https://doi.org/10.48047/AFJBS.6.2.2024.3134-3144

African Journal of Biological Sciences

Journal homepage: http://www.afjbs.com

Research Paper Open Access

An Overview about Anatomy and Development of Adrenal Gland

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Article History

Volume 6, Issue 2, Apr-Aug 2024

Received: 5 August 2024

Accepted: 15 August 2024

Published: 15 August 2024

doi: 10.48047/AFJBS.6.2.2024.3134-3144

Abstract: The adrenal (suprarenal) glands are 2 retroperitoneal organs that are present at the upper pole of each kidney. Each gland is enclosed by a separate compartment of the renal fascia, containing perinephric fat. The glands are separated from the kidneys by a thin septum which is a part of the renal fascia. The glands lie opposite T12 but they are asymmetrical, where the right gland usually lies slightly lower than the left one. In human, the suprarenal gland develops during embryogenesis from two distinct embryological tissues the intermediate mesoderm, which differentiate forming the adrenal cortex and neuroectodermal tissue, the neural crest, which differentiate into the adrenal medulla. Regarding the development of adrenal cortex, at about the fourth week of gestation, the earliest recognizable primordium of the cortex is "the adrenal blastema" which are the cells that developed from the intermediate mesoderm that appear as a plate of condensed mesothelial coelomic epithelium in the notch between the dorsal mesentery of the gut medially and the urogenital ridge laterally. Regarding the development of adrenal medulla, at about the 6th week of gestational age, the primordium of adrenal medulla appears, where pheochromoblasts from adjacent sympathetic ganglia (neuroectodermal origin) that derived from the neural crest migrate to invade the primitive cortex (mesodermal origin), these pheochromoblasts are arranged in cords and clusters

Keywords: *Anatomy, Development of Adrenal Gland*

Introduction

The adrenal (suprarenal) glands are 2 retroperitoneal organs that are present at the upper pole of each kidney. Each gland is enclosed by a separate compartment of the renal fascia, containing perinephric fat. The glands are separated from the kidneys by a thin septum which is a part of the renal fascia. The glands lie opposite T12 but they are asymmetrical, where the right gland usually lies slightly lower than the left one [1,2,3].

The right adrenal gland is pyramidal in shape. The posterior surface lies against the right crus of the diaphragm. The medial surface lies in contact with the inferior vena cava. This surface is related to the celiac ganglion & right inferior phrenic artery. The anterior surface has 2 distinct facets: a narrow medial facet that is overlapped by the inferior vena cava and a triangular lateral facet that lies in contact with the right lobe of the liver and is covered below by the peritoneum of the posterior wall of hepatorenal pouch. The right suprarenal vein emerges from the hilum of the right gland to join the inferior vena cava [1,2,3].

The left adrenal gland is semilunar in shape & it overlaps the medial border of the left kidney above the hilum. This gland has 3 surfaces. The posterior surface lies on the left crus of the diaphragm. The medial surface is related to the left celiac ganglion below & the left gastric artery above. The anterior surface is covered above by the peritoneum of the the posterior wall of the lesser sac forming a part of the stomach bed & below it is directly related to the body of pancreas & the splenic vessels. The hilum of the left gland faces inferiorly [4,5] as in figure (1).

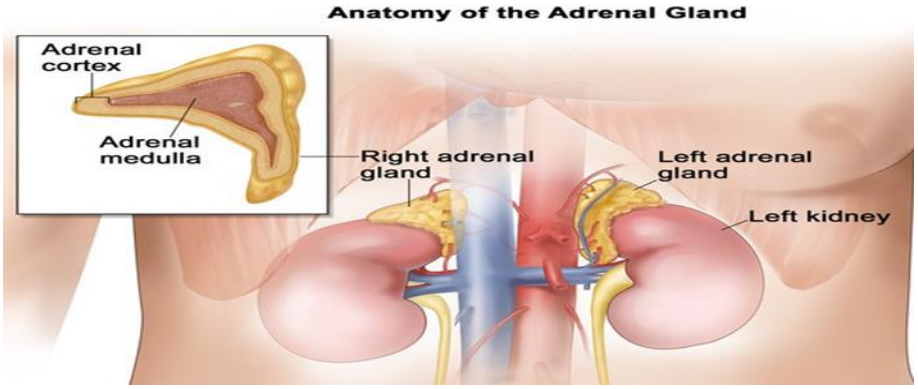

Figure (1): Site of adrenal gland at the upper pole of both kidneys [6].

The normal adult adrenal gland has a mean maximum body width of 61 mm (right) and 79 mm (left), weighting approximately 5gm. Interestingly, the weight of each gland is about 8 to 10 gm in the newborn, but loses half of this weight by the age of 2 years, mainly because of involution of the adrenal fetal cortex. The glands begin to grow again by the end of the second year and reach their final weight by puberty. There is a little further increase in the weight in adult life [7].

Blood supply of adrenal gland: (Fig.2)

The adrenal glands have rich blood supply, they have the highest arterial blood flow rates per gram of tissue (up to 5 ml/g/min) among different endocrinal glands of the body because of its high metabolic rate. Each adrenal gland is supplied by 3 different arteries that arise from three different sources; the superior suprarenal artery arises from the inferior phrenic artery, the middle suprarenal artery arises from abdominal aorta & inferior suprarenal artery arises from the renal artery [6,2].

The suprarenal arteries branch freely before entering each gland, where they converge & anastomose on the capsule, & send 50–60 end arteries which penetrate the capsule. After penetrating the capsule, these branches form a subcapsular plexus, from which 3 groups of vessels arise arterioles of the capsule, arterioles of the cortex & arterioles of the medulla. Also, from the subcapsular plexus, fenestrated sinusoids pass around the clustered zona glomerulosa cells & between the columns of zona fasciculata cells to end in a deep plexus in zona reticularis [6,2].

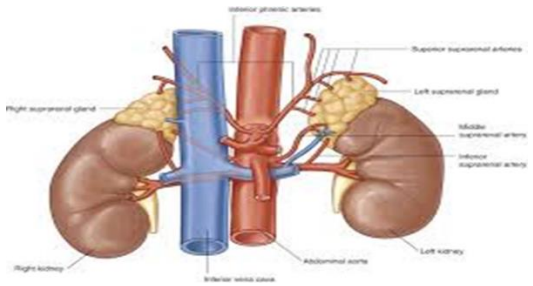

Figure (2): Topography &Blood supply of the adrenal gland [6].

Regarding the venous drainage of the suprarenal glands, small venules arise from deep venous plexuses in the center of the gland & pass through the suprarenal medulla to drain into the suprarenal vein that emerges from the hilum. The right suprarenal vein drains into the inferior vena cava while the left suprarenal vein drains into

the left renal vein [8]. The adrenal veins may drain into the hepatic vein or the inferior phrenic vein. Therefore, it is important to understand this variation to avoid bleeding during adrenalectomy [9,10,11].

The suprarenal cortex has a rich autonomic nerve supply more than any other organ. The right and left adrenal nerve plexuses contain preganglionic sympathetic fibers which originate from the lower thoracic spinal segments & reach the adrenal plexus through celiac ganglion& greater splanchnic nerve. These fibers synapse on the large chromaffin cells of the suprarenal medulla, so it is considered homologous to the sympathetic ganglion [3].

Considering the lymphatic drainage of the suprarenal gland, small lymphatic channels from cortex and medulla drain to the hilum, from where large caliber lymphatics emerge to drain directly into the lateral groups of para aortic lymph nodes [2].

Histology of the adrenal gland

Histologically, sections of the adrenal gland show a covering dense collagenous connective tissue capsule, peripheral cortex& central medulla (Figs.3&4). Strands of connective tissue start at the capsule &continue between the cortical cells to end at the medulla. These strands enclose wide sinusoidal blood vessels. They have a network of well-developed reticular fibers that supports the cortical and medullary cells. The suprarenal cortex contains parenchymal cells that synthesize& secrete several steroid hormones. The cortex is subdivided histologically into 3 zona from outward inward, zona glomerulosa (ZG), zona fasciculate (ZF) & zona reticularis (ZR) [12].

The zona glomerulosa (ZG) is the outer layer of parenchymal cells located beneath the capsule. It presents approximately 13% of the cortical volume. Its cells are small columnar that are arranged in closely packed ovoid clusters and curved columns and are continuous with the cellular cords of the ZF. A rich network of fenestrated sinusoidal capillaries surrounds each cell cluster [13,14].

Regarding ZF, it is the intermediate layer of cells in the adrenal cortex. It presents about 80% of the cortical volume. The cells of this zone are arranged in columns. They are polyhedral in shape and larger than the cells of ZG. The ZF cells contain large rounded nuclei and pale stained cytoplasm due to the large number of lipid droplets. Cells of ZF are called “spongiocytes” as they usually appear vacuolated in routine histological sections due to extraction of lipid during dehydration. This zone contains fenestrated sinusoidal capillaries that are arranged longitudinally between columns of parenchymal cells [13,14].

As regards ZR, it is a heavily stained dark band forming the border between cortex and medulla. The cells of ZR are smaller than cells of the ZF & ZG. These cells are arranged in anastomosing cords separated by fenestrated capillaries and this arrangement gives this zone a reticular appearance. The cells in this zone have less cytoplasm than the cells in the ZF, hence the nuclei appear more closely packed. The ZR cells have few lipid droplets, large lipofuscin pigment granules & deeply stained nuclei [14].

Regarding the histology of the suprarenal medulla, it forms the centre of the gland & appears red in fresh sections, the medulla is not sharply demarcated from the cortex. It contains anastomosing cords of basophilic staining cells with granular cytoplasm without lipid droplets. The cytoplasm of these cells appear clear while after tissue fixation in potassium bichromate, fine brown granules are visible in the cells of the medulla (called the chromaffin reaction), these granules indicate the presence of the catecholamines in the cytoplasm. These large ovoid secretory cells are called chromaffin cells which are grouped wide fenestrated medullary capillaries. The medulla also contains sympathetic neurons that are seen singly or in small groups. The neurons exhibit a vesicular nucleus [12,15].

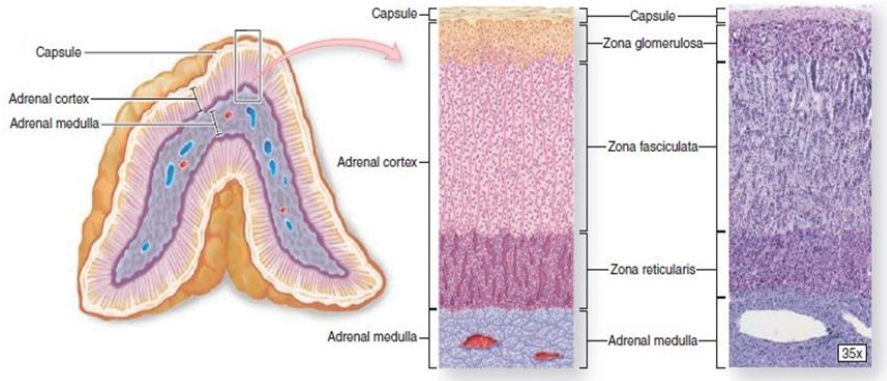

Figure (3): Photomicrograph showing cross section of adrenal gland. It includes capsule, the 3 layers of the adrenal cortex & medulla(HX&E) [16].

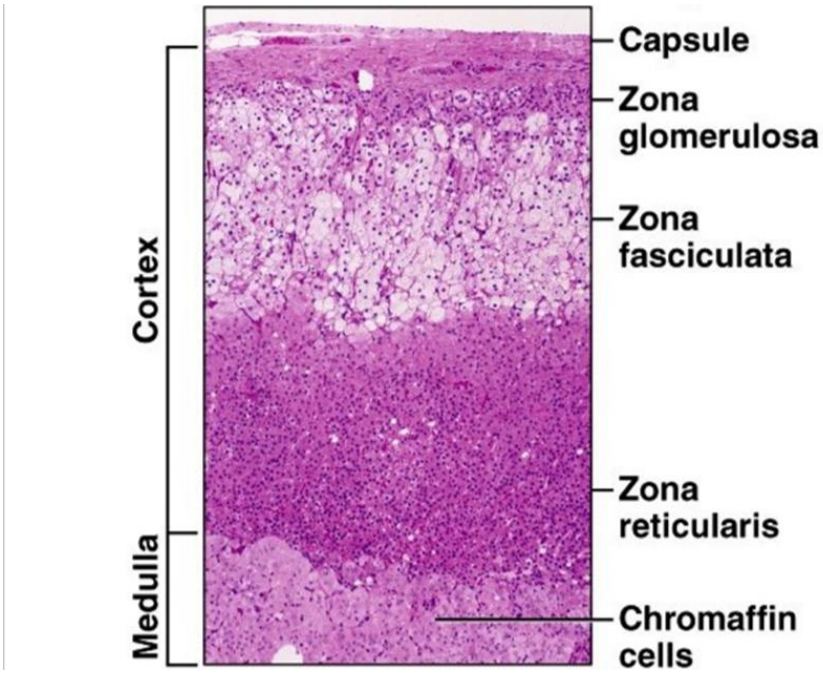

Figure (4): Cross section of adrenal gland showing surrounding capsule, 3 layers of the adrenal cortex & medulla(HX&E) [16].

Anatomy of mouse adrenal gland

The adrenal of the mouse consists of the cortex& medulla. Subcapsular proliferation of fusiform cells, occurrence of accessory proliferative cortical nodules& deposition of lipogenic pigment are characteristics features of mouse adrenal gland. The mouse adrenal cortex volumes reached their maximum at an age 7 weeks & then decreased by 40 &20% in male &female respectively. The cortex consists of a zona glomerulosa, zone fasciculata & an x-zone. In contrast to most mammals, there is no clearly defined zona reticularis in the mouse adrenal cortex. The ZG &ZF are distinguishable in the adult but often not clearly demarcated from one another. ZG cells are smaller, more basophilic, contain small uniform perinuclear lipid droplets &form small arches. ZF cells are eosinophilic forming columns &have cytoplasmic lipid droplets. The mouse has spindeloid cells which contain vitamin A in the ZF [17].

X-zone is transitional region, unique to the mouse adrenal with no clearly defined function. The X-zone is a transient cortical region enriched in eosinophilic cells located in the cortical–medullary boundary of the mouse adrenal gland. Similar to the fetal zone in human adrenals is also a transient cortical compartment, comprising the majority of the human fetal adrenal gland as in figure (5).

The mouse medulla occupies 20% of the adrenal volume & consists of irregular packets of polyhedral chromaffin &ganglion cells along with a rich vascular structure of venules & capillaries [18]. Ganglion cells are randomly distributed throughout the medulla. Chromaffin cells are basophilic with granuler cytoplasm because of secretory granules. There are 2 types of chromaffin cells: epinephrine& norepinephrine [19]. The cells closest to the cortex are norepinephrine secreting cells with the epinephrine representing 75% of the medulla [17].

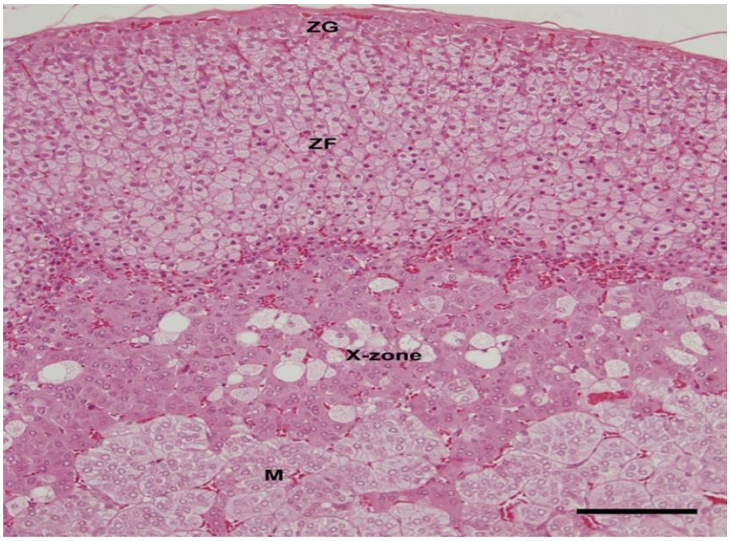

Figure (5): Cross section of mouse adrenal gland showing zona glomerulosa (ZG),zona fasciculata(ZF), x-zone &medulla(M) (Hx&E) [17].

Physiology of the adrenal gland:(fig.6)

Physiologically, the adrenal cortex is subdivided into 3 zones, each of which secretes different set of hormones which are steroid in nature. The outer zone (ZG) secretes mineralocorticoids as they affect mainly the mineral homeostasis, the middle zone (ZF) secretes glucocorticoids, so named because they affect mainly the glucose homeostasis& the inner zone (ZR) secretes small amounts of weak androgens [20].

The adrenal cortex produces more than 25 steroid hormones collectively known as the corticosteroids & includes mineralocorticoids, glucocorticoids and androgens. Only 5 of these corticosteroids are secreted in physiological significant amounts while the others are secreted in a minute negligible quantity [21,22]. These corticosteroids are synthesized from cholesterol which is taken up from blood and esterified to be stored as lipid droplets within the cytoplasm of the adrenal cortical cells. When these cells are stimulated, cholesterol is freed and used in hormone synthesis in the mitochondria., the corticosteroids are rapidly released into the blood stream & this is facilitated by a dense vascular network within the adrenal cortex in which each adrenocortical cell is in contact with at least one capillary [21,22].

Regarding the mineralocorticoids, they include aldosterone hormone and other hormones with a slight mineralocorticoid activity including deoxycorticosterone, corticosterone, 9α-Fluorocortisol and cortisol [23]. Aldosterone increases reabsorption of sodium and simultaneously increases secretion of potassium by the renal tubular epithelial cells, especially in the principal cells of the distal tubules and collecting tubules of the kidney. The secretion of aldosterone is controlled mainly by the renin–angiotensin–aldosterone (RAA) pathway. The stimuli that trigger this RAA signaling pathway include dehydration, sodium deficiency or hemorrhage which cause a decrease in blood volume. Another stimulator of aldosterone secretion is the rise of potassium concentration in the blood [24].

Interestingly, in cases of Addison's disease, there is mineralocorticoid deficiency in which the total extracellular fluid volume and blood volume greatly reduced, with diminished cardiac output, which progresses to a shock like state. This can be prevented by systemic administration of aldosterone. Therefore, the mineralocorticoids are said to be acute "lifesaving" hormones [25,23].

The glucocorticoids are secreted mainly from ZF & include cortisol mainly &little corticosterone. These hormones regulate carbohydrate, fat& protein catabolism, stimulate gluconeogenesis and induce release of fatty acids and glucose into the blood [22]. Consequently, these hormones help the body to adapt and resist the destructive effects to the tissues upon physical and mental stresses [25,23]. Also, glucocorticoids have an anti-inflammatory effect. In addition, they suppress the immune system and decrease the number of eosinophils and lymphocytes in the blood. It was reported that large doses of cortisol cause significant atrophy of almost all lymphoid tissue [22].

Secretion of glucocorticoids is controlled mainly by corticotrophin releasing hormone (CRH) from hypothalamus and ACTH secreted from anterior pituitary gland. Almost all types of stressors cause an immediate and marked increase in ACTH secretion with subsequent a great increase of cortisol from the adrenal cortex. The stressors include hypoglycemia, hemorrhage, hypoxia, high altitude, pain, exercise, fasting, fright, extremes of temperature, infection, surgery and trauma [23].

Long-term elevation of cortisol secretion reduces immunity. It inhibits the synthesis of protective leukotrienes and prostaglandins, suppresses antibody production, and kills immature T and B cells (two important families of immune cells). A person under chronic stress is more susceptible to infections and gastritis, ulcerative colitis, irritable bowel syndrome, hypertension, asthma, rheumatoid arthritis (RA), migraine headaches, anxiety, and depression [26,20].

Mechanism for regulation of glucocorticoid secretion adrenocorticotropic hormone (ACTH), corticotropin releasing factor (CRF) [23].

The secretory rate of CRF, ACTH& cortisol shows a circadian rhythm, where they are high in the early morning but decrease in the late evening. This effect results from a 24-hour cyclic alteration in the signals from the hypothalamus to the retina. The circadian rhythm of these hormones is related to the activity phase of the individuals so they act as endogenous biological time keeper. However, when a person changes his daily sleeping rhythm, the circadian rhythm of these hormones changes correspondingly [27].

Physiologically, ZR secretes adrenal androgens that are continually secreted especially during the fetal life. Normally, the adrenal androgens have weak effects in humans relative to the strong androgens of the gonads. It is possible that part of the early development of the male sex organs results from childhood secretion of adrenal androgens. Also, progesterone and estrogens, which are female sex hormones, are secreted in minute quantities from ZR. Also, much of the growth of the pubic and axillary hair in the females results from the action of these hormones [20].

Regarding the physiology of the adrenal medulla, their chromaffin cells secrete catecholamine hormones (about 80% epinephrine and 20% norepinephrine). These hormones of the adrenal medulla intensify sympathetic responses that occur as a result of stress. In stressful situations, impulses from the hypothalamus stimulate sympathetic preganglionic neurons, which in turn stimulate the chromaffin cells to secrete epinephrine and norepinephrine. Thus, the adrenal medulla has a dual function, acting as both an endocrine gland and a ganglion of the sympathetic nervous system [20].

Also, epinephrine and norepinephrine are released in response to hypoglycemia. In such situation, these hormones mobilize high-energy fuels such as lactate, fatty acids and glucose, thus they prepare the body to face the stressful condition. Also, they stimulate the liver to increase glucose production by glycogenolysis (breakdown of glycogen) into glucose and gluconeogenesis (conversion of fats, amino acids, and other non-carbohydrates to glucose). Epinephrine is said to have a glucose-sparing effect inhibits the secretion of insulin, so the muscles & other insulin-dependent organs depend on alternative fuels such as fatty acids, while the blood glucose is left for use after repeated noise exposure.

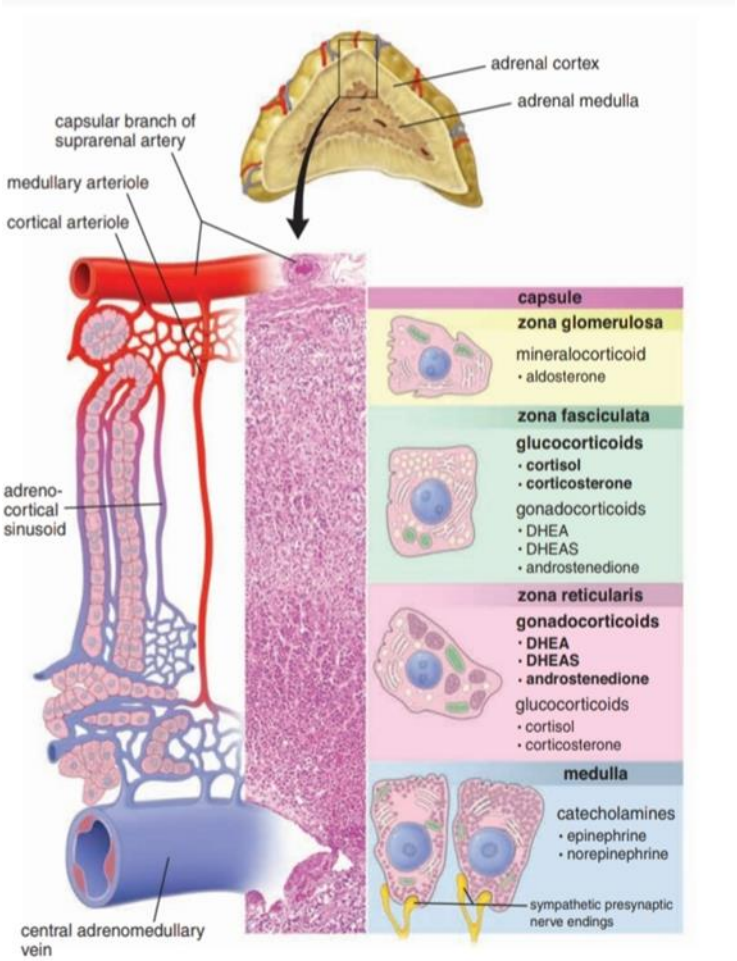

Figure (6): photomicrograph showing blood supply & hormones secreting from adrenal cortex &medulla [28].

Development of the adrenal gland

In human, the suprarenal gland develops during embryogenesis from two distinct embryological tissues the intermediate mesoderm, which differentiate forming the adrenal cortex and neuroectodermal tissue, the neural crest, which differentiate into the adrenal medulla [29] as in figures 7&8.

Regarding the development of adrenal cortex, at about the fourth week of gestation, the earliest recognizable primordium of the cortex is "the adrenal blastema" which are the cells that developed from the intermediate mesoderm that appear as a plate of condensed mesothelial coelomic epithelium in the notch between the dorsal mesentery of the gut medially and the urogenital ridge laterally [30,31]. Actually, the medial portion of the urogenital ridge forms the mesonephric blastema (mesonephros, primitive nephrons), while its lateral portion forms the primitive gonad. By the fifth week, the coelomic epithelial cells that constitute the primitive adrenal cortex begin to migrate and stream cranially, eventually accumulating at the cranial end of the mesonephric blastema.

By the eighth week of the embryonic life, the primitive cortical cells that migrate to the cranial end of the mesonephric blastema organize into anastomosing cords, proliferate and penetrate the underlying mesenchyme and eventually differentiate into large polyhedral acidophilic cells that constitute the fetal cortical zone (primordial adrenal cortex) that circumvents and encloses the primordial adrenal medulla [31].

At about the 9th week of gestation, a second wave of coelomic mesothelial cells, which are smaller than those of the first wave, proliferate and penetrate the mesenchyme at the cranial end of the mesonephric blastema forming the definitive zone (the definite adrenal cortex) that circumvent the fetal cortex [31]. Therefore, by the 9th week of human pregnancy, the fetus has a distinct adrenal cortex made up of two zonal compartments. The

large eosinophilic cells in the inner part of the adrenal blastema form the fetal zone (FZ), whereas the peripheral small basophilic cells form the definitive zone (DZ) [32].

At the 10th week of gestation, the 2 zonal compartments of the adrenal cortex are completely enclosed by the adrenal capsule, which is composed of specialized mesenchymal cells migrating from the area of Bowman's capsule. At the same time, an extensive network of sinusoidal capillaries develops between the cords of the FZ. This vasculature predominates in the central portion of the fetal zone and persists throughout fetal life. Consequently, the adrenal cortex is one of the most highly vascularized organs in the primate fetus. Abundant vascularization is likely required to facilitate access of hormonal products to the circulation. After 10–12 weeks of gestation, the morphology of the adrenal cortex remains relatively constant [33,34].

By mid-gestation (16–20 weeks), the FZ clearly dominates and is composed of large eosinophilic cells that exhibit ultrastructural characteristics typical of steroid-secreting cells. In the outer regions of the FZ, the cells are arranged in tightly packed cords. However, the cells in the central portion are more widely spaced into a reticular pattern and separated by many vascular sinusoids. Clusters of immature neuroblasts that will aggregate eventually into a functional medulla are also present between the innermost fetal zone cells [33,34]. On the other hand, the DZ is composed of a narrow band of small tightly packed basophilic cells that exhibit structural characteristics typical of cells in a proliferative state (i.e. small cytoplasmic volume containing free ribosomes; small, dense mitochondria with lamelliform cristae and scant lipid). Its inner layers form arched cords that send finger-like columns of cells into the outer rim of the FZ. Although definitive zone cells are lipid-poor during midgestation, they accumulate some cytoplasmic lipid and begin to resemble steroidogenically active cells with increasing age. Ultrastructural studies have also demonstrated a third zone between the FZ and DZ zones, the cells of which have intermediate characteristics. This cortical area is termed the 'transitional zone' (TZ). Some studies indicate that after midgestation, TZ cells may have the capacity to synthesize cortisol and thus be analogous to cells of the zona fasciculata of the adult adrenal [33,34].

By the 30th week of gestation, the fetal adrenal cortex manifests a rudimentary form of the adult adrenal cortex while the DZ and TZ zones begin to take on the appearance of the zona glomerulosa and the zona fasciculata, respectively [34,35].

By full term, the adrenal gland becomes equivalent in size and weight to those of the adults. At birth, under the influence of the nearby permanent cortical cells, a great involution of the FZ occurs except for its outermost layer which differentiates into ZR of the cortex. While the FZ is regressing, the ZG and ZF grow more, and the ZR starts to appear. Accordingly, it was found that at the first postnatal month, the adrenal gland reaches a quarter of its full term size [36,35].

At the end of the second year, the fetal cortical cell mass is suppressed and completely disappears, however the permanent cortex persist and its development continues with appearance of a primitive zonation that carries out the same functional properties as that of the adult cortex [33,37]. Interestingly, the development of the definitive cortex is not completed until 18 to 21 months after birth [38].

Regarding the development of adrenal medulla, at about the 6th week of gestational age, the primordium of adrenal medulla appears, where pheochromoblasts from adjacent sympathetic ganglia (neuroectodermal origin) that derived from the neural crest migrate to invade the primitive cortex (mesodermal origin), these pheochromoblasts are arranged in cords and clusters [39]. The medulla is not recognized as a distinct structure in the human primate fetal adrenal throughout most of gestation, except for small clusters or nests of chromaffin cells scattered throughout the body of the cortex. These cells loss their nerve processes and axons and begin to secrete epinephrine and norepinephrine during gestation [40]. A more structurally distinct medulla does not form until after birth. After the involution of the fetal zone during the first postnatal week, the chromaffin cells coalesce around the central vein and begin to form a rudimentary medulla. By the fourth postnatal week, all of the chromaffin cells have clustered in the center of the gland. However, the medulla doesn't become adult-like in appearance until 12 to 18 months [38,31].

The cells of adrenal medulla are called chromaffin cells because they contain granules that stained yellow-brown with chromium salts. This staining is probably due to presence of epinephrine and norepinephrine in the medullary cells, a characteristic feature not present in all sympathetic tissues [41].
At birth, the adrenal medulla is slightly developed and is not yet functioning, the whole gland consists of the medulla, definitive cortex and fetal cortex that constitute approximately 5%, 80% and 15% of the adrenal mass respectively [35].

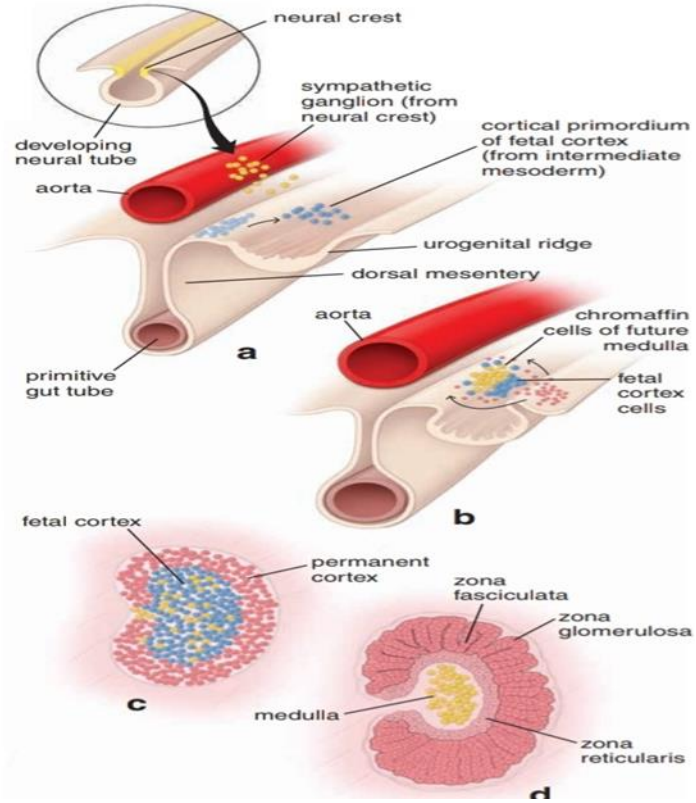

Figure (7): Photomicrograph showing development of the adrenal gland [28].

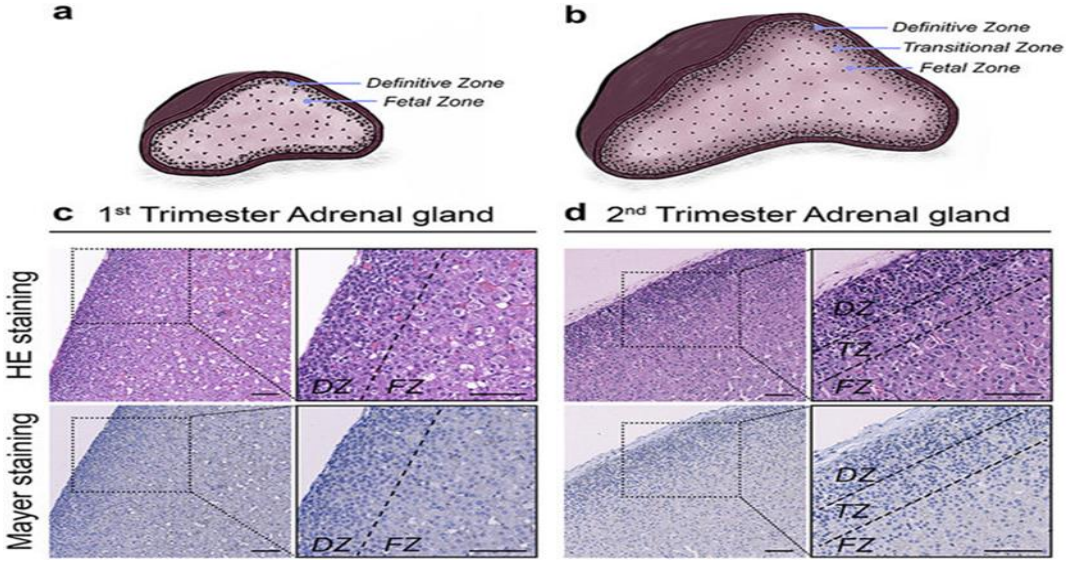

Figure (8): Schematic illustrations of the morphological zonation of fetal adrenal gland in first &second trimesters [35].

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