DEVELOPMENT OF THE ADRENAL GLAND; TESTES AND MESONEPHRIC DUCT

Reading Assignment: The Developing Human, Clinically Oriented Embryology pp. 264-273.

Objectives:
1. Be able to describe the normal development of the adrenal gland, with particular attention to development of fetal and adult cortex and medulla.
2. Describe the timing of development of fetal and adult cortex with regards to production of androgens, glucocorticoids and prostaglandins, and thromboxaine.
3. Be able to describe the tissue of origin for the adrenal cortex and adrenal medulla.
4. Be able to describe the three zones derived from the fetal cortex and their relative importance.
5. Be able to define the zones derived from the permanent cortex (z. fasiclata, z. reticularis, and z. glomerulosa) and define the timing of their development.
6. Be able to describe the development of the gonadal blastema, the cells that contribute to the formation of the gonad.
7. Be able to define the origin of primary sex cords and the role of primary sex cords in developing testes.
8. Be able to describe the abnormal development of the gonads such as ectopic germ cells etc.
9. Be able to define the period of time in which the gonads are in the indifferent stage.
10. Be able to describe the genetic factors that contributes to testicular development (Y chromosome, H-Y antigen, Testis determining factor).
11. Be able to describe the formation of the seminiferous tubules, intracordal compartment and extracordal compartment.
12. Be able to define the cells that can be found in the intracordal compartment and those in the extracordal compartment.
13. Be able to define the origin of the Sertoli and Leydig cells, their secretory products and the importance and function of these products (MIS and genital duct inducer substance).
14. Be able to describe and define the origin and adult product of the Tunica albuginea and rete testis.
15. Be able to describe the development of the epididymis and mesonephric duct and their derivatives (efferent ductules, ductus epididymis, ductus deferens, seminal vesicle and ejaculatory ducts).

I. Adrenal (suprarenal) Gland:

A. Normal Development:
1. The adrenal gland is composed of two regions, a cortex and a medulla, each of which has a different embryologic origin.
2. The fetal cortex initially develops from mesenchymal cells that aggregate bilaterally on each side of the root of the dorsal mesentery.
a. Cortical cells are derived from mesoderm or mesothelium that lines the posterior abdominal wall.

b. Later, additional mesothelial cells will encapsulate the fetal cortex to form a permanent cortex.

3. The adrenal medulla is derived from cells of adjacent sympathetic ganglia.
   a. These ganglion cells are of neural crest cell origin.
   b. The neural crest cells migrate to a position on the medial aspect of the fetal cortex and are encapsulated by the fetal cortex.
   c. Once encapsulated, these medullary cells differentiate into cells (chromaffin cells) that secrete norepinephrine.

4. Developmental events:
   a. The adrenal anlagen first becomes evident during the 4th week as a thickening in the coelomic epithelium (mesothelium) from T6-12.
   b. During the 6th week:
      1) The cortical blastema develops from the thickened mesothelium.
      2) The medullary blastema forms from neural crest cells.
   c. During the 7th week: The fetal cortex differentiates forming a permanent zone (the primordium of the adult cortex) and a transient zone.
   d. During the 3rd month: Androgen production is significantly reduced and may possibly have terminated while the fetal cortex begins to produce large quantities of glucocorticoid and mineralocorticoids.
   e. During the 7th month: the adult cortex begins cellular differentiation forming the three distinctive zones (the zona glomerulosa, the zona fasiculata and the zona reticularis). It is important to note that although the initial components of these zones are present at birth, they will not be fully evident until 2-3 years after birth.

5. Adrenal cortex:
   A. Normal Development:
      Only the zona glomerulosa and fasiculata are present at birth while the zona reticularis will not be evident until about 3 years after birth.
      a. Fetal zone: is most often referred to as the fetal cortex.
         1) The fetal zone (cortex) differentiates from the cortical blastema during the 6th week. By the 5th month the fetal cortex comprises 75% of the adrenal volume, only 50% by the 9th month and involutes rapidly postpartum.
         2) The cortex begins to function very early and prior to the 3rd month it almost exclusively produces androgens. In the 3rd month under hypothalamo-hypophysial stimulation (ACTH) the fetal cortex begins to produce mineralocorticoids and glucocorticoids with the exception of aldosterone.
3) Also during this period, androgen production declines while prostaglandin and thromboxane production increases. The production of the latter two increases significantly during the 9th month and may influence the time of parturition.

b. The fetal cortex differentiates into three zones:
   1) A permanent zone which postpartum differentiates into the 3 zones of the adult cortex (glomerulosa, fasciculata and reticularis).
   2) An intermediate zone of which very little is known.
   3) A transient zone often referred to as the fetal cortex. It is this zone that prior to the 3rd month produces almost exclusively adrenal androgens. After the 3rd month it produces glucocorticoids and involutes after birth.
   4) During fetal life the adrenal gland is a comparatively large organ, almost 1/3 the size of the kidney. However, the majority of its bulk is derived from the fetal cortex, which involutes, so that postnatally (adult) it is only about 1/30th the size of the kidney.

c. The permanent cortex:
   1) Is the outermost of all the cortical zones, and differentiates from the mesothelium. Its cells will undergo differentiation and arrange themselves into three definitive zones in the adult adrenal.

6. Fetal medulla: These cells develop from neural crest cells. They stain yellow-brown with chrome-salts and are therefore, referred to as chromaffin cells. These cells begin producing epinephrine during the 8th week and will give a chromaffin reaction at that time.

7. The double origin of the cortex and medulla is reflected in the differences in function between the two parts of the gland in the adult.

B. Abnormal Development:
   1. adrenal agenesis: failure of adrenal glands to develop. Because the adrenal gland develops adjacent to the mesonephros, and possibly in part from the mesonephric tissue, adrenal agenesis is often accompanied by renal agenesis.
   2. adrenal cortical hyperplasia: results in an overproduction of adrenocortical hormones (Androgen). This will be covered in detail with the lecture of external genitalia.
   3. adrenal cortical hypoplasia: is associated with anencephaly and is the result of inadequate ACTH secretion from the pituitary gland.
   4. adrenal ectopia: sometimes the adrenal may develop in an abnormal location such as beneath the capsule of the liver or kidney.
   5. accessory adrenal cortex-follows the path of gonads.
   accessory adrenal medulla-follows the migration of neural crest cells.

II. Development of the Gonadal Blastema:
A. Normal Development:
1. In mammals, including man, some cells segregate early in development and can be identified as primordial germ cells. They can be characterized by many ribosomes and polysomes, dense granulofibrilar bodies, very dense nuclei, and a scant amount of endoplasmic reticulum and Golgi complex.
2. Many large primordial germ cells are seen in the endoderm of the yolk sac of the week 4 embryo. From this point, as the embryo folds, these cells migrate along the dorsal mesentery of the hindgut to a position on the medial aspect of the mesonephros.
3. Gonadal ridge
   a. Is a thickened area of mesodermal epithelium that appears during the 5th week on the medial side of the mesonephros as the primitive germ cells migrate into the region.
   b. By week 6, all of the primordial germ cells have entered this gonadal ridge which will ever enter it; over 1000 primordial germ cells.
   c. As these germ cells (mesothelial cells) proliferate, they produce a large bulge initially at the C7-T8 levels.
   d. The developing gonad, whether ovary or testis, will shift caudally and descend to the T10-L2 level by the 7th week.
4. 6th and 7th weeks:
   a. Finger-like projections of epithelial cells, the primary sex cords, grow into the underlying mesenchyme in both males and females.
   b. The primordial germ cells lie between these primary sex cords.
   c. The gonadal blastema (which Moore refers to as the indifferent gonad) is a compact mass of mesodermal cells that are derived from three distinct sources (coelomic epithelium, mesonephric tubules, and mesonephric mesenchyme) with primordial germ cells scattered among the mesenchymal cells.

B. Abnormal Development:
1. Ectopic germ cells:
   a. Results from abnormal migration of primordial germ cells.
   b. They do not induce the formation of ectopic gonads.
   c. In some situations ectopic germ cells may give rise to extragonadal germ cell tumors (yolk sac tumors).
2. If primordial germ cells fail to invade the genital ridges, the gonads do not develop. So the primordial germ cells appear to have an inductive influence on the development of the gonad.

III. Development of the Testes
Although the sex of the embryo is genetically determined at the time of fertilization, the gonads do not acquire male or female morphological characteristics until around the 7th week of development. Prior to the 7th week the gonads of the two sexes are identical in appearance and are referred to as indifferent gonads.
A. Genetic Factors:
1. The Y chromosome has a potent sex-determining effect on the medulla of the indifferent gonad.
2. The Y chromosome regulates the production of the H-Y antigen (testis organizing factor) which stimulates testicular differentiation.
3. If the Y chromosome is absent, ovaries will develop.

B. Development of Testicular Cords (seminiferous tubules):
1. In response to the H-Y antigen (testis determining factor) and the presence of the Y chromosome, the primary sex cords condense and spread to the medulla of the gonad.
2. These primary sex cords will shed their basal laminae, allowing germ cells to enter the cords.
3. A basal laminae will be re-established around the cords forming two compartments; an intracordal compartment and extracordal compartment.
4. Fate of the testicular cords or seminiferous cords:
   a. Each cord is surrounded by a basal laminae- which separates the cord (intracordal compartment) from the extracordal compartment.
   b. The seminiferous cords will eventually develop into the seminiferous tubules, tubuli recti and the rete testis.
      1) germ cells - will eventually develop into spermatogonia.
      2) Sertoli cells (supporting or sustentacular cells) - support the developing spermatogonia and are believed to be of mesonephric origin. They are thought to produce a meiosis inducing substance and an anti-Mullerian hormone. In the fetus, the Sertoli cells make up most of the seminiferous epithelium.
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5. The extracordal compartment of the testis includes the Leydig cells which begin to develop in the 8th week.
   a. The Leydig cells are believed to originate from the mesonephric mesenchyme.
   b. Leydig cells have a very rich vascular supply and are the site of androgen synthesis, particularly the male sex hormone testosterone and dihydrotestosterone.
   c. In addition, these interstitial cells (Leydig cells) produce genital duct inducer and suppressor substances.
      1) genital duct inducer substance - induces the development of the mesonephric ducts.
6. Tunica albuginea - develops as a loose mesenchymal layer after primary sex cords lose their attachment with the coelomic epithelium. The development of a thick, dense tunica albuginea is a characteristic feature of testicular development.
7. The testes change in shape; testes rapidly becomes rounded and reduce their area of contact with mesonephros, this minimizes the feminizing influences of the mesonephros.
8. **Rete testis** - are initially a network of cords that are derived from the mesonephric tubules and mesonephric mesenchyme. These channels have developed a lumen by the 12th week.

9. By the 8th week: the testes show (1) distinct testicular cords; (2) a tunica albuginea of loose mesenchyme; (3) a rounded shape; (4) a narrow connection with the mesonephros.

IV. **Development of the Epididymis and Mesonephric Duct Derivatives:**

A. The mesonephric ducts are important structures in the development of the male reproductive system. These ducts drain the mesonephric kidneys. In the male the proximal portion of these ducts persist, while in the female the mesonephric duct, for the most part, degenerates.

1. As the fetal testes develop, they produce testosterone and **Mullerian inhibiting substance**.

2. The androgens (testosterone) produced by the Leydig cells stimulate the mesonephric ducts to form.

3. The Mullerian inhibiting substance, which is produced by the Sertoli cells, suppresses the formation of the paramesonephric ducts (Mullerian ducts).

4. The portion of the mesonephric tubules adjacent to the testes persist and are converted into efferent ductules.

5. These efferent ductules open into the mesonephric duct which becomes the **ductus epididymis**.

6. The region of the mesonephric duct distal to the ductus epididymis becomes invested by a thick layer of smooth muscle and will give rise to the **ductus deferens**.

7. The **semenal vesicle** arises as a lateral outgrowth of the caudal end of each ductus deferens.

8. The **ejaculatory duct** develops from the region of the mesonephric duct between the seminal vesicle and the urethra.

B. Table 13-1 in Moore has a listing of the derivatives of the mesonephric ducts and tubules.

Embryo Collection: F6, A30, B30

V. **Development of the Gonadal Blastema (review):**

Although the sex of the embryo is determined genetically at the time of fertilization, the gonads do not acquire male or female characteristics until the 7th week of development.

A. Normal Development:

1. In the four-week embryo, a pair of longitudinal elevations, the **gonadal ridges** are formed on each side of the midline between the dorsal
mesentery and the mesonephros by proliferation of the coelomic epithelium along with condensation of the underlying mesenchyme (coelomic epithelium and mesenchyme).

2. During the 6th week of development, these ridges are invaded by germ cells which migrate from the wall of the yolk sac near the allantois up the dorsal mesentery of the hindgut into the ridge.

3. These primordial germ cells have an inductive influence on the gonadal ridge. If the germ cells do not reach the ridges, the gonads do not develop.

4. Before and during the arrival of the germ cells, the coelomic epithelium proliferates and forms many irregularly shaped primitive sex cords.

5. These cords surround the invading germ cells and in both sexes retain their connection back to the surface of the gonadal ridge.

B. Abnormal development: refer to earlier lecture on testis.

VI. Ovary:

A. Weeks 9-10:
1. The ovary is not identifiable until about the 10th week.
2. Unlike its male counterpart, in the female gonad, the primary sex cords do not continue to proliferate after the 6th week.
3. Initially, the developing ovary is composed of a primitive cortex, which is composed of the invading germ cells and mesothelial cells, and a primitive medulla, consisting of mesenchyme and primary sex cords.

B. 11th and 12th weeks:
1. The primary sex cords remain indistinct and extend only into the medulla to form rudimentary rete ovarii.
2. Eventually the rete ovarii and remaining sex cords will be broken up by invading mesenchyme into irregular cell clusters and will degenerate and disappear.
3. Development of the cortical portion of the gonad distinguishes the ovary from the testis.
4. Shortly after week 10, the coelomic epithelium undergoes secondary proliferation to form cortical or secondary sex cords.
5. These secondary sex cords penetrate into the underlying mesenchyme and the germ cells are incorporated into them.
6. Folliculogenesis and mitosis begin and a follicular or germ cell compartment is quickly established.

C. 16th week:
1. The secondary sex cords begin to break up into cell clusters called primordial follicles.
2. A primordial follicle consists of a single layer of flattened cells, follicular cells, derived from the cortical or secondary sex cords, surrounding an oogonium, which is the derivative of a primordial germ cell.
D. 5th month:
1. The secondary medulla forms as the rete ovarii degenerate in the deeper part of the cortex.
2. Much of the medullary cells degenerate and are replaced by a vascular stroma to form most of the ovarian medulla.
3. A secondary cortex is established from the part of the cortex remaining after the secondary medulla has been established and by the gradual conversion of oogonina into oocytes.

E. 7th month:
1. Most of the oogonia have been converted to oocytes, some of which become surrounded by a layer of cuboid follicular cells to form a primary follicle.
2. Some oogonia degenerate before birth so that by birth around 2 million oogonia have matured into oocytes.
3. Most primary follicles remain arrested, but a few escape to form secondary follicles, in response to maternal gonadotropins.
4. These follicles will not mature and will become atretic.
5. A thin fibrous capsule forms just deep to the surface epithelium of the ovary, this is the tunica albuginea.
6. As the ovary develops and the mesonephros degenerates, the ovary becomes suspended in a mesentery, the mesovarium, which develops from the degenerating mesonephros.

Note: Proliferative activity in the ovary ceases prior to birth and the formation of new or additional germ cells does not take place again. Thus, the human female at birth contains in her ovaries all of the germ cells she will ever produce.

VII. Paramesonephric Ducts or Mullerian Ducts:

A. Initial development:
1. In the sixth week, male and female embryos have both mesonephric (Wolffian) ducts and paramesonephric (Mullerian) ducts running parallel to each other.
2. The mesonephric duct arises from the union of the caudally directed tips of the mesonephric tubules.
3. The paramesonephric ducts develop on each side from longitudinal invaginations of the mesodermal (coelomic) epithelium on the lateral aspect of the mesonephros.
4. The margins of the invaginations move towards each other and fuse with each other to form the paramesonephric duct.
5. Course and segments:
   a. Cranial segment: which is oriented vertically and opens into the coelomic cavity. This segment will form the Fallopian tube.
b. **Horizontal or transverse segment:** which crosses over the mesonephric duct and will give rise to the intramural part of the fallopian tube and the fundus of the uterus.

c. **Caudal segment:** is oriented vertically and will fuse with the paramesonephric duct from the opposite side to form a Y-shaped uterovaginal primordium or canal.

6. By week 9 the paramesonephric duct reaches the cloaca at the junction of the vesico-urethral canal and urogenital sinus.

7. Its further development will be taken up after a brief review of cloacal development.

B. **Review of cloacal development:**

1. During 4th-7th weeks the cloaca is subdivided into two segments by the urorectal septum:
   a. **Posterior segment:** which forms the rectum and superior part of the anal canal.
   b. **Anterior segment:** which is also termed the **primitive urogenital sinus**.

2. **Parts of the primitive urogenital sinus:**
   a. The upper and largest part (vesicular region) will form the **urinary bladder**.
   b. A narrow region of the **pelvic part of the UG-sinus** will form part of the vestibule of the vagina and, in the male, the inferior portion of the prostatic urethra.
   c. The **phallic part** which is the region closet to the urogenital membrane, will form the remainder of the vestibule of the vagina and the urethra.

C. **Paramesonephric and mesonephric ducts: early development in both sexes:**

1. By the 5th week the mesonephric ducts have reached the cloaca.
2. By the 7th week the inferior segment of each mesonephric duct has been incorporated into the trigone of the developing bladder.
3. In the 9th week the paramesonephric ducts reach the junction of the primitive urethra and the urogenital sinus medial to the mesonephric ducts.

D. **Paramesonephric ducts (Mullerian ducts) further development in the female:**

1. In embryos with ovaries or without testes, the mesonephric ducts will regress and the paramesonephric ducts develop into most of the female genital duct.
2. In the testes, a non-steroidal Mullerian inhibiting substance is produced by the Sertoli cells, which inhibits the complete formation and induces the regression of the Mullerian or paramesonephric ducts.
3. In addition, testosterone, produced by the Leydig cells within the testes, stimulates the mesonephric duct development.
4. In the female these are not present. Therefore, the paramesonephric ducts continue to develop while the mesonephric ducts (Wolffian ducts) regress.

5. As seen earlier:
   a. The cranial segment of the paramesonephric ducts develop into the ampulla and isthmus of the Fallopian (uterine) tube.
   b. The transverse segment forms the intra-mural part of the Fallopian tube and the fundus of the uterus.
   c. The caudal segment forms the utero-vaginal canal, which gives rise to the body and cervix of the uterus and the fundus of the vagina.

6. As the paramesonephric ducts have fused in the midline, a broad transverse pelvic fold, the broad ligament, is established which extends from the lateral sides of the ducts to the walls of the pelvis.

7. The broad ligament contains the uterine tube in its upper margin and the ovary on its posterior surface and divides the pelvic cavity into two compartments.
   a. The rectouterine pouch posteriorly.
   b. The vesicouterine pouch ventrally.

8. Mesenchyme in the broad ligament and on the sides of the developing uterus differentiates to form a smooth muscle coat, the myometrium, and loose connective tissue, the perimetrium, which are collectively known as the parametrium.

VIII. Development of the Vagina:

A. Normal development:
   1. Initially it was believed that the paramesonephric ducts gave rise to both the uterus and the entire vagina.
   2. This concept has been abandoned since it was observed that solid evaginations of the posterior wall of the urogenital sinus canalized and helped form the vagina.
   3. The current belief is:
      a. Superior part is derived from the utero-vaginal (uterine) canal.
      b. Inferior part (lower 2/3) is derived from the Urogenital sinus.
      c. The vaginal epithelium is believed to be derived from the endoderm of the urogenital sinus.
   4. As the paramesonephric ducts reach the UG-sinus two evaginations, sinovaginal bulbs, grow from the pelvic portion of the sinus.
   5. The sinovaginal bulbs proliferate, increasing the distance between the developing uterus and the UG-sinus. This solid mass of cells is known as the vaginal plate.
   6. By the 5th month this vaginal plate has completely canalized and wing-like expansions of the vagina, vaginal fornices, have formed around the uterus.
   7. Until late in fetal life, the lumen of the vagina remains separated from that of the UG-sinus by a thin membrane, the hymen.

B. Abnormal development:
1. Incomplete fusion or lack of fusion of the paramesonephric ducts in a localized area or throughout the complete length of the ducts will result in several different forms of duplication of the uterus.
   a. **Uterus didelphis**: is the most extreme form with two completely separate uteri.
   b. **Uterus bicornuous**: uterus has two horns entering a common vagina.
   c. **Uterus bicornuous unicollis**: due to complete or partial atresia of one paramesonephric duct. One side of the uterus is well developed while the other side is a rudimentary appendage.
   d. **Atresia of the cervix**:

2. Failure of sinovaginal bulbs to form:
   a. **Double vagina**:
   b. **Atresia of the vagina**:

Embryo Collection: A41, A73, B100, C32, D3