Adrenal Gland Embryology, Anatomy, and Physiology

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Surgical intervention may be required for definitive treatment of adrenal gland disorders; therefore, every surgeon involved in treating children with adrenal pathology needs a thorough understanding of adrenal gland embryology, physiology, and anatomy. This chapter reviews these topics with special emphasis on how they relate to diseases of the adrenal gland and especially their surgical treatment. Adrenal gland embryology is reviewed first as it explains many unique aspects of adrenal anatomy, histology, and physiology. Adrenal physiology is then reviewed as it forms the basis to understand problems of deranged adrenal function, especially the unregulated secretion of steroids or catecholamines that are common manifestations of adrenal tumors. Finally, the anatomy of the adrenal glands and surrounding structures is considered as this explains the clinical findings of mass effects on adjacent organs of functional and nonfunctional adrenal tumors and, most importantly, forms the basis to understand the conduct of adrenal operations.

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Embryology

The adrenal gland is made up of two distinct types of tissue that arise from two separate origins. These two tissue types are responsible for the dual functions of the adrenal gland—steroid and catecholamine metabolism. At 5–6 weeks postconception, bilateral mesothelial proliferation occurs between the root of the dorsal mesentery and the gonadal ridges (Fig. 7.1) [1]. This tissue eventually forms the fetal cortex of the immature adrenal glands. The fetal adrenal cortex surrounds the developing adrenal medulla (Fig. 7.2), and the entire gland is encapsulated by a mesodermal layer that separates the adrenal gland from the adjacent developing gonad and kidney. The close approximation of the nascent adrenal cortex to the mesoderm destined to become the kidney and gonads explains both the normal anatomic relationship to the kidney and the occasional finding of ectopic adrenal tissue or adrenal "rests" associated with the gonadal vessels and gonads [2–4]. Up to 50% of newborns have ectopic adrenal tissue, either cortical tissue alone (if it migrated before invasion of the medullary cells) or a combination of cortical and medullary tissue. This ectopic adrenal tissue atrophies in most children so that adrenal rests are found in only 1% of adults [1].

At 9 weeks gestation the fetal adrenal cortex differentiates into histologically distinct zones—the definitive zone and the fetal zone [5]. During gestation, the fetal cortex primarily produces androgens, which along with hormones produced

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by the developing gonads influence sexual differentiation of the fetus [6, 7]. In the third trimester, a third layer called the transitional zone forms between the definitive zone and fetal zone. By 6 months of life the definitive and transitional zones give rise to the zona glomerulosa, the outermost layer of the adrenal cortex which produces mineralocorticoids, and the zona fasciculata, which produces glucocorticoids. Over the first year of life, the fetal cortex involutes and the zona reticularis which produces androgens begins to develop as the inner most layer of the adrenal cortex [8]. The zona reticularis becomes a distinct layer by 3–4 years of age (Fig. 7.2).

Chromaffin cells are the functional cells of the adrenal medulla and are derived from the neural crest (Fig. 7.1). Along with chromaffin cells the neural crest also supplies the chief cells of the paraganglia and the parafollicular C cells of the thyroid to the developing endocrine system by the neural crest [9]. Chromaffin cells in the adrenal produce catecholamines, and are the cells of origin of pheochromocytomas and neuroblastomas. Chief cells, found in the varied anatomic locations of the paraganglia, are the cells of origin of extra-adrenal pheochromocytomas and neuroblastomas [9, 10].

The merging of the primitive medullary and cortical cells to create the adrenal gland is accomplished by migration of medullary cells into the cortex which begins during the seventh week of gestation. This process continues so that by the second trimester the fetal adrenal cortex surrounds the medulla and the entire gland becomes encapsulated by a mesodermal layer separating the adrenal glands from the surrounding retroperitoneal structures (Fig. 7.2) [1, 11]. Interestingly, while in mammals the medullary and cortical tissues merge into a single organ, in pre-vertebrates, they develop as two separate organs [10].

Adrenal Cortex Histology and Physiology

The fully mature adrenal cortex is made up of three layers with distinct hormonal functions (Fig. 7.3). The outer layer is the zona glomerulosa, which makes up about 10% of the adrenal cortex and consists of columnar epithelium arranged in cord-like structures [12, 13]. The cells of the zona glomerulosa have sparse cytoplasm, rounded nuclei, and a characteristic

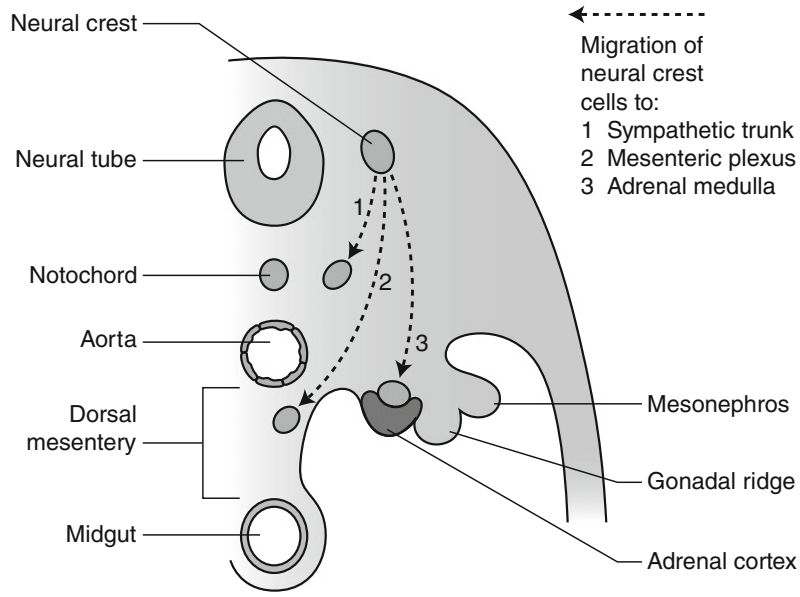

Fig. 7.1 Adrenal embryology—origins of the cortex and medulla left half of a cross section of the embryo. Adrenal cortex originates as a mesothelial proliferation between the root of the dorsal mesentery and the gonadal ridge. Adrenal medulla originates from the neural crest and migrates into the developing adrenal cortex

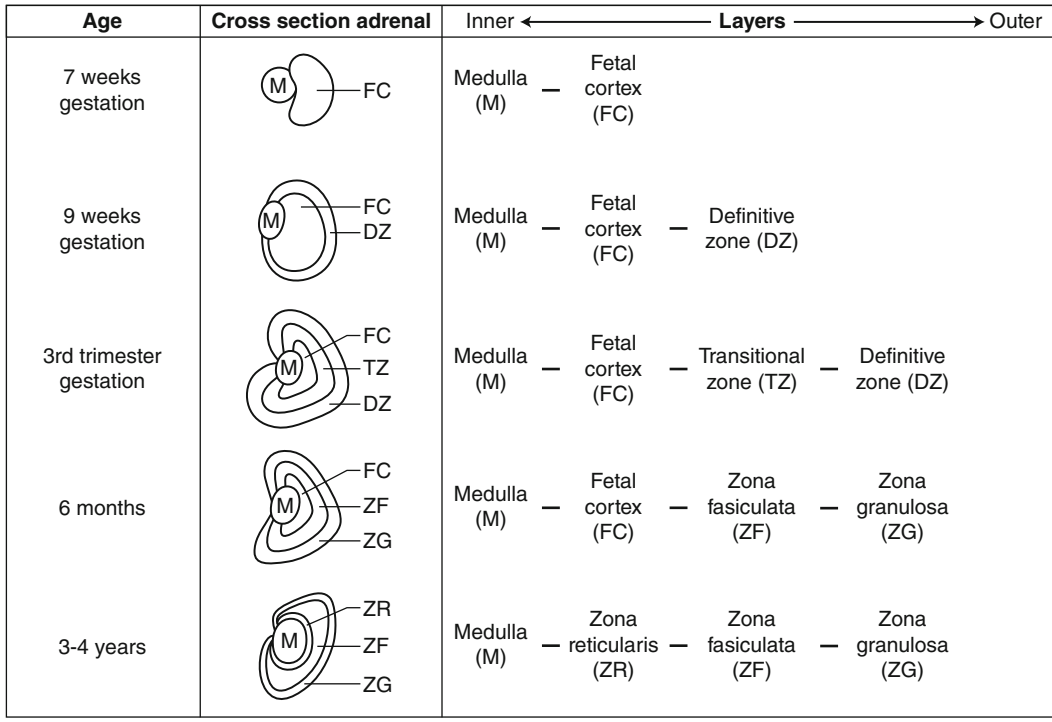

Fig. 7.2 Adrenal embryology—development of the mature adrenal gland. Adrenal medullary cells migrate to and begin merging with the developing adrenal cortex during the 7th week of gestation. By the second trimester the cortex surrounds the medulla and the entire gland is encapsulated by a mesodermal layer separating the adrenal glands from surrounding retroperitoneal structures. At 9 weeks gestation the cortex begins to differentiate into histologically and physiologically distinct zones and this process continues until the first few years after birth

transverse infolding of the mitochondrial cristae [13].

Activation of the renin-angiotensin axis stimulates the zona glomerulosa layer to produce and secrete aldosterone. The juxtaglomerular cells of the kidney are stimulated to secrete renin when the intrarenal blood pressure is low, when the macula densa cells in the distal renal tubule sense a decreased concentration of sodium chloride or when renal sympathetics are activated. Circulating renin then converts angiotensinogen, a serum globulin produced in the liver, to an oligopeptide, angiotensin I. Angiotensin I is converted by angiotensin-converting enzyme (ACE) to angiotensin II. Angiotensin II is a vasoconstrictor and also directly stimulates zona glomerulosa cells to synthesize and secrete aldosterone. Aldosterone causes the kidney to save sodium and lose potassium [8]. ACE inhibitor drugs decrease angiotensin II and aldosterone and are a mainstay in the treatment of hypertension.

The middle layer of the adrenal cortex is the zona fasciculata which makes up about 80% of the mature adrenal cortex. This layer has large, lipid-rich, polyhedral cells that store large amounts of cholesterol which is a precursor of cortisol [13, 14]. Zona fasciculata cells, unlike the cells in the zona glomerulosa, possess the enzymes 17α-hydroxylase and 11β-hydroxylase, which promote the conversion of progesterone to cortisol [15]. During stress cholesterol is converted to cortisol and the zona fasciculata decreases in size [14]. The adrenal cortex respond to the hypothalamic-pituitary axis (HPA) via corticotropic releasing factor (CRF) from the hypothalamus which causes the pituitary to secrete adrenocorticotropic hormone (ACTH)

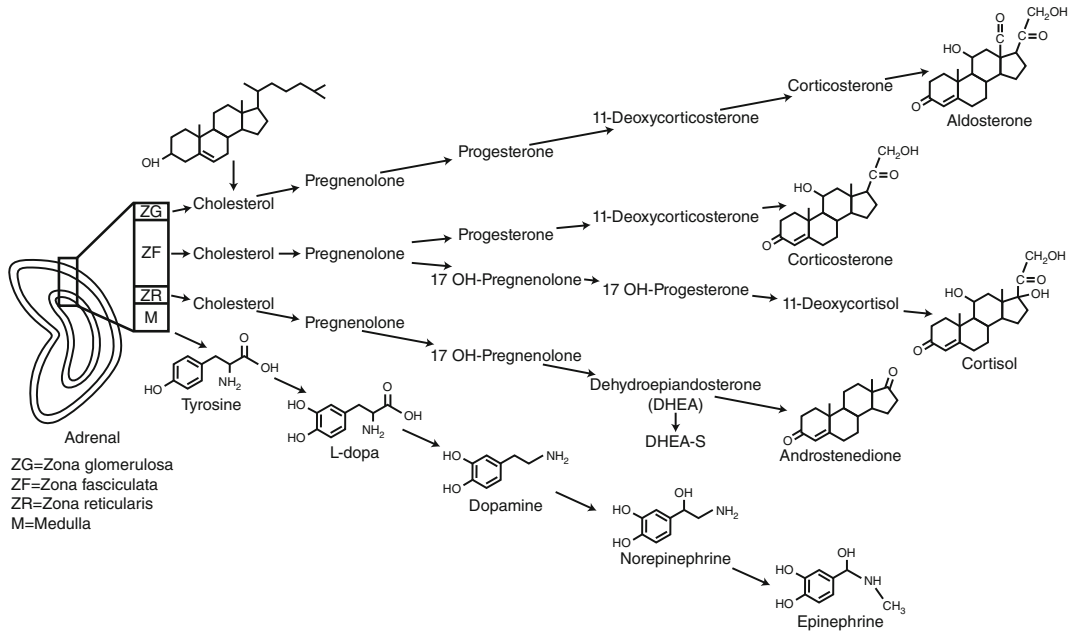

Fig. 7.3 Adrenal gland physiology. The three layers of the mature adrenal cortex produce a distinct pattern of corticosteroids from cholesterol. The adrenal medulla produces catecholamines by a stepwise enzymatic alterations of tyrosine

which acts on the zona fasciculata cells to produce cortisol. Cortisol secretion from the zona fasciculata is controlled by circadian secretion of ACTH, the stress-induced stimulation of the HPA, and the negative feedback regulation of the HPA by cortisol [8]. During stress, the adrenal medulla and zona fasciculata of the cortex can interact directly. The sympathetic nervous system can directly stimulate cortisol secretion from cells of the zona fasciculata and cortisol stimulates the chromaffin cells of the medulla to increase synthesis of catecholamines.

The innermost layer of the adrenal cortex adjacent to the medulla is the zona reticularis which makes up about 10% of the entire adrenal cortex and has a darker color than the other layers due to the pigment lipofuscin [14]. It is made up of small eosinophilic cells arranged in a cord-like fashion [16]. The zona reticularis is the site of production and secretion of dihydroepiandrosterone (DHEA) and DHEA-sulfate. Production of these androgens is also regulated by ACTH [15].

Adrenal Medulla Histology and Physiology

The adrenal medulla produces catecholamines and is regulated by the sympathetic nervous system. The central nervous system activates the sympathetic nervous system via preganglionic fibers from the spinal cord. These preganglionic fibers synapse with postganglionic fibers within the sympathetic ganglion and the postganglionic fibers carry the stimulus to end organs [17]. The adrenal medulla is unique in that it is supplied by preganglionic fibers that directly synapse to chromaffin cells which produce catecholamines. There are no postganglionic nerve fibers [17, 18]. Chromaffin cells are arranged in a reticular pattern around multiple venous channels which allows secreted catecholamines to rapidly enter the bloodstream [17].

Some medullary chromaffin cells secrete epinephrine and others secrete norepinephrine [15]. The primary substrate for catecholamine

production is tyrosine. Tyrosine comes directly from dietary sources or is synthesized in the liver from dietary phenylalanine. Through stepwise enzymatic alterations, tyrosine is converted to dopamine via tyrosine hydroxylase and aromatic-L-amino acid decarboxylase (see Fig. 7.3). Dopamine can be converted to norepinephrine by dopamine-β-hydroxylase. The conversion of norepinephrine to epinephrine requires Phenylethanolamine N-methyltransferase (PNMT), an enzyme that is present in chromaffin tissue (Fig. 7.4). Cortisol from the adrenal cortex increases PNMT which, in turn, increases epinephrine production [8, 19].

Adrenal Anatomy

At birth the adrenal glands together weigh about 8 g and are nearly the size of adult adrenal glands [20]. Therefore, by weight, newborn adrenal glands are 10–20 times proportionally larger than adult adrenal glands [1, 21]. The relatively large size of the adrenal gland is obvious on newborn imaging studies where the adrenal gland may be up to one-third the size of the adjacent kidney [1]. After one year of age, the fetal cortex involutes and the adrenal gland approaches normal adult dimensions (approximately $5 \times 3 \times 0.6$ cm) and weight (4–6 g each) [10]. The right

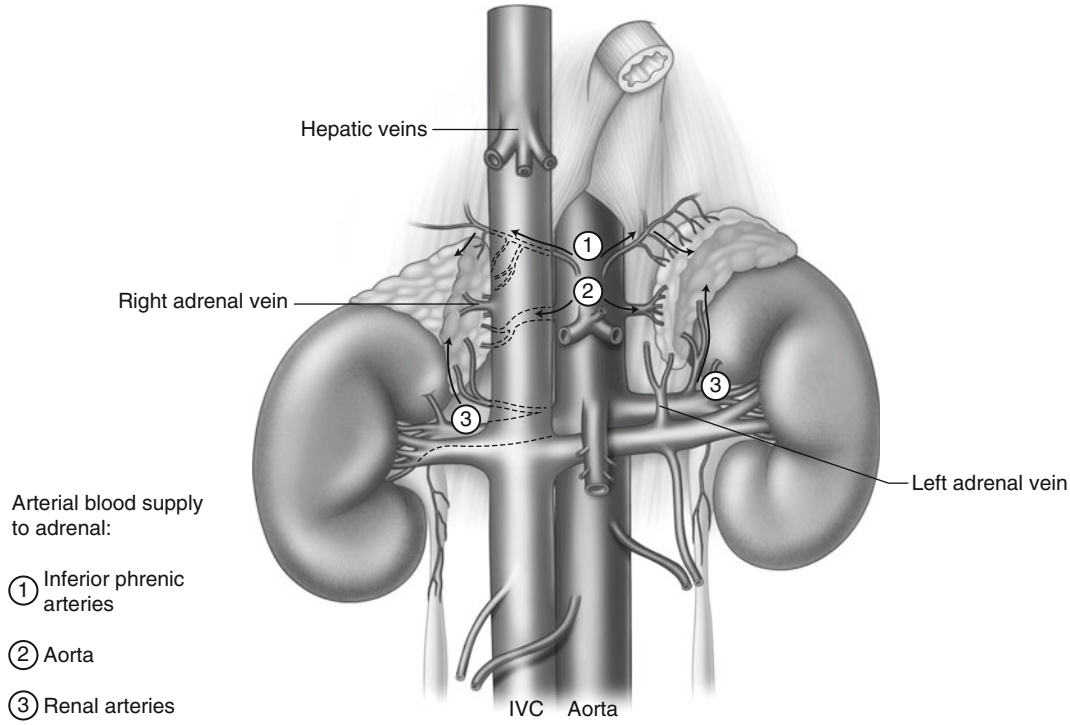

Fig. 7.4 Adrenal anatomy. Both adrenal glands are within Gerota's fascia at the superior-medial pole of the kidneys lateral to the vertebral column, in front of the 12th rib *on the right* and in front of the 11th and 12th rib *on the left*. The *right* adrenal is located against the bare area of the liver and is partially covered by the vena cava anteriorly. The *left* adrenal is behind the tail of the pancreas and is anterior to the diaphragm. The *right* adrenal vein drains directly into the inferior vena cava and is usually less than a centimeter in length. The *right* renal vein is short and drains directly into the inferior vena cava. The *left* adrenal vein is longer than the *right* adrenal vein and merges with the left inferior phrenic vein prior to draining into the *left* renal vein. The arterial blood supply to the adrenal is variable and consists of multiple small branches from the inferior phrenic arteries superiorly, the abdominal aorta medially, and the renal arteries inferiorly

adrenal gland tends to be a more triangular shape than the larger, more crescent shaped left adrenal gland [19]. The surface of the adrenal has a characteristic bright yellow-orange color which is distinct from the surrounding retroperitoneal fat. The distinctive color of the adrenal gland is more noticeable in infants and young children than in adults due to the paucity of retroperitoneal fat in younger children. This distinct color is often present in adrenal tumors and their metastases and is a helpful guide when performing gross total resections of adrenocortical carcinomas, neuroblastomas, and involved lymph nodes.

Relationship to Retroperitoneal Structures

The adrenal glands are located in the retroperitoneum, superior and slightly anterior and medial to the kidney. They are lateral to the vertebral column, in front of the 12th rib on the right and in front of the 11th and 12th rib on the left (see Fig. 7.4) [10]. On the right, the adrenal is located against the bare area of the liver and is partially covered by the vena cava anteriorly [11]. On the left, the adrenal lies behind the tail of the pancreas and is anterior to the diaphragm [11]. Both adrenal glands lie within the pararenal fat at the superior-medial pole of the kidneys within Gerota's fascia [10]. There is a fusion of the anterior and posterior Gerota's fascia between the adrenal gland and the superior pole of the kidney [10]. This connective tissue plane separates the adrenal gland and kidney and facilitates dissection of the adrenal away from the superior pole of the kidney during adrenalectomy. The renal fascia envelops the adrenal and extends cranially, where it attaches to the diaphragm and fixes the adrenal glands to the posterior abdominal wall [10]. The lateral attachments are to the superior pole of the kidney and pararenal fat. In distinction to the posterolateral anatomy, which is essentially the same for the two glands, the anterior and medial relationships are different on the right and left sides (Fig. 7.4).

Venous Anatomy

Adrenal capillaries drain into a central vein which exits the cortex at the inferomedial aspect of the gland. Each gland has a dominant vein, although smaller accessory veins are often found adjacent to the adrenal arteries [10]. Anatomic variants have been reported to occur in up to 50% of patients, although most variants are minor [22]. Significant variations probably occur in 3–5% of patients [22, 23]. Multiple adrenal veins draining via their usual pathway into the inferior vena cava IVC on the right and the left renal vein on the left are the most common anomalies [11]. Other anomalies include accessory venous drainage to the inferior phrenic vein and venous connections to the azygous vein and/or posterior gastric veins. These connections could act as shunts around an obstructed IVC or portal vein [10]. During resection of large adrenal tumors the superior pole arteries to the kidney can easily be mistaken for the adrenal vein and care must be taken to avoid inadvertent ligation of these arteries [11].

The right adrenal vein drains directly into the inferior vena cava and is usually less than a centimeter in length [10]. The short length of the right adrenal vein can make its ligation difficult during right adrenalectomy. In addition, large, right adrenal masses can significantly displace the adrenal vein and occasionally requiring circumferential mobilization of the inferior vena cava for adequate exposure and control. Anomalous drainage, such as a right adrenal vein draining into the retrohepatic vena cava at the confluence of the hepatic veins has been reported.11 [23]. The left adrenal vein is longer than the right adrenal vein and merges with the left inferior phrenic vein prior to draining into the left renal vein [10]. When dissecting large left-sided adrenal tumors, one often finds the adrenal vein flattened against the mass and stretched to a length significantly longer than normal. Once the left adrenal vein has been identified, early ligation is preferable prior to full dissection of the mass due to the risk of avulsing the attenuated vein from the left renal vein. In general, anatomic

variants in venous drainage on the left are associated with an anomaly in the left renal vein. Drainage of the left adrenal vein directly into the IVC in a patient with retroaortic left renal vein has been reported [24].

Arterial Anatomy

Unlike the venous system, the arterial branches to the adrenal glands are not as distinct. These branches arise from three sources—the inferior phrenic arteries superiorly, the abdominal aorta medially, and the renal arteries inferiorly (Fig. 7.4) [10, 12, 19]. The anatomy of the arterial system is unpredictable and variable and adrenal arteries can also arise from the intercostal or gonadal arteries [11].

The arteries enter on the medial side of the glands and give rise to a dense network of vessels that supply the three layers of the adrenal cortex and the medulla. In infants and children, adrenal arteries are usually small and can be are ligated with cautery, harmonic scalpel, or fine ties. Larger arterial branches are seen when with mass lesions within the adrenal gland cause neovascularization and engorgement of the vessels. In these cases, meticulous dissection and ligation of vessels is necessary to avoid bleeding.

Lymphatic Anatomy

On the right, adrenal lymphatics drain to paracrural, paraaortic, and paracaval lymph nodes. On the left, adrenal lymphatics initially drain into paraaortic and left renal hilar lymph nodes. Adrenal lymphatics also may drain directly to the thoracic duct and posterior mediastinal nodes [10, 12]. Extension of lymphatic spread to adjacent retroperitoneal lymph node groups is common so a thorough knowledge of the adrenal lymphatic drainage patterns is critical for appropriate surgical therapy of advanced stage adrenocortical carcinoma, neuroblastoma, or malignant pheochromocytoma when gross total lymphadenectomy is often indicated.

Anatomic Basis of Surgical Approaches to the Adrenal

Operations on the adrenal glands can be done using open or minimally invasive techniques from either an anterior or posterior approach. Because the posterolateral anatomy is basically the same for both adrenal glands, the surgical approach through the flank is the same for both glands. The glands are fixed to the posterior abdominal wall by the renal fascia, allowing direct access to the glands. The posterior approach is begun with an incision made along the 12th rib, which is usually removed to facilitate exposure. The latissimus dorsi muscle is divided and the peritoneum is reflected away. To improve exposure the diaphragm can be divided to, after bluntly mobilizing the pleura. Once this is accomplished, the transversalis muscle is divided and the kidney is retracted inferiorly to expose the adrenal [10]. The posterior minimally invasive or retroperitoneoscopic approach is not commonly used in children, unless there has been extensive previous abdominal surgery or the child is obese [21]. The retroperitoneoscopic approach begins with a small incision at the tip of the 12th rib. With blunt finger dissection, a space is created to insert the first trocar. The space is opened using a balloon trocar and high (20–24 mmHg) insufflation pressures prior to placing additional trocars [25].

The anterior approach to the right and left glands is different because of the asymmetric anatomy of the glands. Open anterior adrenal procedures are most commonly performed through a subcostal incision. For bilateral lesions a chevron or midline incision can be used. The most common approach used for laparoscopic adrenal surgery is an anterior approach with the patient in a lateral position, although the procedure can be performed in the supine position as well [26]. Although single incision (SILS) laparoscopic adrenal surgery has been described, most surgeons continue to prefer a standard laparoscopic approach for adrenal procedures [27]. Whether an open or minimally invasive technique is used, the steps of the procedure are

the same. On the right side, the posterior attachments of the liver to the diaphragm are divided [11]. The liver can them be retracted superiorly to expose the fascia covering the adrenal gland. If additional exposure is needed, the small veins draining the caudate lobe into the vena cava can be divided [11]. If necessary, the duodenum can mobilized medially with a Kocher maneuver to further expose the vena cava and the kidney [10, 11]. On the left side, the omentum is divided off the colon and the lesser sac entered. The inferior, avascular border of the pancreas can be dissected free and elevated to reveal the adrenal [11]. For small tumors, this direct approach through the lesser sac usually provides adequate exposure, however for large tumors visceral rotation may be required to adequately expose the adrenal gland and aorta. In this maneuver, the splenic flexure of the colon, spleen, and tail of the pancreas are mobilized and retracted medially [10]. Once the gland is adequately exposed, identification and ligation of the adrenal vein is usually carried out first. As previously noted, the right adrenal vein empties directly into the vena cava; the left vein joins the inferior phrenic vein to empty into the left renal vein. Once the vein is divided, medial and superior dissection to identify the arteries supplying the gland can be carried out.

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