

# Pediatric Graves' Disease

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## Abstract

Graves' disease is the most common cause of hyperthyroidism in children. It is characterized by suppressed thyroid stimulating hormone and elevated thyroxine levels with varying levels of thyroid stimulating immunoglobulins; and evidence of increased iodine uptake on thyroid scan. It is a multisystem disease with interplay of genetics and environmental factors. Due to the insidious onset of symptoms, diagnosis is often delayed leading to poor growth and development. The disorder could present at any age including neonatal period due to transfer of maternal antibodies in context of maternal Graves' disease. Herein, we review the current literature for Graves' disease affecting children and adolescents.

**Keywords:** Graves' disease; Hyperthyroidism; Children; Adolescents

## Introduction

Graves' disease (GD) is the most common cause of hyperthyroidism in children. It is an immunologic disorder that unfolds when a combination of genetic susceptibility and environmental factors leads to the development of autoimmunity. It can affect multiple organ systems and is classically associated with thyroid enlargement and laboratory findings of hyperthyroidism. Severe ophthalmopathy and dermatologic manifestations are relatively uncommon in children [1,2]. Accurate diagnosis of the etiology of hyperthyroidism is essential for management and prognosis. Overall, treatment modalities include oral therapy, radioactive iodine and surgery. When this condition is left untreated, it could be life threatening and adversely compromise growth and development. Hence, it is imperative to identify thyroid dysfunction at an early stage by maintaining an appropriate index of suspicion [3,4]. Here, we review the literature on pediatric Graves' disease.

## Epidemiology

GD accounts for approximately 10–15% of childhood thyroid disease [5]. It is often associated with other autoimmune disorders, which may provide evidence for common factors involved on their pathogenesis [6]. Twin concordance studies suggest that genetic factors contribute 80% with environmental factors including smoking contributing the rest in development of the disease [7,8]. As per Leger et al. [9], the incidence of GD in young children is 0.1 per 100,000 person-years while is 3 per 100,000 person-years in adolescents. The prevalence in United State for children is 1:10,000 person-years [9,10] with female preponderance of 7:1 across all ages [11]. GD can occur at any age but is rare in children less than 5 years of age with a peak incidence at 10–15 years of age [5].

## Etiology and Pathophysiology

The exact cause of GD remains unknown but majority believe that

the combination of genetic susceptibility and environmental encounters leads to breakdown of tolerance to multiple thyroid antigens, in this case, thyrotropin receptor (TSHR); and hence, emergence of autoimmunity.

The role of T cells in development of autoimmunity is being studied extensively. Activation of T cell response leads to cytokines production and local inflammation and stimulation of B-cells leading to production of autoantibodies [12]. Pathogenesis of GD is postulated to be either related to presence of abnormal copies of autoreactive T-cells or abnormal antigen presentation by thyroid follicular cells either independently or in response to cytokines released by infiltrating T-cells [13]. An imbalance between the pathogenic and regulatory T cells is thought to be involved in the development of GD and its severity [14].

The TSHR is a G-protein coupled receptor present in thyroid, lymphocytes, fibroblasts and adipocytes. The binding of TSH to TSHR results in signaling pathway downstream that results in actions of thyroid hormone production [15]. The excess thyroid hormone production [thyroxine (T<sub>4</sub>), free thyroxine (FT<sub>4</sub>) and/or triiodothyronine (T<sub>3</sub>)] in this condition is attributed to the presence of thyroid stimulating antibodies (TSHR-Ab). The TSHR-Ab belongs to the Immunoglobulin G1 subclass [16]. These antibodies could either stimulate [thyroid stimulating immunoglobulins (TSI)] or block thyroid hormone secretion overall. TSI bind and activate the TSHR on thyroid cells [17]. Besides thyroid hypersecretion, they lead to hypertrophy and hyperplasia of the thyroid follicles which contribute to the formation of a diffuse goiter and increased vascularity [18]. TSI promote the synthesis and activity of the sodium-iodide symporter, explaining the increased uptake of iodide by thyroid tissue in GD in the absence of TSH [19]. These antibodies are mostly specific for Graves' disease. TSI, however, could be present in some patients with Hashimoto's thyroiditis (chronic lymphocytic thyroiditis)

during Hashitoxicosis state. Conversely, TSHR-Ab could also be blocking antibodies, which inhibit the binding and action of TSH. Antibodies to thyroglobulin and thyroid peroxidase, are commonly associated with Hashimoto's thyroiditis [20]. GD patients may have blocking antibodies as well as stimulating antibodies such that the symptomatology may depend upon the net effect of these different antibodies [21]. A third group of TSHR-Ab is of the neutral variety, binding to the receptor and not influencing TSH binding. These antibodies, however, may not be entirely neutral and may possess cell signaling of unknown effect [22]. The variation in biological function of TSHR-Ab may be caused by their specific molecular binding, which leads to difference in signaling pathways [23]. Multiple assays have been developed in an effort to accurately identify the etiology of hyperthyroidism. However, the mixture of antibodies directed to the TSHR, the lack of standardization in technique and nomenclature together with varying availability of specific tests hinder the ability to specify which assay aids in predicting the clinical course [5,24].

Graves' ophthalmopathy (GO) is characterized by edema and inflammation of the extraocular muscles and an increase in orbital connective tissue and fat [25]. The edema is due to the hydrophilic action of glycosaminoglycans secreted by fibroblasts. The inflammation is due to infiltration of the extraocular muscles and orbital connective tissue by lymphocytes and macrophages. The resultant increase in the volume of retrobulbar tissue is responsible for most of the clinical manifestations of GO [26]. The muscle cells of the eyelid are hypertrophic but have little lymphocytic infiltration [27]. Dermopathy in GD is characterized by lymphocytic infiltration of the dermis, the accumulation of glycosaminoglycans and non-pitting edema in the pretibial region [28].

Genetic and environmental factors play a role in the pathogenesis of GD. It is associated with other autoimmune disorders (e.g., type 1 diabetes mellitus, Addison's disease, celiac disease, rheumatoid arthritis, systemic lupus erythematosus and vitiligo) [6]. Linkage analysis from families with a history of autoimmune thyroid disease (GD and Hashimoto thyroiditis) has provided evidence for involvement of several loci, including the human leukocyte antigen (HLA) region on chromosome 6p21, cytotoxic T lymphocyte antigen 4 (*CTLA-4*) on chromosome 2q33, and lymphoid protein tyrosine phosphatase (*PTPN22*) [6,29]. Each locus confers a 1.4 to 4-fold relative risk for disease. In addition, several other regions have been identified on 2q36, 11p15, 18p11, 5q23, and Xp11; however, no single locus has been found to explain the familial association of autoimmune thyroid disease [29].

## Clinical Presentation

The onset of symptoms is often subtle, and the changes may be present for months or years before the diagnosis is made. In children, the clinical manifestation is similar to adults [Table 1] [6,9,15,30-36]. However, a high index of suspicion is required especially in pediatric age group due to its effects on growth and pubertal development, impaired neurodevelopmental outcome and deterioration in school performance.

GD symptoms could initially present as mood changes and emotional lability, fatigue, sleep disturbance and increased appetite, which are common otherwise in childhood and adolescent age group and can be easily misinterpreted. School-aged children and adolescents could present with attention-deficit hyperactivity disorder, poor school performance, irritability, fatigue, palpitations, heat intolerance, fine tremor and a goiter. Prepubertal children more commonly present with poor weight gain and frequent bowel movements. However, the symptomatology and clinical presentation varies between prepubertal and pubertal patients although GD could present differently within these 2 subset populations as well. Studies have shown that the younger patients are diagnosed with GD much later than the adolescents [2,4].

Thyroid gland	Smooth, symmetric, diffuse goiter, non-tender [9]
Cardiovascular	Rapid heart rate; Rarely atrial fibrillation [66] Heart murmur [9]
Gastrointestinal	Increased frequency of bowel movements (hyperdefecation), increased appetite, weight loss or failure to gain weight [6,36]
Neuro-psychological	Hyperactive deep tendon reflexes, tremors, irritability, restlessness, difficulty sleeping, poor school performance, decreased attention span, hyperactivity, mood swings [67]
Musculoskeletal	Proximal muscle weakness and wasting [68]
Ophthalmologic	Staring, infrequent blinking, lid lag, diplopia, exophthalmos [69]
Dermatologic	Warm, moist, smooth skin; heat intolerance, hyperhidrosis; pretibial myxedema [15]
Reproductive	Oligomenorrhea, secondary amenorrhea; anovulatory cycles [70] Decreased libido
Skeletal	Advanced bone age and height velocity [71] (Improves with treatment)

**Table 1:** Clinical features of Graves' disease in children and adolescents

Thyroid storm, also referred to as thyrotoxic crisis, is an acute life-threatening endocrine emergency characterized by increased metabolism with excessive release of thyroid hormones. This could be the initial presentation in undiagnosed children, particularly in neonates. Diagnosis is primarily clinical with severe hyperthyroid symptoms. Because thyroid storm is almost invariably fatal if left untreated, rapid diagnosis and aggressive treatment are critical. This condition is rare in children.

## Diagnostic Evaluation

### Laboratory workup

High index of suspicion for GD based on history and exam warrants laboratory investigation. It is associated with elevated T4, FT4 and/or T3 with suppressed TSH; and positive TSI, in the majority of cases. Due to thyroxine binding globulin levels interfering with total thyroid hormone levels, it is the standard of care to obtain free levels of T4 and/or T3. In some cases, only the T3 is elevated with suppressed TSH, condition known as T3 toxicosis [37]. The ratio of total T3 to total T4 can also be useful in assessing the etiology of thyrotoxicosis when scintigraphy is contraindicated. Since relatively more T3 is synthesized than T4 in a hyperactive gland, the ratio is usually >20 ng/mcg in GD and toxic nodular goiter while is <20 ng/mcg in painless or postpartum thyroiditis [38].

TSI is a functional assay which is measured by the production of cyclic AMP in cultured thyroid follicular cells. A recent large, multicenter study established that TSI level is a sensitive, specific and reproducible biomarker and is present in 94% of pediatric patients with GD with higher levels in those with GO [39]. This is in contrast to previous studies which pointed that TSI may not be present in all patients with GD [40]. Although TSI is very useful for diagnosis of GD, they are not always used as the initial and confirmatory test. The 2011 guidelines by the American Thyroid Association (ATA) and the American Association of Clinical Endocrinologists (AACE) recommend thyroid scan as the primary differential diagnostic test [38]. However, now there are increased recommendations for TSI use as an initial and diagnostic test for GD [41,42]. The 2007 Endocrine society guidelines for hyperthyroidism in pregnancy and postpartum recommended that measurement of TSHR-Ab in pregnant women may also help to distinguish GD from gestational

thyrotoxicosis. They are also important to identify the neonates at risk due to maternal disease [30]. However, TSHR-Ab does have a turnaround time of three to seven days.

### Imaging studies

**Scintigraphy:** Besides those cases of GD that have negative TSHR-Ab and unclear etiology of hyperthyroidism, thyroid scan is not routinely done on every patient. As the thyroid gland actively concentrates iodine and radioactive iodine [RAI ( $^{131}\text{I}$ )], radioiodine uptake scan (RAIU) is useful to aid in identifying the etiology of hyperthyroidism. Radiolabelled technetium ( $^{99}\text{Tc}$ ) can also be used as technetium is trapped by the thyroid gland but not organified.  $^{99}\text{Tc}$  use is on the rise due to lower total body radiation [38].

Normal values for RAIU 24 hours after the administration of a tracer dose of RAI are ~20% in iodine sufficient and ~40% in iodine deficient areas [43]. The uptake is elevated to 50-80% in GD and is as low as  $\leq 2\%$  in subacute thyroiditis [44].

In addition, in GD, RAIU can be useful for individualizing the dose of RAI for the treatment of hyperthyroidism [45]. Even though these scans are reliable methods to diagnose GD, they are expensive and time consuming, moreover involve radiation exposure [46].

**Thyroid ultrasound and color flow Doppler:** Thyroid ultrasound is a very sensitive and reliable diagnostic tool, which is not necessary to conclude the etiology of hyperthyroidism as GD. Classically, the gland is hypoechoic due to lymphocytic infiltration, thyrocyte hyperplasia, decrease in colloid and increase in vascularity. It provides an accurate estimation of the thyroid size, which is important in the therapeutic planning. It also allows the detection of non-palpable thyroid nodules [41].

Color flow doppler (CFD) is useful for detection of blood flow, which is typically increased in patients with GD. Similar to iodine uptake scans, CFD is useful in the differential diagnosis between GD and other causes of thyrotoxicosis characterized by a low blood flow to the thyroid such as factitious thyrotoxicosis, subacute thyroiditis and type II amiodarone-induced thyrotoxicosis, but with a lower sensitivity and specificity. It is particularly useful in cases where uptake scans are not available or contraindicated (for example, during pregnancy or lactation) [43].

### Treatment

After biochemical confirmation of disease, a choice between three main treatment options is required: antithyroid drugs (ATD), radioiodine therapy or surgery. While the former may cause remission of disease, the latter two provide definitive treatment options. Treatment is best customized to the individual patient based on multiple factors including the chances of remission with oral medications, desire and timing of future pregnancies in older youth, thyroid gland size and other coexisting conditions besides the patient's choice (Table 2) [38].

#### Anti-thyroid drugs (ATD)

Thionamide derivatives such as methimazole (MMI), propylthiouracil (PTU) and carbimazole (not available in USA) are commonly used as initial ATD therapy. These drugs inhibit thyroid hormone synthesis by disturbing the thyroid peroxidase-mediated iodination of tyrosine residues in thyroglobulin [47]. These agents are actively concentrated by the thyroid gland against a concentration gradient [48]. Although it is controversial, ATD may also have an immunosuppressive effect including apoptosis of intrathyroidal lymphocytes [49]. PTU, unlike MMI, additionally inhibits peripheral conversion of T4 to T3.

ATD are used as the first line therapy in pediatric population with GD hoping for spontaneous remission. MMI is superior to PTU due to longer

half-life requiring once or twice daily dosing, thus improving treatment adherence. Also, PTU has a higher risk of liver failure (1 in 2000-4000) including fulminant hepatic necrosis [47,50]. Hence, PTU is only used for a short course on patients with adverse reaction to MMI who are not candidates for radioiodine therapy or surgery [38]. The MMI dose typically used is 0.2-0.5 mg/kg/day orally, with a range from 0.1-1.0 mg/kg/day [38]. Maximal clinical response to ATD occurs in approximately 4-6 weeks into treatment. Initially, 50-100% higher doses can be used if patient has severe clinical or biochemical hyperthyroidism. Once thyroid function tests (TFT) are normal, either MMI dose could be reduced or levothyroxine could be added to the treatment to achieve euthyroid state, practice known as "block and replace therapy". However, because meta-analyses suggest a higher prevalence of adverse events using block and replace regimens than dose titration [47,51,52], ATA and AACE 2011 guidelines recommend avoiding this practice in general.

Once started on ATD, patients are initially monitored via history of symptomatic relief and TFT every month and then every 2-4 months [38]. Medication dose is titrated based on TFT and once biochemical euthyroidism is reached, patient can be followed up at every three to four month intervals.

**Adverse drug reactions:** MMI and PTU have similar side effects although they occur more often and are more severe with PTU. Side effects from ATD can be divided as *minor* and *major* depending on the severity. Minor side effects are dermatitis, including rash, urticaria; gastrointestinal upset, arthralgia, pruritus and fever [42]. It is generally recommended to discontinue the drug for a few days until the symptom subsides. Major side effects include agranulocytosis, even life-threatening pancytopenia, vasculitis (lupus-like syndrome), hepatitis and liver failure. Side effects of MMI usually occur within the first 6 months of starting therapy [47]. Because patients with hyperthyroidism can have slightly low white blood cell counts (WBC) and slightly high serum aminotransferase and gamma glutamyl transpeptidase concentrations due to the disease itself or side effect of treatment, it is recommended to measure these at baseline before beginning antithyroid drug therapy [47]. While routine monitoring of WBC may occasionally detect early agranulocytosis, it is not recommended because of the rarity of the condition and its sudden onset, which is generally associated with symptoms [53]. The 2011 ATA and AACE guidelines recommend informing patients and guardians about the medication side effects, necessity to discontinue the medication immediately and informing their physician if they develop pruritic rash, jaundice, acolic stools or dark urine, arthralgias, abdominal pain, nausea, fatigue, fever or pharyngitis. Some endocrinologists recommend written instructions and re-emphasis at clinical follow up visits. If the granulocyte count is normal, antithyroid drug treatment may be restarted. If the granulocyte count is low but not meeting criteria for agranulocytosis, neutrophil counts usually recover spontaneously within one to two weeks [54]. Agranulocytosis ( $<500/\text{mm}^3$ ) is a contraindication to future antithyroid drug treatment [53] and occurs in 95% of cases during the first 100 days of therapy [52].

ATD treatment can cross the placenta and have an increased risk of birth defects if continued during pregnancy. Hence, this prospect should be discussed with adolescent females of reproductive age. MMI embryopathy is characterized by minor dysmorphic features, choanal atresia and/or esophageal atresia, growth retardation, and developmental delay [55,56]. PTU leads to malformations of the face and neck. Both drugs are associated with urinary tract malformations [57]. Because MMI does not result in teratogenic effects after first trimester compared to PTU and theoretically reduced risk of placental transport, which causes severe hepatotoxicity, it is consensus to use PTU to treat maternal hyperthyroidism during the first trimester of pregnancy, and to switch to MMI for the remainder of the pregnancy [58].

	Indications	Contraindications	Advantages
Antithyroid drugs	Patients with greater chance of remission (e.g. mild disease, small goiters and negative or low-titers of TSHR-Ab), unavailability of a high-volume thyroid surgeon, moderate to severe active GO	History of major adverse reactions including agranulocytosis	Non-invasive, no requirement of inpatient hospital stay, less expensive, avoidance of surgery and radioactivity exposure, low risk of permanent hypothyroidism, possible immune-modulatory effects
Radioactive iodine	Individuals with coexisting conditions that increase surgical risk, those who have had surgery in the past, less likely to enter remission, or unavailability of a high-volume thyroid surgeon or contraindications to ATD use	Pregnancy, breastfeeding, coexisting thyroid cancer or suspicion of thyroid cancer, those who are not able to follow radiation safety precautions, those that desire pregnancy within 4–6 months	Definitive cure of hyperthyroidism, outpatient therapy, easily applicable with no surgical/anesthesia risk, reduction in goiter size
Surgery	Patients with features of posterior compression or presence of large goiters ( $\geq 80$ g); patients with relatively low uptake of radioactive iodine e.g., large non/ hypo functioning nodule; in presence /suspicion of thyroid malignancy, coexisting hyperparathyroidism that itself requires operative intervention, if planning a pregnancy in <4–6 months, especially if TSHR-Ab levels are particularly high; and patients with moderate to severe active GO	Presence of other coexisting conditions which increase risk of anesthesia and surgery e.g., end stage cancer, pulmonary disease. Pregnancy is a relative contraindication; usually avoided in the first and third trimesters, optimally, performed in the second half of the second trimester	Rapid symptomatic and etiologic control of hyperthyroidism and compression, if present, definitive cure, avoidance of radioactivity exposure

\*[Adapted from 2011 guidelines for hyperthyroidism treatment by ATA and AACE(31)]

**Table 2:** Treatment options characteristics\*.

**Role of beta blockers:** Until the signs and symptoms of hyperthyroidism are controlled and euthyroidism is achieved with ATD, beta-blockers such as atenolol or propranolol can be used to counteract symptoms of adrenergic over activity, such as palpitations, tremors or neuropsychological symptoms [38]. Atenolol is preferred for its cardio-selective nature. Therefore, risk of bronchospasm in patients with asthma is reduced as compared with other beta blockers [59]. In addition, it is administered once daily, resulting in better compliance.

**Remission and relapse on ATD:** In children, when ATD are used for 1–2 years, remission rates are generally <30% [4,60]. Current 2011 ATA and AACE guidelines recommend continuing ATD if no major side effects for 2 years in children. If remission (euthyroid after 1 year of cessation of therapy) is not achieved, consider definitive treatment options with radioiodine therapy or surgery [38]. Retrospective studies have suggested that the chance of remission after 2 years of ATD is low if the thyroid gland is large (>2.5 times normal size for age), the child is young (<12 years) or not Caucasian, serum TSHR-Ab levels are above normal on therapy, or free T4 levels are substantially elevated at diagnosis (>4 ng/dL; 50 pmol/L) [2,4]. One prospective study suggested that the likelihood of remission could be best predicted by the initial response to antithyroid medication, with achievement of euthyroid state within 3 months. Younger children and those with high initial thyroid hormone levels were also found to be less likely to achieve remission within 2 years in the prospective study [61].

### Radioactive iodine treatment

Radioiodine therapy provides definite treatment for GD. Following oral administration of the radioiodine  $^{131}\text{I}$ , it is actively taken up by the hyperactive gland and leads to an intense radiation thyroiditis, progressive interstitial fibrosis and glandular atrophy and hence, results in hypothyroidism. It could result in transient increase in thyroid hormone levels with possible worsening of thyrotoxic symptoms including thyroid storm due to the release of the preformed hormone due to the acute gland destruction. Also, can worsen GO if present prior to the treatment with radioiodine [62].

Pediatric patients, who are not candidates for ATD, should be offered Radioiodine therapy or surgery. These include patients who failed to undergo remission or had major side effects with ATD. As mentioned

above, as per ATA and AACE guidelines, radioiodine treatment is an acceptable therapeutic regimen in children between 5 years of age and older if the appropriate dose of  $^{131}\text{I}$  is administered [38].

The aim of  $^{131}\text{I}$  treatment is to induce hypothyroid state rather than euthyroidism as the lower dose may lead to the remainder of the gland susceptible to increased risk of developing thyroid nodules and cancer [63]. Some centers administer a fixed dose of 15 mCi  $^{131}\text{I}$  to all children [64], while others calculate the dose based on measurement of gland using ultrasonography and  $^{123}\text{I}$  uptake [65]. In adults, similar conclusion has been reported with the two approaches although there is no data currently available comparing the outcomes in children [66]. However, dose calculation could allow requirement of lower doses especially when associated with high  $^{123}\text{I}$  uptake and small gland.

After  $^{131}\text{I}$  therapy, TFT are obtained monthly to assess for hypothyroidism which usually occurs within 1 to 3 months, although could occur much later until 6 months and hence, the need to start replacement [67].

When children receiving MMI are to be treated with  $^{131}\text{I}$ , the medication is usually stopped 3-5 days before treatment [65] and a beta-blocker is started and continued until total T4 and/or FT4 levels normalize following radioactive iodine therapy. Thyroid hormone levels in children begin to fall within the first week following radioactive iodine therapy. ATD can complicate assessment of post-treatment hypothyroidism, since it could be the result of the MMI rather than the  $^{131}\text{I}$  therapy [30,68].

Radioactive iodine is excreted in saliva, urine, and stool. Significant radioactivity is retained within the thyroid for several days. It is therefore important that patients and families be informed of and adheres to local radiation safety recommendations following this regimen especially avoiding exposure to pregnant or young children who are more susceptible to radioactivity. Information for patients and families can be accessed from the ATA website (<http://www.thyroid.org/radioactive-iodine>).

Side effects of radioiodine therapy treatment in children are uncommon except for permanent hypothyroidism. Less than 10% of children have mild tenderness over the thyroid in the first week after therapy that responds well to acetaminophen or nonsteroidal anti-inflammatory agents for 24–48 hours [65]. There is theoretical possibility of thyroid neoplasia development in remnant thyroid tissue, but that is suspected

to be more related to iodine deficiency rather than treatment itself. In addition, there has been no increased risk of non-thyroid malignancies in long-term studies of children treated with radioiodine [69]. Hence, due to these theoretical possibility of future neoplasia, ATA and AACE recommend to assess the risk to benefit ratio for all treatment options and to avoid radioiodine ablation in very young children (<5 years) and to consider for children 5 years of age and older [38].

### Surgery

Although surgery is not often recommended as initial therapy for children or adolescents with GD, it offers definitive treatment as total or near-total thyroidectomy with the side effect of lifelong hypothyroidism. In adults, subtotal thyroidectomy may have an 8% chance of persistence or recurrence of hyperthyroidism at 5 years [53]. It is useful when ATD fails or causes side effects especially in children <5 years of age. Surgery may be particularly appropriate for those with very large goiter, as studies in adults suggest that individuals with large thyroid glands (greater than 80 g) are unlikely to respond to RAI treatment [61]. If surgery is planned, the patient should be treated with an ATD for 1–2 months in preparation for thyroidectomy. Ten days before surgery, potassium iodide (50 mg iodide/drop) can be given as 3–7 drops (i.e., 0.15–0.35 mL) three times daily for 10 days. Iodides block the release of thyroid hormones and reduce the vascularity of the thyroid gland, making them particularly useful for preparing a thyrotoxic patient for surgery [70].

Guidelines recommend that surgery should be performed by a “high-volume thyroid surgeon”, at least 30 thyroid/neck surgeries per year [38]. If local pediatric thyroid surgery expertise is not available, it is important to refer the patient to a specialized center because complication rates are twofold higher when surgery is performed by pediatric or general surgeons who do not have extensive current experience in this procedure [71].

Surgical complication rates are higher in children than in adults, with higher rates in younger than in older children. Postoperatively, younger children also appear to be at higher risk for transient hypoparathyroidism than adolescents or adults [71].

### Conclusion

GD is the most common cause of thyrotoxicosis in children in iodine-sufficient areas and is also one of the most common autoimmune conditions. The autoimmune origin of GD has been described in terms of the identification of pathogenic antibodies as well as the coexistence and clustering of diseases of autoimmune origin in same individual and family. The exact etiology as to what leads to the loss of tolerance and development of autoimmunity is not clearly identified yet. The clinical presentation can be subtle in children and hence, high index of suspicion is needed. Anti thyroid drugs are the first line of treatment although ultimately, definitive treatment may be required.

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