for Graves' disease in adults in the United Kingdom. Those who favour total thyroidectomy argue that it is the only operation that essentially eliminates the risk of relapse and has an increased efficacy in patients with severe ophthalmopathy [39]. The fact that it leads to permanent hypothyroidism which requires a lifelong replacement therapy is of minimal medical and financial consequence in the western world. In areas of the world where access to medication is limited the argument will be different.

Subtotal thyroidectomy has fewer advocates but is the standard treatment of thyrotoxicosis in Japan. It can be performed either as a bilateral subtotal resection (bilateral remnants of ~3 g) or lobectomy plus subtotal lobectomy (Dunhill procedure, unilateral remnant of ~5–7 g). Some suggest the remnant size of 3–4 g provides an optimal balance between low relapse rate (4% recurrence after 2–3 years) and acceptable complication rate in both pediatric and adult population [40]. The argument against subtotal resection is the high risk of recurrence of hyperthyroidism ranging between 1.2 and 16.2% (9) to 30% [41]. Though similar comparative studies have not been undertaken in children, one

can safely assume that subtotal thyroidectomies in children would have an even higher risk of recurrent disease compared with adults. Near-total thyroidectomy with a total thyroid remnant of 2–4 g may minimise risk of relapse and at the same time may prevent permanent hypothyroidism.

Most published series report the results of traditional thyroidectomy and there is minimal data available on minimally invasive video-assisted thyroidectomy (MIVAT) in children. In a small study of children undergoing MIVAT, the cosmetic results were better and postoperative recovery was shorter than after open thyroidectomy and no complications were recorded [42] but this technique is seldom available. No reports have been published regarding the use of robotic transaxillary thyroidectomy in children.

Whatever the surgical approach is, there is evidence that an individual surgeon's experience is associated with of better treatment outcomes. Higher volumes of thyroidectomies performed result in lower complication rates and shorter hospital stay [43] therefore it seems reasonable to refer this group of patients to national referral centres where surgeons with adequate level of experience can deal with this relatively rare condition.

Postoperative Care

Patients should be able to drink fluids immediately after surgery. Patients with RLN injury may have difficulty swallowing and are at risk for aspiration so when there is a clinical suspicion of RLN injury they should be observed when attempting to drink water for the first time after the operation.

Development of a neck haematoma that can lead to airway compromise is the most severe complication of thyroidectomy. The risk is highest in the first 6 h postoperatively but it remains a possible risk for the first 24 h. Close monitoring by nursing staff and early assessment

and treatment by clinicians with appropriate experience is mandatory. Most such haematomas can be dealt with conservatively but some require emergency removal of the sutures and return to the operating theatre for evacuation of haematoma and control of bleeding.

The morning after the operation calcium and PTH levels should be checked. If hypocalcaemia is present (<2.0 mmol/l) or if patient is symptomatic, oral calcium supplements should be instituted. It is desirable to avoid development of severe hypocalcaemia that needs administration of intravenous calcium.

Voice should be assessed within few weeks after the operation. If there are changes suggestive of laryngeal nerve injury, further evaluation is necessary and referral to a specialised voice clinic may be beneficial.

Results of Thyroidectomy for Hyperthyroidism

Published series from the Mayo Clinic (1986–2003, 78 children) [44] Japan (1989–1998, 74 children) [45], Chicago (2000–2007, 12 children) [46] show no recurrent hyperthyroidism after total thyroidectomy and definite recurrence risk (4–10%) after less-than total thyroidectomy.

With the limited published data on the outcomes of treatment of children with hyperthyroidism, it is necessary to balance the pros and cons for each of the methods available to choose the treatment that is be offered to an individual patient (Table 2.2). Clinicians have to balance not only the published data and the experience of individual surgeons but also the other resources available, parent and child preferences, and the family's cultural and social beliefs. Surgeons involved in the care of these children should work as part of a multidisciplinary team that includes pediatric endocrinologists and anesthesiologists, pediatricians, nuclear medicine physicians and pathologists to afford children the best clinical outcomes.

Table 2.2 Pros and cons of methods available for treatment of Graves' disease in children (see text for details)

Treatment	Pro	Con
Antithyroid drugs	<ul style="list-style-type: none"> • Controls thyrotoxicosis • Ambulatory treatment • Long-term remission in up to a third of patients 	<ul style="list-style-type: none"> • High relapse rates (60–80% long term) • Hypothyroidism • Minor side effects (25%) <ul style="list-style-type: none"> – Pruritus, hives, myalgia, elevated liver enzymes, leukopenia • Major side effects (0.5%) <ul style="list-style-type: none"> – Liver failure, bone marrow failure, death • Need for monitoring and follow-up
Radioactive iodine	<ul style="list-style-type: none"> • Cost effective • Ambulatory treatment • Remission rate 95% • No clear increased risk of thyroid malignancy • No increased risk of malignancy in off-spring 	<ul style="list-style-type: none"> • No long-term follow-up data after high dose radioactive iodide • Possible increased risk of malignancy (thyroid, brain, stomach, kidney) • Potential to induce hyperparathyroidism and benign thyroid nodules • Transient hypocalcaemia (6%) • Hypothyroidism (27–92%) • Recurrent hyperthyroidism (0–40%) • Nausea and vomiting (0–12%) • Transient pain over the thyroid • Worsening ophthalmopathy • Radiation thyroiditis (0–33%)
Thyroidectomy	<ul style="list-style-type: none"> • Appropriate for children <5 years of age • High cure rate (97–100%) • Low complication rate, in experienced hands (1–3%) • Ophthalmopathy improvement (up to 85%) • Controls compressive symptoms • Avoids non-compliance of medical treatment • Detection of occult malignancy (up to 5%) 	<ul style="list-style-type: none"> • Risks related to surgical expertise and experience • Higher cost • Lifelong hypothyroidism with total thyroidectomy • Risk of recurrent hyperthyroidism if less than a total thyroidectomy <ul style="list-style-type: none"> – 30% for subtotal thyroidectomy – 5% in near-total thyroidectomy • RLN palsy/paralysis (0–2%) • Transient hypocalcaemia (6–71%) • Permanent hypoparathyroidism (0–7%) • Neck haematoma (0.2–2%) • Keloid scar (0–12%) • Postoperative pain (100%)

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Endocrine Surgery in Children

Ledbetter, D.; Johnson, P. (Eds.)

2018, XX, 462 p. 116 illus., 35 illus. in color., Hardcover

ISBN: 978-3-662-54254-5