Chapter 20: Anesthetic Considerations for Endocrine Disorders

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INTRODUCTION

FOCUS POINTS

1. Preoperative evaluation for elective surgery should include assessment of glycemic control (glycohemoglobin and serum blood sugar), electrolyte status, and presence or absence of ketones. Additional testing is dictated by patient comorbidities.
2. Patients who use glargine (Lantus®) should take their full dose on the evening prior to surgery or the morning of surgery and omit their short- or rapid-acting insulin dose on the day of surgery.
3. Hyperglycemia impairs wound healing, decreases chemotaxis and phagocytosis, and has been shown to increase rate of surgical infection.
4. Graves disease, an autoimmune disease producing TSH-receptor stimulating antibodies resulting in excess production and release of T_3 and T_4, is the most common cause of hyperthyroidism in children and adolescents.
5. Postoperative thyroid surgery concerns include hypocalcemia from parathyroid trauma causing muscle weakness, respiratory insufficiency due to vocal cord paresis/paralysis, tracheomalacia from a large compressive tumor, and obstruction from surgical site hematoma.
6. The average age of presentation of pheochromocytomas (PCC) and paragangliomas (PGL) in pediatrics is 11 to 13 years, with presentation varying from headaches, sweating, flushing, and nausea to paroxysmal and sustained hypertension.
7. Prior to resection of PCC and PGL, α-blockade and fluid resuscitation should be initiated followed by β-blockade. The order of blockade is critical to prevent the unopposed β effect resulting in cardiac dysfunction and pulmonary edema.
8. Post PCC and PGL resection, profound hypotension may require vasopressin infusion.

GLYCEMIC CONTROL

Diabetes Mellitus

Diabetes mellitus (DM) is hallmarked by the dysregulation of glucose homeostasis leading to hyperglycemia. The causes may be attributed to absence of insulin, diminished insulin levels, or insensitivity of the peripheral tissues to insulin. Gluconeogenesis and lipolysis are affected and may result in lactic acidosis and ketosis. The incidence and prevalence of all diabetes types appear to be on the rise. According to Centers for Disease Control and Prevention (CDC) data, approximately 200,000 children and adolescents are affected across the United States.[1] The mortality rates from diabetes and its complications among young people appear to be stable at approximately 1/1,000,000. Diabetes may be divided into the following subtypes that define some of the pathophysiological processes.[2,3]

Type 1 diabetes mellitus (DM-1)

Type 2 diabetes mellitus (DM-2)

Genetic defect of β-cell function

- Mature onset diabetes of the young (MODY)[3,4]
- Mitochondrial disorders
- Exocrine pancreas disease
- Cystic fibrosis
- Thalassemia
- Congenital rubella
- Insulin resistance
- Rabson-Mendenhall
- Endocrinopathies
- Autoimmune polyglandular syndrome
- Cushing syndrome
- Drug induced
- Steroids
- Chemotherapy agents
- Genetic
- Down syndrome
- Klinefelter syndrome
- Myotonic dystrophy
- Prader-Willi syndrome
- Turner syndrome
- Werner syndrome
- Wolfram syndrome

DM-1 is characterized by autoimmune-mediated pancreatic insulin-secreting β-cell destruction, and an absolute deficiency of insulin. New theories on etiology link onset of autoimmune DM-1 (anti-pancreatic β-cell) to genetic susceptibility and to an infectious etiology, as diagnosis rates increase during autumn and winter months mirroring increased rates of viral infections in the pediatric population.[2] The prevalence of DM-1 in U.S. youth (0 to 19 years of age) is on the rise, and increased from 1.48 per 1,000 in 2001, to 1.93 per 1,000 in 2009.[5] The etiology of the increase is unclear.

DM-2 is hallmarked by insulin resistance and relative insulin deficiency. Previously, DM was thought to be a disorder of the aging and overweight adult population but with the increase in youth obesity rates, DM-2 has been rising in the pediatric population as well. DM-2 correlates with family history of diabetes, suggesting a genetic link.[5] In 2009, the prevalence of DM-2 in adolescents (ages 10 to 19) was 0.46 per 1,000, a 30% increase from 2001[5] and the incidence of diabetes in the adult population is expected to surpass 40% by 2025.[6]

MODY is a non-insulin-dependent DM that is inherited in an autosomal dominant manner and presents in childhood or early adolescence with mild hyperglycemia, and slowly progressive disease.[3,4] Patients are initially asymptomatic, and may be treated with diet and oral agents. Insulin is rarely

required during initial phase, lasting 5 years, or longer. MODY can be further divided into subtypes 1 to 5 by the causative genetic defect and varying severity.

Other genetic conditions that are often associated with DM include cystic fibrosis, Prader-Willi syndrome, Down syndrome, Turner syndrome, Wolfram syndrome, Cushing syndrome, as well as some chronic steroid regimens and chemotherapy agents.

There are significant ethnic and racial disparities in the incidence, prevalence, and mortality rates related to diabetes. The incidence of DM-1 and prevalence of DM-2 among white children and adolescents is higher than among black children and adolescents. But the mortality rate among the black population was reportedly higher for the same time period.[7] The incidence of obesity, DM-2, and MODY with dyslipidemia has been rising in the Asian adolescence population as well.[8]

Preoperative Planning for Glycemic Control

Preoperative planning must be tailored to the patient's treatment regimen optimizing glycemic control perioperatively. Preoperative evaluation for elective surgery should include assessment of glycemic control, electrolyte status, and presence or absence of ketones, as well as any additional tests such as ECG and chest x-ray guided by clinical history and other comorbidities. Goals of glycemic control, as evaluated by hemoglobin A1c (HbA1C) are age dependent (Table 20-1). A diabetic patient case should be scheduled as first case of the day, if possible, to minimize duration of preoperative fasting. If metabolic studies are unacceptable, patients should be referred back to their endocrinologist for adjustment of therapy. Glycemic control goals and regimen should ideally be coordinated with the endocrinology service.[9]

Table 20-1

Glycemic Control by Age[9]

Age	HbA1c levels
<5 years	7–9%
5–13 years	6–8.5%
>13 years	6–8%

Data from Rhodes ET, Ferrari LR, Wolfsdorf JI. Periopertaive management of pediatric surgical patients with diabetes mellitus. *Anesth Analg.* 2005;101:986-999. https://journals.lww.com/anesthesia-analgesia.

Acceptable glycemic control for patients with DM-1 is most commonly achieved with "split-mixed" insulin regimen[9] (intermediate or long-acting baseline regimen, and rapid or short-acting boluses for meals). For those who use insulin pumps, adjustments to the pump infusion rate are to be made on the day of surgery.[10] For DM-2, similar workup is needed, and endocrinology should be consulted regarding adjustments to insulin or oral agents in preparation for surgery.[11]

Day of Surgery and Intraoperative Management

"Split-mixed" regimen plan requires adjustments to insulin dosing on the day of surgery. The recommended modifications are as follows:

1. Hold rapid/short-acting insulin [regular or lispro (Humalog®)].
2. Administer half (50%) of AM dose of intermediate (NPH or Lente) or long-acting (ultralente) insulin dose.
3. Skip breakfast and follow appropriate NPO guidelines for surgical/imaging procedures.
4. Recheck blood glucose, electrolytes, and ketones (blood or urine) upon arrival.

5. Proceed with case if patient is normoglycemic (glucose <250 mg/dL) and electrolytes are normal. If patient is hyperglycemic (glucose >250 mg/dL), correct glucose level with short-acting insulin dose subcutaneously, according to patient's usual sliding-scale insulin regimen. In the absence of a sliding-scale regimen, the appropriate dose of insulin may be calculated using the "1500 rule" (Box 20-1).
6. Follow blood glucose levels once hyperglycemia is treated to confirm normoglycemia.
7. For patients using electronic continuous glucose monitoring, correlating monitor with on-site lab is suggested.

Box 20-1

Insulin Correction Factor Calculation[9]

The 1,500 rule calculates the anticipated reduction in glucose level per unit of insulin, based on the patient's daily dose of insulin. This "insulin correction factor" is obtained by dividing 1500 by the total units of insulin required daily to treat the child.

When the patient is using an *insulin pump* to manage his or her diabetes, there are a number of issues to consider[10]: For short procedures (less than 2 hours) where the pump does not interfere with the procedure:

1. Eliminate preprandial bolus.
2. Maintain basal infusion rate with hourly glucose checks.
3. Know typical bolus rate required to decrease glucose 50 mg/dL, and use if necessary (learn sequence to program pump for bolus, or have a supplemental dose for SC administration available).
4. Resume preoperative diet schedule as soon as possible.

Procedures lasting more than 2 hours require conversion to insulin infusion with D101/2 NS at the maintenance fluids rate. Glucose levels should be followed intraoperatively at least hourly, and infusion rates adjusted accordingly. The goal of insulin therapy with insulin infusion is 150 mg/dL.[9]

To initiate an insulin infusion, initial rate should be at 1 unit per 5-g dextrose for children 12 or younger, and 1 unit per 3-g dextrose for patients older than 12. The insulin and dextrose should be administered via the same IV line, via Y-connector, if possible, minimizing the risk of unintended bolus or interruption of the infusions. Interruption of either one without the other can be catastrophic, leading to severe hyperglycemia or hypoglycemia.[9]

Patients who use glargine (Lantus®) should take their full dose on the evening prior to surgery or the morning of surgery and omit their short- or rapid-acting insulin dose on the day of surgery. Rapid-acting insulin [Lispro (Humalog®)] should be used according to the child's "correction factor" to achieve glucose level of 150 mg/dL.

For children with DM-2 and MODY on oral regimen, the preoperative adjustments start prior to the day of surgery. Metformin (Glucophage®) should be held 24 hours prior to surgery; sulfonylureas [glipizide (Glucotrol®), glyburide (Micronase®)] and thiazolidinediones [rosiglitazone (Avandia®), pioglitazone (Actos®)] should be discontinued on the morning of surgery. Preoperative hyperglycemia should be treated with rapid-acting [Lispro (Humalog®)] insulin 0.1 U/kg SC and continue to monitor hourly.[9]

Postoperative Management

Insulin/dextrose infusion should be discontinued as soon as the patient is able to tolerate oral intake. Glucose levels should be monitored postoperatively. For those who are unable to resume oral intake, maintain dextrose-containing maintenance fluids, and consider intermittent insulin dosing instead of infusion for the duration of their postoperative fasting.

Associated Comorbidities

Overweight and obese patients with DM-2 exhibit signs of insulin resistance, including acanthosis nigricans, precocious puberty, hypertension,

dyslipidemia, and polycystic ovary syndrome. Many of the advanced complications of diabetes are present long before they become symptomatic. Microangiopathy leads to nephropathy, renal insufficiency, and retinopathy. Dyslipidemia and hypertension lead to atherosclerotic vascular changes affecting both cardiac and peripheral vasculature. Autonomic dysfunction related to chronic hyperglycemia and hypertonicity may be present, and manifest as orthostatic hypotension, resting tachycardia, lack of respiratory variation of heart rate, and blunted or absent symptoms of hypoglycemia. Gastroparesis increases aspiration risk, and peripheral neuropathy can lead to perioperative injury.[12]

Hyperglycemia impairs wound healing, decreases chemotaxis and phagocytosis, and has been shown to increase rate of surgical infection.[13] Surgery and anesthesia are stressful, and as such can have profound effect on glucose metabolism. While minimally concerning in a healthy patient, derangement can be dramatic in the diabetic patient. Stress response encompasses catabolism with elevated cortisol, glucagon, catecholamine, and growth hormone levels, increased gluconeogenesis and lipolysis, and decreased insulin levels. The potent inhaled anesthetics can induce hyperglycemia due to fatty acid mobilization and inhibition of insulin secretion. Propofol may increase lipid load, benzodiazepines decrease ACTH levels, and opioids may block the hypothalamic-pituitary axis. While spinal and epidural anesthetic techniques may attenuate the metabolic changes associated with surgical stress, there is no evidence that neuraxial anesthesia affects morbidity or mortality in the diabetic patient.[2]

THYROID DISORDERS

Thyroid hormone production and release is autoregulated by a negative feedback loop involving the hypothalamic-pituitary-thyroid axis (Figure 20-1). The hypothalamus releases thyrotropin-releasing hormone (TRH), which stimulates the anterior pituitary to release thyroid-stimulating hormone (TSH), which, in turn, stimulates the thyroid gland to release thyroid hormone. Thyroid hormone inhibits the release of TRH and TSH, closing the feedback loop.[14]

Figure 20-1

Hypothalamic-pituitary-thyroid axis.

Production of thyroid hormone depends on the hormonal controls and on availability of iodine in the diet. Iodine is easily absorbed by the gut, and as much as 90% of the body's iodine is stored in the thyroid gland. After iodine is taken up by the follicular cells in the thyroid gland, it is rapidly oxidized, and combined with tyrosyl residues within thyroglobulin to form monoiodotyrosine (MIT) and diiodotyrosine (DIT). MIT and DIT then combine to form T_3 (triiodothyroxine) and T_4 (thyroxine), and are subsequently stored bound to thyroglobulin in the colloid center of the follicular cells. Thyroid hormone in circulation is protein bound, attached to thyroxine-binding protein (TBG), albumin, and transthyretin. Once dissociated from its protein, the lipophilic thyroid hormone rapidly diffuses into the cells, and acts as a prohormone in the cell's nucleus and mitochondria.[15]

Hyperthyroidism (Box 20-2)

Hyperthyroidism is defined as the excess production and release of thyroid hormone, resulting in inappropriately high levels of serum thyroid hormone and a hypermetabolic state.[15] Thyroid hormone affects every organ system and can present with varied symptoms.[15] Symptoms of hyperthyroidism in the pediatric population are non-specific, and easily overlooked.[16] They can range from nervousness, fatigue, sleep disturbances, and behavioral and learning disorders to congestive heart failure, altered mental status, and death.[15,16]

Box 20-2

Causes of Hyperthyroidism in Children[15,17]

Graves disease (diffuse toxic goiter)
Toxic multinodular goiter
Toxic thyroid adenoma
TSH-secreting pituitary adenoma
Thyrotoxicosis
Hashimoto's chronic lymphocytic thyroiditis
DeQuervain's subacute granulomatous thyroiditis
Subacute lymphocytic thyroiditis
Thyroid storm
Malignancy (MEN-2A, MEN-2B)

Graves disease, an autoimmune disease producing TSH-receptor stimulating antibodies resulting in excess production and release of T_3 and T_4, is the most common cause of hyperthyroidism in children and adolescents, with incidence of 0.02%.[13,17] As in the adult population, the treatment options range from antithyroid medication to radioactive iodine ablation (RIA) to thyroidectomy. In contrast to the adult population, RIA is controversial in the pediatric population, owing to concerns about radiation exposure during periods of growth, and potential long-term complication from exposure (although there is no data to support these concerns). Antithyroid medication is limited to methimazole, as propylthiouracil is contraindicated in children due to high incidence of liver injury and liver failure requiring liver transplantation.[16,18] Methimazole is associated with minor side effects, but does carry more serious risks of agranulocytosis in a dose-dependent fashion—Stevens-Johnson syndrome, vasculitis, and lupus-like syndrome. Methimazole is not curative for Graves disease; it merely mitigates the symptoms until the disease goes into spontaneous remission.[17] Remission rates range from 20% to 30%, and are worse for patients with high antibody levels, very high free T_4 levels at diagnosis, and with large gland. Relapse rates range from 25% to 60% after withdrawal of medication.[17] Younger children have higher relapse rates and lower remission rates, necessitating definitive treatment.[16,19,20] The most common cause of treatment failure in the pediatric population remains noncompliance due to prolonged course of therapy (Table 20-2).[17]

Table 20-2

Thyrotoxicosis in Children[15,17]

Differential Diagnosis	Thyroid Storm
Acute pulmonary edema	Heat stroke
Malignant hyperthermia	Sepsis/septic shock
Sympathomimetic overdose	Seratonin syndrome
Tachyarrhythnia	

Data from Devereaux D, Toweled S. Hyperthyroidism and thyrotoxicosis. *Emerg Med Clin N Am*. 2014;32:277-292. https://www.sciencedirect.com/journal/emergency-medicine-clinics-of-north-america. Knollman PD, Giese A, Bhayani MK. Surgical intervention for medically refractory hyperthyroidism. *Pediatric Annals*. 2016;45(5):e171-e175. https://www.healio.com/pediatrics/journals/pedann.

Thyroid surgery for Graves disease and other thyrotoxic conditions can present numerous challenges perioperatively. Thyroid hormone level should be suppressed with antithyroid drugs (methimazole) preoperatively, and symptoms must be treated supportively (β-blockers). The gland is inflamed, and more vascular, and thus, more challenging to resect. In fact, several recent publications cite increased risk of complications in the pediatric population compared with adults after thyroidectomy.[16] Electromyogram (EMG) endotracheal tubes have been used successfully to detect proximity to the recurrent laryngeal nerve during thyroid resection and reduce risk of nerve injury. The possibility of a difficult intubation must be considered, although reports of difficult intubation correlate with advanced age, and have not been reported in the pediatric population.[21–24]

Intraoperative management of thyroidectomy for a secretory condition should avoid sympathomimetics and vagolytics, and include medications to treat a potential thyroid storm, such as β-blockers. The astute clinician must also consider a differential diagnosis in the event of a hypermetabolic crisis (malignant hyperthermia, sepsis, etc.) (Table 20-3).[13] If available, EMG endotracheal tube can be placed with the aid of a video laryngoscope to ensure proper placement and allow monitoring of pharyngeal/vocal cord innervation during thyroid resection.

Table 20-3

Treatment Strategies for Hyperthyroidism[15]

Drug Type and Name	Mechanism of Action	Neonatal Dose*	Pediatric Dose**	Adult Dosing	Thyroid Storm Dosing***
Antithyroid					
Propylthiouracil (PTU)	Prevents T_3/T_4 production in thyroid gland	5–10 mg/kg/day PO divided in q8h dosing	Initial: 5–7 mg/kg/day PO divided in q8h	Initial: 100–200 mg PO q6–8h	500–1,000 mg loading dose 250 mg q4–6h PO/NG/OG
	Blocks T_4 to T_3 conversion		Maintenance: 1/3 – 2/3 initial dose, divided in q8h dosing	Maintenance: 50–100 mg/d	
	Maintenance: 1/3 – 2/3 initial dose, divided in q8h dosing				
Methimazole (MMI)	Prevents production of thyroid hormone	N/A	Initial: 0.4–0.7 mg/kg/day PO divided in q8h dosing	Initial: 10–20 mg PO q8–12h	60–80 mg/day POnNG/OG

			Max: 30 mg/day	Maintenance: 2.5–10 mg/day	
Iodides					
Lugol solution	Blocks release of stored thyroid hormone from gland	1 drop PO q8h	N/A	4–8 drops q6h–q8h PO/NG/OG	10 drops q12h PO/NG/OG
			1–5 drops q8h PO/NG/OG	5–10 drops q6–8h PO/NG/OG	5–10 drops q6–8h one hour after PTU or MMI
Glucocorticoids					
Dexamethasone	Blocks conversion of T_4 to T_3			2 mg q6h PO	2 mg q6h IV/PO/NG/OG
Hydrocortisone			2 mg/kg q6h PO/IV		300 mg IV load, 100 mg IV q6–8h
Prednisone				40–60 mg PO daily ×1 week, then taper	
Beta-blockers					
Propranolol	Reduces symptoms of catecholamine response, blocks T_4 to T_3 conversion	2 mg/kg/day PO divided in q6–12h dosing	0.5–1 mg/kg/d divided q6–8h	10–40 mg PO q6–8h	1 mg/min IV as needed
Atenolol			0.5–1 mg/kg PO qd (up to 100 mg/day)	25–100 mg PO qd (up to 200 mg/day)	60–80 mg q4h PO/NG/OG
Esmolol		100–500 mcg/kg IV load, then 100 mcg/kg/min	100–500 mcg/kg IV load, then 25–100 mcg/kg/min		500 mcg/kg/min for one minute, then 50–100 mcg/kg/min

*Neonatal thyrotoxicosis is a result of maternal Graves disease, and transplacental passage of thyroid-stimulating antibodies. It is self-limited, as antibodies decline in 3–4 months.[15]

**PTU is associated with hepatotoxic reaction and fulminant liver failure in children, and is therefore contraindicated.[15,20]

***Avoid salicylates during thyroid storm, as they can increase free thyroxin level by decreasing thyroid-binding protein. Use acetaminophen and cooling devices for hyperthermia.[15]

Reproduced with permission, from Devereaux D, Toweled S. Hyperthyroidism and thyrotoxicosis. *Emerg Med Clin N Am.* 2014;32:277-292. https://www.sciencedirect.com/journal/emergency-medicine-clinics-of-north-america.

Postoperative Considerations

Postoperative concerns include hypocalcemia from parathyroid trauma causing muscle weakness, respiratory insufficiency due to vocal cord

paresis/paralysis, tracheomalacia from a large compressive tumor, and obstruction from surgical site hematoma.[23,25–27] Although the incidence of post-op hypocalcemia was similar in adults and children, children reported more symptoms of transient hypocalcemia (35% vs. 21% of adults) and were prescribed calcitriol more frequently and for a longer duration compared with adults.[16,27] The rate of parathyroid reimplantation was significantly higher in children who had a total thyroidectomy (10.9%) vs. partial thyroidectomy (3.1%).[25] The rate of transient nerve palsy was slightly higher in children (10%) than adults (5%) but not statistically significant except for patients <1 year old: incidence of >14%,[25] and the rate of permanent complications was low in both adults and children.[16] It is notable that children <6 years old, especially those <1 year of age having a total thyroidectomy, do carry a significantly higher risk of postoperative complications (Figure 20-2).[25]

Figure 20-2

Post-thyroidectomy complication rates by patients' age.[25] (Adapted from Hanba C, et al. Pediatric thyroidectomy: hospital course and perioperative complications. *Otolaryngol Head Neck Surg.* 2017;156(2):360-367. https://journals.sagepub.com/home/oto.)

Hypothyroidism

Hypothyroidism is the most common cause of preventable intellectual disability. Its incidence has been rising since the mid-1970s, with the advent of newborn screening and reduction of threshold to include milder cases.[18] At present, congenital hypothyroidism affects 1:2,500 live births in North America, with wide variations across demographics. Eighty-five percent of cases of congenital hypothyroidism are caused by gland dysgenesis, and approximately two-thirds of cases are related to ectopic location of the gland. Most cases of thyroid dysgenesis or agenesis are sporadic and idiopathic. Iatrogenic congenital hypothyroidism is seen in infants whose mothers received radioactive iodine after the tenth week of gestation. Transient hypothyroidism may be seen in newborns of mothers on thyroid suppression drugs, and mothers who are iodine deficient. Notably, newborns with large congenital hepatic hemangiomas may present with hypothyroidism as well.[18] Symptoms of hypothyroidism are varied (Table 20-5), from early decreased activity, prolonged jaundice, hypotonia, hypothermia, edema of the eyelids and extremities, and a protuberant abdomen, to late findings of poor sucking effort, developmental delay, poor growth, hoarse cry, decreased activity, and lethargy, to myxedema and coma.

Table 20-5

Congenital Hypothyroidism Signs and Symptoms[18]

Onset	Signs and Symptoms
Early findings	Macrosomia
	Decreased activity
	Large anterior fontanelle
	Edema of eyelids, hands, and feet
	Prolonged jaundice
	Hypotonia
	Coarse facial features
	Hypothermia
	Pallor
	Goiter
	Protuberant abdomen
Late findings	Poor sucking
	Developmental delay
	Lethargy, decreased activity
	Poor growth trajectory
	Umbilical hernia
	Mottled, cool, dry skin
	Difficult breathing
	Macroglossia
	Myxedema (generalized swelling)
	Hoarse cry

Source: Reproduced with permission, from Diaz A, Lipman-Diaz EG. Hypothyroidism. *Pediatr Rev.* 35(8):336-347; quiz 348-9. Copyright © 2014 by the AAP. https://pedsinreview.aappublications.org/.

Acquired primary hypothyroidism is most commonly a result of autoimmune (Hashimoto) thyroiditis but may also be a side effect of medication (Table

20-6).[32] It may present with a goiter, poor growth velocity, decreased energy, declining school performance, constipation, and in girls with precocious puberty and hyperprolactinemia. It may also coexist with Graves disease, and signs and symptoms may alternate between the two autoimmune conditions.[18] Secondary (central) hypothyroidism is a result of hypothalamic or pituitary dysfunction which can be congenital, neoplastic, or traumatic (Table 20-7).

Table 20-6

Medication Effects on Native Thyroid Function[32]

Decreased TSH	Dopamine, glucocorticoids, octreotide, metformin, opiates, rexinoids, carbamazepine/oxcarbamazepine, metformin
Decreased thyroid hormone secretion	Lithium, iodine/iodinated contrast, amiodarone, aminoglutethimide
Increased thyroid hormone metabolism	Phenobarbital, rifampin, phenytoin, carbamazepine
Inhibition of T_4/T_3 synthesis	Propylthiouracil, methimazole
Thyroiditis	Interferon, interleukin-2, sunitinip, amiodarone

Source: Data from Haugen BR. Drugs that suppress TSH or cause central hypothyroidism. *Best Pract Res Clin Endocrinol Metab.* 2009;23(6):793-800. https://www.journals.elsevier.com/best-practice-and-research-clinical-endocrinology-and-metabolism.

Table 20-7

Syndromes and Disorders Associated with Hypothyroidism[14,18]

Down Syndrome	Turner Syndrome	Williams Syndrome
Costello syndrome	Septo-optic dysplasia	
Craniopharyngioma	Pituitary adenoma	Meningioma
Rathke's cleft cysts	Empty sella/Sheehan syndrome	
Combined pituitary hormone deficiencies	Lymphocytic hypophysitis	Polyglandular autoimmune syndrome
Sarcoidosis—Langerhans histiocytosis	Infection (syphilis, tuberculosis)	
Head trauma	Head and neck irradiation	Surgery

Source: Data from Dubbs SB, Spangler R. Hypothyroidism: causes, killers, and life-saving treatments. *Emerg Med Clin N Am.* 2014;32:303-317. https://www.sciencedirect.com/journal/emergency-medicine-clinics-of-north-america. Diaz A, Lipman-Diaz EG. Hypothyroidism. *Pediatr Rev.* 2014;35(8):336-347; quiz 348-9. Copyright © 2014 by the AAP. https://pedsinreview.aappublications.org/.

Hypothyroid condition should be corrected, and patient should have laboratory testing to confirm euthyroidism prior to operative interventions. Since thyroid hormone is essential for all organ systems' appropriate function,[23] anesthesia in the setting of hypothyroid condition has an increased incidence of morbidity, and potential mortality. In the emergent situation, thyroid hormone replacement can be initiated in the perioperative setting.[31] Caution should be exercised in patients with heart disease. The need for replacement should be weighed against potential complications of increased

myocardial contractility and myocardial oxygen demand. For those with undergoing procedures for ischemic and coronary heart disease, replacement of thyroid hormone may best be reserved for the postoperative period (Box 20-3).[18]

Box 20-3
Key Anesthetic Considerations for Thyroid Disorders.

Hyperthyroidism does not change minimum alveolar concentration of anesthesia. However, a deeper plane of anesthesia may be needed to blunt sympathetic response.
Caution/avoid sympathomimetics as they may cause exaggerated sympathetic response. Avoid salicylates, as they displace thyroid hormone from protein-binding sites.
Hypothyroidism does not reduce anesthetic requirement. Clinical observation suggests that increased sensitivity to anesthetics is likely due to decreased cardiac output and blunted physiological safeguards (baroreceptors, etc.).
Caution with airway due to edema or compressive mass.

Thyroid Malignancy and Multiple Endocrine Neoplasia

Thyroid nodules are uncommon in children and adolescents, with an incidence of 1% to 2% of the pediatric population, and up to 13% in adolescents. The rate of malignancy can be as high as 20% to 26%, especially in larger nodules and those associated with lymphadenopathy.[28,29] Papillary thyroid cancer (PTC) is the most common malignancy of the thyroid in children. As many as 70% of pediatric patients have lymph node involvement at presentation, and 19% to 25% have pulmonary metastases. Even so, the prognosis for PTC in children is favorable, with >95% survival rates at 15 years and 90% to 99% survival rate at 30 years.[28]

Surgical intervention requires total or near total thyroidectomy, given an increased incidence of bilateral and multifocal disease in pediatrics, and the increased risk of complications at reoperation.[28] Radioactive iodine (^{131}I) therapy for residual disease carries the risk of a secondary malignancy (1:112) at 8 years after treatment, and pulmonary fibrosis (1:11). This must be weighed against the low disease-specific mortality rate (2.68%).[28,29]

Medullary thyroid carcinoma (MTC) arises from the calcitonin-producing C-cells of the thyroid gland. Twenty-five percent of MTC are associated with germ-line mutation of chromosome 10 (10q11.2) RET proto-oncogene, encoding a transmembrane tyrosine kinase receptor. The mutation is inherited in an autosomal dominant fashion, and results in multiple endocrine neoplasia type 2 (MEN-2). MEN-2 is further divided into three subtypes: MEN-2A and MEN-2B, and familial medullary thyroid carcinoma (FMTC) (Table 20-4).[26]

Table 20-4

Familial Endocrine Neoplasia

Familial Neoplasm syndrome	MEN-1 (Wermer Syndrome) 2–3:100,000	MEN-2A (Sipple Syndrome)	MEN-I2B 1:200,000	Familial Medullary Thyroid Carcinoma (FMTC)
Genetics	Chr.11, *PYGM* gene, menin (11q13), autosomal dominant	RET proto-oncogene, (codone 634) Chr.10 autosomal dominant	RET proto-oncogene, (codone 918) Chr.10 autosomal dominant	RET proto-oncogene, Chr.10 (10q11) autosomal dominant
Endocrine manifestation	Parathyroid hyperplasia: hyperparathyroidism (100% by age 50)	Parathyroid hyperplasia (10–20%)		
		Medullary thyroid cancer (>90%)	Medullary thyroid cancer (>95%)	Medullary thyroid cancer (100%)
	Pituitary tumor: anterior pituitary adenoma (10–20%), prolactinoma/galactorrhea, acromegaly			
	Pancreatic islet cell tumor (pNET): gastrinoma (Zollinger-Ellison syndrome), insulinoma, VIPoma, carcinoid			
		Pheochromocytoma (40–50%)	Pheochromocytoma (50%)	
Cutaneous and connective tissue manifestations	Facial angiofibromas (88%)	Cutaneous lichen/amyloidosis	Marfanoid habitus (80%)	
	Facial collagenomas (>70%)		Mucosal neuromas (>95%), intestinal ganglio-neuromas, megacolon, chronic constipation	
	Lipomas (20–30%)			
	17% present before age 21; screening by age 11	Thyroidectomy by age 5	Thyroidectomy ASAP Screen for pheochromocytoma at age 11	Screen by age 5
		Screen for pheochromocytoma at age 11		

Sources: Data from Norton JA, Krampitz G, Jensen RT. Multiple endocrine neoplasia: genetics & clinical management. *Sure Once Clin N Am.* 2015;24(4):795-832. https://www.journals.elsevier.com/surgical-oncology-clinics-of-north-america. Wasserman JD, Tomlinson GE, et al. Multiple endocrine neoplasia and hyperparathyroid–jaw tumor syndromes: clinical features, genetics, and surveillance recommendations in childhood. *Clin Cancer Res.* 2017;23(13):e123-e132. https://clincancerres.aacrjournals.org/.

MEN-2 is rare with an incidence in the population of 1:200,000. One hundred percent of patients with RET mutation will develop MTC. Survival depends

on complete resection of MTC, and absence of metastatic disease at the time of resection.[30] MEN-2A is the most common of the three syndromes accounting for 55% of patients. FMTC accounts for 35%, whereas MEN-2B is the rarest and most virulent accounting for 5% to 10%.

With 100% of the patients with MEN-2 developing MTC, screening for malignancy should start as early as 5 years of age. Total thyroidectomy is recommended in cases where the gland is affected. MEN-2B commonly develops more aggressive tumors, and initiation of screening for MTC at the time of diagnosis of MEN-2B is indicated. A more radical thyroid resection with central lymph node resection is the surgery of choice. FMTC (the least virulent) screening should start at age 21, barring symptoms and surgical removal of the thyroid gland without central lymph node dissection are adequate, with serum levels of calcitonin and carcinoembryonic antigen (CEA) monitored starting at 6 months postoperatively. Normal levels at 5 years are considered a cure, and no further follow-up is needed.[30]

Half the patients with MEN-2A will develop pheochromocytoma (PCC). Mean age at presentation is 36 years, and most tumors are benign and confined to the adrenal gland. In 65% of patients, the tumors are bilateral, and those with unilateral tumor will develop a contralateral lesion within 10 years. Surgical excision of PCC takes precedence to thyroid resection due to the significant morbidity of untreated PCC. If patient requires bilateral adrenalectomy, they are at very high risk of Addisonian crisis, and should have the appropriate steroid and mineralocorticoid replacement postoperatively.[30]

MEN-1 is an autosomal dominant, germ-line mutation–driven syndrome, with several endocrine neoplastic conditions. Its prevalence in the population is 2–3:100,000. The mutation is on the long arm of chromosome 11 (11q13) tumor suppressor gene, encoding the protein menin (Table 20-4). The initial presenting disorder in patients with MEN-1 is hyperparathyroidism (>90%), followed by pancreatic neuroendocrine tumors (pNET) of which gastrinoma is the most frequent, pituitary adenomas, adrenal tumors, and thyroid adenomas (<10%).[30]

Hyperparathyroidism treatment is controversial. Some advocate complete removal, others removal only of the adenoma. Current recommendations settled on removing 3-1/2 of the parathyroid, leaving 50-g gland in the neck and marked with a hemoclip.[30]

Pituitary adenomas associated with MEN-1 secrete prolactin most frequently. Medical treatment with bromocriptine and cabergoline is recommended for prolactin-secreting adenomas, and octreotide and lanreotide for growth hormone–secreting adenomas <1 cm in size. Transsphenoidal surgery is recommended for discrete macroadenomas (>1 cm). Although surgery may offer a definitive cure, tumors have recurred on long-term follow-up. Surgery carries major morbidity, including permanent diabetes insipidus (DI).[30]

pNETs carry the greatest mortality risk for MEN-1 patients. They are typically multicentric and multifocal, spread throughout the pancreas and duodenum. Surgical resection of duodenal gastrinomas and nonfunctioning pancreatic tumors is controversial. Secretory pancreatic tumors should be removed. Malignant behavior pNET is the cause of death in >60% of patients, followed by thymic carcinoid (10% to 25%).[30]

Adrenal tumors are infrequent in MEN-1 and should be treated in similar manner to sporadic adrenal tumors. Most are discovered incidentally; they are small, nonfunctioning, benign, and asymptomatic.[30]

PARATHYROID DISORDERS

The parathyroid, like the thyroid and thymus, originates from the embryonic foregut, specifically from the third and fourth branchial pouches. Histologically, the gland is comprised of chief cells, oxyphil cells, fibrovascular stroma, and adipose tissue. Chief cells constitute almost the entirety of the gland's parenchyma. They are large (6 to 8 µm) clear cells and contain lipid and argyrophilic cytoplasmic granules. Oxyphilic cell content is small in children and increases with age. Oxyphil cells' function is unclear, but they do not seem to be degraded chief cells.[33,45]

Parathyroid hormone (PTH) is a large protein encoded by three exons of chromosome 11 (11p15). Its secretion is regulated by a direct negative feedback loop with serum calcium (Figure 20-3). The calcium sensor on chief cell membrane [calcium sensing receptor(CaSR)] is a 500-kD protein with a single-membrane spanning domain and is structurally related to the low-density lipoprotein receptor superfamily. The target tissues for PTH include bone, kidney, gut, smooth muscle cells, and fat cells (Figure 20-3). Serum half time for PTH is short, and it's degradation depends on hepatic Kupffer cells, GFR (reabsorption), and proteolysis.[34] PTH receptor (CaSR) is a large peptide with seven transmembrane domains and G-protein coupling. The receptor expression is sensitive to PTH level in a negative feedback loop. Parathormone is an 84 amino acid protein stored in secretory granules in the parathyroid gland and released when decreased calcium concentration results in decreased CaSR signaling.[43]

Figure 20-3

Parathyroid hormone homeostasis.[43] (Data from Mannstadt M, Bilezikian JP, Thakker RV, et al. Hypoparathyroidism. *Nat Rev Dis Primers.* 2017;3:17055. https://www.nature.com/nrdp/.)

Most of the body's calcium (98%) is in the insoluble hydroxyapatite crystal form, deposited in bones.

A little more than 1% of the total body's calcium is in its soluble form, and approximately 1% of it is in the extracellular fluid. Fifty percent of the soluble calcium is bound to protein (mostly albumin) and 50% is in an ultra-filterable form, mostly as ionized calcium (Figure 20-4).[35]

Figure 20-4

Total body soluble calcium distribution.[35] (Data from Clark OH, Duh QY, Kebebew E, eds. *Textbook of Endocrine Surgery*. 2nd ed. 2005. Copyright © Elsevier Saunders. All rights reserved.)

Hyperparathyroidism (Table 20-8)

Signs and symptoms of hypercalcemia and hyperparathyroidism include painful bones, kidney stones, abdominal discomfort, psychosis, cardiac conduction abnormalities, hypertension, and fatigue (Box 20-4)

Table 20-8

Genetic and Metabolic Hyperparathyroid and Hypercalcemic Syndromes[38,39]

Syndrome (chromosome, gene)	Inheritance	PTH	Ca	Frequency	Presentation
Familial Hypocalciuric Hypercalcemia (FHH) FHH-1 (3q21.1, CaSR loss-of-function) FHH-2 (19p13, GNA11) FHH-2 (19q13.2-13.3, AP2S1 loss-of-function)	Autosomal Dominant (AD)	↑/nl	↑	~65% <5% ~20%	Asymptomatic Failure to thrive Learning disabilities
Familial Isolated Hyperparathyroidism (FIHP) (11q13, MEN1) (1q31.2, CDC73) (3q21.1, CaSR) (6p24.2, GMC2)		Nonsense mutation	nl	>100 families	Diagnosis of exclusion
Neonatal Severe HPT (NSHPT) (3q21.2, CaSR)	AD or AR		↑↑		Osteoclast hyperactivity. At birth: respiratory distress, hypotonia, bone demineralization, fatal by 3 months, if untreated
Non-Syndromic Primary HPT (nsPHPT) (11p15.3-15.1, PTH) (6p21.2, CDKN1A) (9p21, CDKN2B) (1p32, CDKN2C) (6p24.2, GMC2 activating mutation)	AD		↑		
Multiple Endocrine Neoplasia (MEN) MEN-1 (11q13, MEN1 menin) MEN-2 (10q11.2, RET proto-oncogene) MEN-3 (10a11.2, RET) MEN-4 (12p13, CDKN1B)	AD	↑ or nl	↑	>95% ~20% rare 100%	As early as 8 yrs old
Hyperparathyroid–Jaw Tumor (PHT_JT) (1q31.2, CDC73 aka HRPT2 parafibromin inactivation)	AD		↑		Brown tumor of the jaw, often recurrent

Source: Data from Stokes VJ, Nielsen MF, Hannan FM, Thakker RV. Hypercalcemic disorders in children. *J Bone Mineral Res.* 2017;32(11):2157-2170. https://asbmr.onlinelibrary.wiley.com/journal/15234681.

Box 20-4

Stress Steroid Considerations[1,2]

Stress steroid replacement should not be necessary after a short (<2 week) course of steroids that ended >2 weeks ago, or treatment that lasted longer than 2 weeks, but has been discontinued >6 months ago.

Primary hyperparathyroidism (HPT) is common in adults (approx. 3 per 1,000) but infrequent in children (2 to 5 per 100,000).[36] Most pediatric HPT is sporadic. Less than 5% of cases of pediatric HPT can be attributed to familial inherited genetic causes. Many patients with genetic HPT harbor an inherited or sporadic germ-line mutation.[37,38]

HPT most commonly presents as incidental finding of asymptomatic hypercalcemia. Other common presentations of primary HPT in children include rickets, osteomalacia, short stature, hypercalcemia, and hypercalciuria. Early investigation centers on exclusion of genetic malignancy syndromes[38] and on appropriate follow-up for other malignancies if familial or germ-line cause is discovered. The treatment of symptoms may include calcimimetic drugs, which have been used safely and effectively in adults, with minimal side effects (mostly nausea and vomiting). In the pediatric population, recent publications recommend calcimimetic medications be combined with calcitriol and thiazide diuretics[40] to prevent hypocalcemia and hypercalciuria.

Vitamin levels should be investigated, and if adequate, referral for surgical/oncological evaluation should follow. For secretory adenoma, parathyroidectomy is the only cure, and is frequently combined with thymectomy due to risk of supernumerary, intrathymic glands.[37] Such sporadic presentation and tertiary causes (chronic renal failure, hypophosphatemic rickets, etc.) of HPT are most common.[38] However, even sporadic presentation of HPT has >10% incidence of de novo germ-line mutations.

Hypercalcemia has been reported as a cause of acute pancreatitis at a rate of 2 to 5 per 100,000. Although much less frequent than the adult population, the resulting pancreatitis may be lethal.[36] Pathological fractures, and brown tumors, have also been reported in children.[41]

Hyperparathyroidism is the most common presenting endocrinopathy in MEN-1, with a penetrance of near 100% by age 50. In many young patients (20- to 25-year-olds), it may present concomitantly with Zollinger-Ellison syndrome (ZES) (gastrinoma). Parathyroid carcinomas are rare, occurring in 0.28% of all patients with MEN-1.[30]

In children with hyperparathyroid–jaw tumor syndrome (HPT-JT), presentation may include ossifying fibroma of the jaw (25% to 50%), parathyroid adenoma (70%), or rarely parathyroid carcinoma (15%). Children with known familial pathological genetics must begin surveillance as early as 5 years of age.[37,39]

Hypoparathyroidism

Hypoparathyroidism presents with hypocalcemia, hyperphosphatemia, and low or inappropriately normal PTH. Hypocalcemia manifests as fatigue, confusion, paresthesias, muscle cramps, twitching, bronchospasm, laryngospasm, seizures, congestive heart failure, and myocardial conduction abnormalities such as prolonged QT.[42,43] The etiologies of hypoparathyroidism with hypocalcemia range from iatrogenic to genetic (Table 20-9), and include hormone deficiency and hormone resistance.[41] The most common etiology is removal or injury to the parathyroid gland.[43] Fewer than 10% of all cases of hypoparathyroidism are of genetic etiology.[43] Of the more common genetic causes, DiGeorge syndrome and cardiovelofacial syndrome, with similar genetics owing to deletion of *TBX1* gene on chromosome 22q11, are commonly seen in pediatric hospitals. Hypocalcemia occurs in approximately 60% of patients with DiGeorge syndrome.[42] Hypocalcemia often resolves in the first 2 years of life, but may recur with stress (surgical, sepsis, etc.) or periods of accelerated growth (adolescence).[45,46] As such, preoperative laboratory studies and clinical evaluation are indicated, and careful calcium and electrolyte replacement is necessary to avoid complications related to cardiac conduction problems and generalized weakness.

Table 20-9

Hypoparathyroidism[41–43]

Causes	Associated Condition	Defective Function
Iatrogenic	Post-surgical Radiation	Post-thyroidectomy external radioactive iodine
Acquired	Autoimmune	Anti-CaSR antibodies Graves disease Adrenal insufficiency
Infiltrative	Metastatic/malignant deposition	Iron: Hemochromatosis Copper: Wilson disease
Congenital	DiGeorge syndrome Velocardiofacial syndrome	Chr. 22q11 deletion (*TBX1* gene)
	Hypoparathyroidism–deafness–renal dysplasia syndrome (RDS) Barakat syndrome	Reduced GATA3 transcription factor (autosomal dominant)
	Kenny-Caffey syndrome Sanjad-Sakati syndrome	AR loss of function mutation TBCE, bone dysplasia
	Isolated hypoparathyroidism	Germ-line missense mutation of PTH gene
	Autosomal hypoparathyroidism	Gain of function mutation CaSR
Genetic	Maternally inherited mitochondrial DNA defect (MELAS)	Mitochondrial DNA defect (maternal)
	Kearnes-Sayre syndrome	Mitochondrial DNA
	Mitochondrial trifunctional protein deficiency syndrome (MTPDA)	AR, fatty acid oxidation disorder, CMP, peripheral neuropathy, liver dysfunction, retinopathy
	Familial hypercalciuric hypocalcemia	Autosomal dominant gain–of-function mutation CaSR
	Familial hypoparathyroidism	
	Autoimmune polyglandular syndrome (APS)	AIRE autoimmune regulator gene mutation [thymic T-cell regulation (AR mostly)] Variants may also have Addison disease, DM-1, hypothyroidism, pernicious

		anemia, hepatitis, ovarian atrophy, keratitis, vitiligo, alopecia
Pseudohypoparathyroidism	Maternal GNAS mutation	Peripheral resistance to PTH (uncoupling of cAMP from PTH)
	Albright's hereditary osteodystrophy Blomstrand lethal chondrodysplasia	PTH/PTHrP receptor mutation (autosomal recessive, lethal)
	Pseudopseudohypoparathyroidism	Paternal GNAS mutation, normal labs

CaSR, Calcium Sensing Receptor Antibodies; TBX1, T-box transcription factor; GATA3, protein coding gene; PTH, parathyroid hormone; PTHrP, parathyroid hormone-related protein; AR, androgen receptor; TBCE, Tubulin folding Cofactor E; DNA, Deoxyribonucleic acid; AIRE, autoimmune regulator; GNAS, protein coding gene.

Sources: Data from Mitchell D, Rybak LP, Glatz FR. Hyperparathyroid risis in a pediatric patient. *Int J Pediatr Otorhinolaryngol.* 2004;68:237-241. Al-Azem H, Khan AA. Hyperparathyroidism. Best Pract Res Clin Endocrinol Metabol. 2012;26:517-522. Mannstadt M, Bilezikian JP, Thakker RV, et al. Hypoparathyroidism. *Nat Rev Dis Primers.* 2017;3:17055.

HYPOTHALAMIC-PITUITARY-ADRENAL AXIS

The adrenal gland originates from embryonic mesoderm forming the adrenal cortex, and embryonic neural crest forming chromaffin cells of the adrenal medulla. The adrenal cortex (endocrine system), in conjunction with the hypothalamus and pituitary, controls mineralocorticoid, glucocorticoid, and androgen hormone homeostasis. The cortex is divided into three zones with different secretory functions. The zona glomerulosa regulates mineral balance and volume status by synthesizing and secreting the mineralocorticoid aldosterone. The zona fasciculata synthesizes and secretes glucocorticoids (cortisol) regulating glucose homeostasis and metabolism. Lastly, the zona reticularis synthesizes and secretes androgens (Figure 20-5).[47] The adrenal medulla, part of the neuroendocrine system, secretes vasoactive stress hormones integral to the sympathetic nervous system.

Figure 20-5

Adrenal medulla.[47] (Data from Gallo-Payet N, Battista MC. Steroidogenesis—adrenal cell signal transduction. *Compr Physiol.* 2014;4(3):889-964. https://onlinelibrary.wiley.com/doi/book/10.1002/cphy.)

ADRENAL DISORDERS: ADRENAL CORTEX

Mineralocorticoid Derangements (Zona Glomerulosa) (Figure 20-6)

Primary aldosteronism (*Conn's syndrome*) is a group of conditions of inappropriately high aldosterone secretion, independent of the renin-angiotensin system. Normally, aldosterone synthesis by the glomerulosa cells is stimulated by the renin-angiotensin system in response to hypovolemia or hyperkalemia. Pediatric patients with primary aldosteronism are rare, and in older case reports, many had bilateral adrenal hyperplasia. A more recent investigation describes a genetic mutation in a potassium channel gene $KCNJ_5$($Kir_{3.4}$) that occurs in as many as 34% of patients with a unilateral adrenal gland and has been described in germ-line mutation of familial forms of the syndrome. The typical clinical presentation or primary aldosteronism is moderate to severe hypertension, headaches, polydipsia, polyuria, nocturia, and hypokalemic alkalosis. Muscle weakness, cramping, and intermittent paralysis (likely related to hypokalemia) have also been reported. Severe cases have also presented with cardiac symptoms, ophthalmological and neurological abnormalities, hepatic dysfunction, and renal dysfunction.[48,49,54]

Figure 20-6

Zona glomerulosa and mineralocorticoid production.[47] (Data from Gallo-Payet N, Battista MC. Steroidogenesis—adrenal cell signal transduction. *Compr Physiol.* 2014;4(3):889-964. https://onlinelibrary.wiley.com/doi/book/10.1002/cphy.)

Aldosterone hypersecretion is treated surgically when the source is a solitary adrenal adenoma, and medically for adrenal hyperplasia. Preoperative assessment and planning should be preceded by pharmacological control of hypertension and correction of electrolyte abnormalities. It should include evaluation of electrolytes, renal function, electrocardiogram (ECG) and possibly echocardiogram, aldosterone secretion suppression, and optimization of antihypertensive regimen.[50] The hallmark of medical treatment is spironolactone, a competitive aldosterone receptor antagonist and potassium sparing diuretic. Eplerenone, also a competitive aldosterone receptor antagonist, is a second choice, in the event that spironolactone's side effects (inhibition of testosterone and progesterone) become significant. This must be accompanied with sodium restriction and cautious potassium replacement. Intraoperative and postoperative monitoring of volume status, electrolytes, and renal function should be expected.

Hypoaldosteronism is usually tied to renin production. Both hyperreninemic and hyporeninemic conditions exist. The first condition, usually due to medications, can occur in the setting of adrenal crisis/Addisonian crisis or with aldosterone synthase deficiency due to CYP11B2 deficiency. The second condition is usually related to renal dysfunction from concomitant diseases, such as diabetes.[49]

Glucocorticoid Derangements (Zona Fasciculata) (Figure 20-7)

Primary adrenal insufficiency (PAI—Addison's disease) is defined by the inability of the adrenal cortex to produce appropriate quantities of glucocorticoids and mineralocorticoids. It may be precipitated by an acute illness, genetic factors, or adrenal suppression due to steroid therapy. Symptoms are nonspecific, and include volume depletion, hypotension, hyponatremia, hyperkalemia, fever, abdominal pain, hyperpigmentation, and especially in the pediatric population, hypoglycemia.[44] Treatment for PAI in children should include hydrocortisone 8 mg/m^2 divided into three to four doses per day. The 2016 practice guidelines of the Endocrine Society on PAI also recommend avoiding synthetic long-acting glucocorticoids in children and adjusting the dosage of steroid replacement by clinical assessment of the child's growth velocity, body weight, blood pressure, and energy levels. If true aldosterone deficiency exists, fludrocortisone [Florinef (Teva Pharmaceuticals)] 100 µg/d should be prescribed, and in the newborn and infant population, sodium chloride supplementation is also recommended.[51]

Figure 20-7

Zona fasciculata and glucocorticoid production.[47] (Data from Gallo-Payet N, Battista MC. Steroidogenesis—adrenal cell signal transduction. *Compr Physiol.* 2014;4(3):889-964. https://onlinelibrary.wiley.com/doi/book/10.1002/cphy.)

During times of physiological stress or illness, the adrenal gland increases the rate of cortisol secretion substantially but not so in patients with adrenal insufficiency. It is, therefore, incumbent on the clinician to adjust the steroid dose for the child during episodes of stress. "Stress steroids" dosing is controversial for mild stresses such as immunization and uncomplicated viral illness. "Stress" dosing is absolutely required for more severe illness such as febrile illness (fever ≥38°C), vomiting, diarrhea, inadequate oral intake, lethargy, dental work, and most certainly for trauma, burns, and major surgery. Severe surgical and medical stresses are to be treated aggressively with doses of hydrocortisone up to 100 mg/m^2/day IV divided into every 6 hours dosing. For elective surgical procedures, a preoperative dose of hydrocortisone 50 mg/m^2 IV 30 to 60 minutes before induction, and an additional 50 mg/m^2 divided into 6-hour dosing for the next 24 hours, is recommended.[52]

Addisonian crisis in children in shock should be treated with a rapid bolus of 20 to 60 mL/kg of normal saline over the first hour and then with hydrocortisone bolus of 50 to 100 mg/m^2, followed by 50- to 00 mg/m^2/day divided in 6-hour dosing. Hypoglycemia should be treated with a dextrose-containing solution at 0.5 to 1 g/kg infused slowly at a rate of 2 to 3 mL/min, or D10W at a rate of 5 to 10 mL/kg (Box 20-4).[51]

Glucocorticoid derangement (Cushing syndrome) is a condition of pathological hypercortisolism with significant comorbidities and clinical symptoms, and significantly increased mortality. Major causes of mortality include cardiovascular disease, venous thrombosis, and infections. Major morbidities include obesity, arterial hypertension, insulin resistance, and glucose tolerance, dyslipidemia, osteoporosis, and diminished linear growth leading to

short stature, as well as psychiatric and cognitive dysfunction.[53]

Causes of hypercortisolism (Cushing Disease) can be elucidated with appropriate laboratory testing and radiologic imaging. Secretory lesions include: primary adrenal secretory tumor, adrenal hyperplasia, secretory pituitary adenoma, or paraneoplastic syndrome with ACTH secretion. Surgical excision of malignancies, and medical management may be planned accordingly. Medical management may include ketoconazole (inhibits side-chain cleavage 17,20-lyase and 11β hydroxylase), metyrapone (inhibits 11β hydroxylase), mitotane (used for adrenal cancer, inhibits CYP11A1, and is directly cytotoxic to the adrenal cortex) or glucocorticoid receptor antagonist mifepristone, for nonsurgical disease, and etomidate IV for patients who are unable to tolerate oral medication. Cushing disease, an ACTH-secreting pituitary adenoma, is best treated surgically if possible. ACTH suppression may be achieved medically with cabergoline, a dopamine agonist, or pasireotide, a somatostatin receptor agonist.[53] Cushing syndrome and Cushing disease do not require any specific preanesthesia adjustment but normalized laboratory values (glucose and electrolytes) and symptomatic support (hypertension, obesity, potential for difficult airway, osteoporosis, wound healing, etc.).

DERANGEMENT OF THE ADRENAL CORTEX ZONA RETICULARIS

Derangement of Androgens/Sex Hormones (Zona Reticularis) (Figure 20-8)

Congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency is an autosomal recessive genetic syndrome hallmarked by profound virilization in girls, and potential for life-threatening salt wasting in both genders if unrecognized in the newborn period.[55] The incidence of CAH is 1:10,000 to 1:20,000 live births, with 21-hydroxylase deficiency making up to 95% of the patients. For these children, the synthesis of aldosterone and cortisol is compromised by the enzyme deficiency, and consequently, the steroid metabolic pathway diverts the excess progesterone and 17-(OH) progesterone to the androgen pathway. There are more than 100 described CYP21A2 mutations causing defective 21-hydroxylase.[56]

Figure 20-8

Zona reticularis and androgens (sex hormones).[47] (Data from Gallo-Payet N, Battista MC. Steroidogenesis—adrenal cell signal transduction. *Compr Physiol.* 2014;4(3):889-964. https://onlinelibrary.wiley.com/doi/book/10.1002/cphy.)

In order to suppress virilization, patients are treated with hydrocortisone, the preferred glucocorticoid, since it has some mineralocorticoid function. If salt wasting exists, and persists after initiation of hydrocortisone therapy, fludrocortisone must be added. These children will require “stress-dose” steroid regimen perioperatively.[55]

The newborn girls typically present between 2 and 6 months of age for surgical reconstruction of their external genitals, and vaginoplasty. Boys with feminization syndromes may present for removal of gonadal streak, or for staged hypospadias repair.[57] Earlier surgical urogenital surgery is now recommended. Tissues are softer and more pliable from in utero estrogen exposure, and allow for an easier, one-stage repair.[56]

Adrenal Medulla: Catecholamine Production

The adrenal medulla is a neuroendocrine organ responsible for the production of catecholamines (Figure 20-9). Catecholamine synthetic pathway starts with tyrosine conversion to dihydroxyphenylalanine (DOPA) by tyrosine hydroxylase. This is the rate-limiting step in catecholamine synthesis. DOPA is them transformed to dopamine by DOPA decarboxylase, then to norepinephrine (NE) by dopamine-β-hydroxylase, and finally to epinephrine by phenylethanolamine-*N*-methyltransferase (PNMT). The conversion of NE to epinephrine is dependent on exposure to high cortisol level. Epinephrine and NE breakdown takes place in the mitochondria, where monoamine oxidase breaks both down to dihydroxymandelic acid. Catechol-*O*-methyltransferase (COMT) then methylates catecholamines and their metabolites to their final metabolic waste products.

Figure 20-9

Adrenal medulla catecholamine production. (Data from Gallo-Payet N, Battista MC. Steroidogenesis—adrenal cell signal transduction. *Compr Physiol.* 2014;4(3):889-964. https://onlinelibrary.wiley.com/doi/book/10.1002/cphy.)[47]

The prevalence of hypertension in the pediatric population has risen from 2% to 4.5%, much of which is attributed to increase in the rates of obesity-induced hypertension. Secondary hypertension in young children is more likely to be a result of renovascular or renal parenchymal disease (78% to 80%), endocrine disease (11%), cardiac disease (2%), etc. Only 0.5% to 2% of pediatric hypertension is caused by pheochromocytomas (PCC) and paragangliomas (PGL) (Table 20-10).[58]

Table 20-10

Causes of Secondary Hypertension and Its Differential Diagnosis[37]

Organ System	Differential Diagnosis for Secondary Hypertension
Renal parenchyma	Glomerulonephritis
	Renal failure
	Congenital renal malformation
	Polycystic kidney disease
	Systemic vasculitis (SLE, ANCA, HSP, PAN)
	Parenchymal scar (pyelonephritis, VUR, HUS)
Renovascular	Renal vein thrombosis
	Renal artery stenosis
	Fibromuscular dysplasia
	Syndromes: Williams, Turner, NF-I
	Arteritis: Takayasu, Kawasaki, Moyamoya
	Renal transplant artery stenosis
	Tumor compression of renal vessels
Endocrine	catecholamine excess: PCC/PGL, neuroblastoma, sympathomimetic drugs
	Corticosteroids: Cushing syndrome, ACTH dependent and independent
	Mineralocorticoid excess: CAH, aldosterone-secreting tumor
	Thyroid disease: hyperthyroidism, hypothyroidism
	Hypercalcemia: primary or secondary to malignancy
	Hyperparathyroidism, vitamin D intoxication
Cardiac	Coarctation of the aorta, mid-aortic syndrome

Pulmonary	OSA, BPD
CNS	Intracranial hypertension, seizures
Medications	Steroids, immunosupressants (cyclosporine, tacrolimurs, sirolimus), oral contraceptives, ketamine, erythropoietin
Monogenic HTN	Liddle syndrome, Gordon syndrome (pseudohypoaldosteronism type 3), apparent mineralocorticoid excess, glucocorticoid remediable aldosteronism (familial hyperaldosteronism type 1)
Other	Post-ECMO, cyclical vomiting syndrome

SLE, systemic lupus erythematosus; ANCA, antineutrophil cytoplasmic antibody; HSP, Henoch-Schonlein-Purpura; PAN, Polyarteritis nodosa; VUR, vesicoureteral reflux; HUS, Hemolytic Uremic Syndrome; NF-1, Neurofibromatosis type 1; PCC, Pheochromocytoma; PGL, Paraganglioma; ACTH, adrenocorticotropic hormone; CAH, congenital adrenal hyperplasia; OSA, obstructive sleep apnea; BPD, bronchopulmonary dysplasia; ECMO, extracorporeal membrane oxygenation.

Source: Adapted with permission, from Bholah R, Bunchman TE. Review of pediatric pheochromocytoma and paraganglioma. *Front Pediatr.* 2017;5:155. https://www.frontiersin.org/journals/pediatrics#.

Derangements of the Adrenal Medulla

Pheochromocytomas (PCC) are rare neuroendocrine, catecholamine-secreting tumors arising from chromaffin cells of the adrenal medulla (80% to 85%), while paragangliomas (PGL) are catecholamine-secreting tumors arising in extra-adrenal locations (15% to 20%). PGL can be further distinguished by their origins. Sympathetic PGL arise along the sympathetic ganglion chain in the spine, and parasympathetic PGLs from parasympathetic tissue of the head and neck, and rarely secrete catecholamines.[58] Ninety-five percent of PCC and PGL are intra-abdominal and pelvic, and 90% are benign. Other sites of presentation include the bladder and the organ of Zuckerkandl located at the aortic bifurcation.[59]

Pheochromocytomas and Paragangliomas[58]

The average age of presentation of PCC and PGL in pediatrics is 11 to 13 years, and males are affected at twice the rate of females. The clinical presentation is variable, with sustained hypertension noted in 60% to 90% of children compared with paroxysmal hypertension that affects 50% of adult PCC presentation. Other common symptoms of PCC and PGL in children include headaches (67%), and palpitations, sweating, pallor, nausea, and flushing in 47% to 57% of cases. Polyuria and polydipsia are rarer. Patients may also have retinopathy and cardiomyopathy at diagnosis. The presenting symptoms depend on the type of hormone being secreted. In addition to norepinephrine-secreting tumors' symptoms, patients with epinephrine-secreting tumors can present with hypoglycemia and hypotensive shock/circulatory collapse. Dopamine-secreting tumors may be asymptomatic, delaying diagnosis until mass effect of tumor causes symptoms (Table 20-11).[58] Approximately 80% of PCC/PGL tumors in the pediatric portion of the European-American-Pheochromocytoma-Paraganglioma-Registry (EAPPR) had a germ-line mutation in a known tumorigenic gene. The more common germ-line causes of PCC/PGL include *RET* gene associated with MEN-2, and succinate dehydrogenase gene (SDHA) that is common in neurofibromatosis type I (NF-I) and VonHipple-Lindau syndrome type 2 (VHL-2). Carney triad syndrome, Carney-Stratakis syndrome, and Pacak-Zhuang syndrome also present with germ-line mutations involving SDH complex.[58,59]

Table 20-11

Vasoactive Secretory Tumors: Genetics, Characteristics, and Presentation[58,59]

Syndrome	Mutation	Chromosome	Characteristics	Location
MEN-1	MEN-1 inactivation of tumor suppression gene	11q13		Adrenal
MEN-2A MEN-2B	RET (95%) RET (98%)		Adenoma, 2.9% malignancy rate	Adrenal Adrenal,

	Proto-oncogene			Epinephrine/NE
Paraganglioma				
Type 1	Succinate dehydrogenase subunit D (SDHD)	11q23	Nonfunctional, parasympathetic 3.5% malignant	HNPGL (head & neck PGL)
Type 2	SDHAF2 loss-of-function	11q13.1	Nonfunctional, parasympathetic	HNPGL
Type 3	SDHC missense	1q21	Nonfunctional mostly (NE, rarely dopamine), parasympathetic	HNPGL, GIST (gastrointestinal stromal tumors)
Type 4	SDHB inactivation of tumor suppression gene	1p35-36	Increased malignancy rate (17–30.7%), association with renal cell carcinoma, papillary thyroid cancer	Abdomen, pelvis, mediastinum, skull base, neck
VonHippel Lindau (VHL)	VHL tumor suppressor gene regulates oxygen-sensing pathways, targets hypoxia-inducible factors (HIF) for degradation, nonhypoxia pathways regulation of angiogenesis, tumorigenesis.	3p25-26	Benign and malignant (3%) tumors	Bilateral PPC, PGL in mediastinum, abdomen, pelvis produces NE
Neurofibromatosis type 1	Inactivation of NF1 tumor suppressor gene coding neurofibromin that inhibits RAS activity	17q11.2	2% of patients develop catecholamine-secreting PCC/PGL, 9.3–33% malignancy rate	Mostly benign adrenal adenoma. Rarely bilateral. Rarely abdominal/periadrenal, produce epinephrine/NE
Carney triad	Unknown		47% will have PGL/PCC, 92% PGL	
Carney-Stratakis	SDHB, SDHC, SDHD		58% with PCC/PGL	
Pacak-Zhuang	HIF2		PCC/PGL	

NE, norepinephrine; MEN, multiple endocrine neoplasia; RET, proto-oncogene encoding a receptor tyrosine kinase; SDHAF2, succinate dehydrogenase complex assembly factor 2; RAS, reticular activating system proto-oncogene; HIF, hypoxia inducible factor

Source: Data from from Bholah R, Bunchman TE. Review of pediatric pheochromocytoma and paraganglioma. *Front Pediatr.* 2017;5:155. https://www.frontiersin.org/journals/pediatrics#.

Those mutations have been divided into *Cluster 1*, mutations which reduce the oxidative response (VHL, SDHx, HIF), and *Cluster 2*, mutations which activate the kinase signaling pathways (RET, NF1, KIF1B, TMEM127, MAX). Cluster 1 tumors are more prevalent in children (76%) vs. Cluster 2 tumors (39%).

Preoperative Assessment and Preparation

Patients with catechol-secreting PCC and PGL are at risk of metabolic derangements as well as end-organ damage from excess circulating catecholamines. Patients are volume contracted, and may be hyperglycemic or hypoglycemic, depending on the catecholamine being secreted by the tumor. Assessing plasma catecholamine metabolites including plasma-free metanephrine (MN) and normetanephrine (NMN), and 24-hour urinary fractionated metanephrines are the new gold standard for diagnosis of PCC. For those with levels more than four times the upper limit of normal, imaging and genetic testing for localization should ensue. If levels are only slightly elevated, stop all interfering medications, avoid exercise for one day, and retest, drawing the blood in a supine position. If metabolite levels return at 2 to 4 upper limits of normal, consider suppression (Table 20-12). Patients with MN/NMN <2 are unlikely to have PCC/PGL.[58] Cardiac workup, including 12-lead ECG and echocardiogram, is a must. Unusual forms of cardiomyopathy (Takotsubo cardiomyopathy) and myocardial dysfunction in general have been described in PCC/PGL.[60–62]

Table 20-12

Drugs Used in Preoperative Blockade for Pediatric Catecholamine-Secreting Tumors[58]

Drug Name/Class	Starting Dose	Maintenance Dose	Side Effects
Phenoxybenzamine			
Nonselective α-blocker	0.2 mg/kg/day (max 10 mg/dose)	Increase 0.2 mg/kg/day every 4 days in q6–q8 dosing, max 4 mg/kg/day	Orthostatic hypotension Tachycardia Nasal congestion
Doxazosin			
Selective α-1 blocker	1–2 mg/day	Increase to 4–16 daily, or in q12 dosing	Orthostatic hypotension Dizziness
Propranolol			
Nonselective β-blocker	1–2 mg/kg/day in 2–4 times daily dosing	4 mg/kg/day up to 640 mg/day ÷2–4 times daily	Dizziness, fatigue Asthma exacerbation
Atenolol			
Selective β-1 blocker	0.5–1 mg/kg/day daily or in 2 times daily dosing	2 mg/kg/day up to 100 mg/day	Edema, dizziness fatigue
Labetolol			
α- and β-Blocker	1–3 mg/kg/day in 2–3 times daily dosing	10–12 mg/kg/day up to 1,200 mg/day in 2–3 times daily dosing	Dizziness, fatigue Asthma exacerbation
Metyrosine			
Tyrosine hydroxylase inhibitor	20 mg/Kg/d ÷q6hr, or 125 mg/d	Increase up to 60 mg/kg/day in q6h dosing, or increase 125 mg/day every 4–5 days up to 2.5 g/day	Orthostatic hypotension Diarrhea, sedation, extrapyramidal symptoms, crystalluria

Source: Reproduced with permission, from Bholah R, Bunchman TE. Review of pediatric pheochromocytoma and paraganglioma. *Front Pediatr.* 2017;5:155. https://www.frontiersin.org/journals/pediatrics#.

Intraoperative Management of Pheochromocytoma and Paraganglioma Resection

A thoughtful regimen of antihypertensive polypharmacy and fluid and electrolyte resuscitation is required in preparation for resection of catecholamine-secreting tumors to minimize risk of hemodynamic instability, which can increase morbidity and mortality. The first step is to initiate *α-blockade*, and fluid-resuscitation in the child, in order to control the hypertension. The choices of α-blockers are phenoxybenzamine, a long-acting agent, or doxazosin and prazosin, shorter acting drugs. All three agents are equally effective in controlling hypertension. Phenoxybenzamine-treated patients tend to have a longer period of hypotension postoperatively, requiring medication, likely due to phenoxybenzamine's long half-life. Metyrosine, a catecholamine synthesis inhibitor, has been used in adults in conjunction with phenoxybenzamine or prazosin, resulting in better BP control. The literature on the use of metyrosine in the pediatric population is limited and inconclusive. Once α-blockade is established, *β-blockade* can be added to suppress reflex tachycardia. It is also important to avoid all sympathomimetic medications during this time to avoid triggering a hypertensive crisis.[58]

In the immediate preoperative period, the challenges of preventing a hypertensive crisis continue. Anxiety is a significant factor in catecholamine-mediated preoperative hypertension. *Anxiolysis* is imperative in preparation for the operating room. Invasive hemodynamic monitoring is required, including a preinduction arterial catheter, and a central venous catheter for monitoring and for vasoactive drug infusion. The timing of the central venous catheter placement is at the discretion of the anesthesiologist. Placement of pulmonary artery catheter is rare in children, but transesophageal echocardiography (TEE) probe may be used in its place to assess cardiac function and volume status. In the adult population, whole-body bioimpedance cardiography may offer an alternative to PA catheters and TEE.[61,62]

Intravenous anesthetic agents without sympathomimetic characteristics, such as propofol and etomidate, are safe for the induction of general anesthesia. Dexmedetomidine, remifentanil, sufentanil, as well as a propofol infusion are appropriate for maintaining adequate depth of anesthesia and analgesia. Fentanyl and hydromorphone may be used as well, but morphine and meperidine should be avoided due to their sympathomimetic and histamine release profiles that may trigger a hypertensive episode. In fact, all agents with sympathomimetic properties (ephedrine, ketamine) or that may trigger hypertension (droperidol) should be avoided.

Neuromuscular blockade can be achieved with vecuronium, rocuronium, or cisatracurium. All three agents have few or no autonomic effects, and no histamine release. Atracurium with its histamine release and pancuronium with its vagolytic profile should be avoided.

Regional anesthesia should be utilized with caution. Neuraxial block can cause profound hypotension in the volume-depleted patient, and epinephrine-containing local anesthetics should not be used.

It is essential to maintain adequate depth of anesthesia to blunt response to noxious stimuli such as laryngoscopy, tracheal intubation, skin incision, and insufflation for laparoscopic procedure in order to avoid catecholamine release and a hypertensive crisis.

Inhalation agents sevoflurane, isoflurane, and nitrous oxide have all been used safely to maintain anesthesia in patients undergoing resection of PCC and PGL. Sevoflurane probably has the most hemodynamically favorable profile, lacking arrhythmogenic potential. Desflurane should be avoided, as it is known to have sympathomimetic properties, including tachycardia, hypertension, and bronchial irritation, which may exacerbate hemodynamic disturbance in patients with PCC and PGL.[62]

More severe hypertensive response can be elicited by catecholamine release from the tumor itself during manipulation and resection. Vasoactive drugs are used to attenuate the catecholamine response during this manipulation, and to treat the subsequent vasoplegic hypotension after tumor removal. *Magnesium* infusion acts as a vasodilator by inhibiting catecholamine release, antagonizing catecholamine receptors directly, and directly antagonizing endogenous calcium. In addition to its antihypertensive properties, magnesium is an antiarrhythmic, and it is readily available and cost-effective with a high therapeutic index.[63] *Nitric oxide modulators* such as sodium nitroprusside (SNP) and nitroglycerin (NTG) are commonly used to control intraoperative hypertension. SNP decreases both preload and afterload. Onset is immediate and duration of action is between 1 and 3 minutes. At high concentrations, and prolonged infusion, SNP's degradation products cyanide, thiocyanide, and methemoglobin can cause serious toxicity and side effects. Nitroglycerin has a similar immediate onset of action, but with 3 to 5 minutes duration of action. It mostly affects capacitance vessels, and preload. *β-Adrenergic antagonists* are used to manage tachycardia and tachyarrhythmias. Intraoperative infusion of esmolol is commonly used to control tachycardia. Esmolol is a selective β1-antagonist with fast (1 to 2 minutes) onset and short duration of action (9 minutes). In addition to its chronotropic actions, it works to reduce systolic blood pressure without affecting diastolic blood pressure. *Calcium channel blockers* (CCBs) are an alternative to SNP and NTG. CCBs reduce preload more gently, and therefore have fewer instances of hypotension, and no rebound hypertension or tachycardia on discontinuation of infusion, and no risk of cyanide toxicity. Nicardipine has a strong arterial vasodilatory effect. Its onset of action is between 1 and 5 minutes, but duration of action may last 3 to 6 hours, and can therefore result in prolonged hypotension. Clevidipine is an ultrashort-

acting arterial vasodilator. It has fast onset of action (about 1 minute) and short half-life (approximately 1 minute), since it is metabolized by plasma esterases.[58,62]

After tumor removal, it is not uncommon to have sudden hypotension due to increase in venous capacitance and vasodilation, residual α-adrenergic and β-adrenergic blockade, absence of the tumor's catecholamine supporting vascular tone, all combined with inadequate intravascular volume. The hypotension may be resistant to catecholamine infusions due to adrenergic receptor down-regulation response to the prolonged exposure in the preoperative period. If norepinephrine, phenylephrine, and dopamine are ineffective, *vasopressin* may be a better choice. Vasopressin acts on V_1 receptors on smooth muscle to increase vascular tone, independent of adrenergic receptors. There are anecdotal reports of hemodynamic rescue with methylene blue in response to vasoplegia after tumor removal, but the efficacy has not been adequately validated at this time.

Postoperative Course

Profound hypotension has been described in the immediate postoperative period. If the hypotension is unresponsive to catecholamine infusion and vasopressin, ECMO has been described as a rescue for refractory shock. Additional perturbation may include hypoglycemia, hypertension, hypovolemia, and adrenal insufficiency requiring steroid replacement (when bilateral adrenalectomies were performed). Reduction in circulating catecholamines reduces the inhibitory effects on insulin secretions and gluconeogenesis. Hyperinsulinemia and increased peripheral glucose uptake follow the reduction in circulating catecholamine load and result in hypoglycemia that may last 24 to 48 hours postoperatively.[61]

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