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Article

Urogenital System for Women

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ABSTRACT

Functionally, the urogenital system can be divided into two completely different components : urinary system and genital system. However, embryologically and anatomically, the two are closely related. Both originate from a single *mesodermal ridge* (intermediate mesoderm) along the posterior wall of the abdominal cavity, and initially, the excretory ducts of both systems enter the same cavity, the cloaca. The urogenital system is a system consisting of the urinary system which is divided into the urinary tract and the genital system. Where the urinary system is divided into the upper and lower urinary tracts. The upper urinary tract consists of the kidneys, renal pelvis and ureters, while the lower urinary tract consists of the urinary bladder and urethra. The external genital system in men and women is different, in men it consists of the penis, testes and scrotum, while in women it consists of the vagina, uterus and ovaries. The following will describe the urogenital system in women.

Kidney System

During intrauterine life, in humans three renal systems are formed which slightly overlap in cranial-to-caudal order: pronephros, mesonephros and metanephros. Pronephros is rudimentary and non-functional; the mesonephros may function in the short term during early fetal life; metanephros forms the permanent kidney.

1. Pronephros

At the beginning of the fourth week, the pronephros consists of 7-10 clusters of dense cells in the cervical region (Figure 1). This group forms the vestigial excretory unit, the nephrotome, which regresses before the more caudal group is formed. By the end of the fourth week, all signs of the pronephric system had disappeared.

2. Mesonephros The

mesonephros and mesonephric ducts arise from intermediate mesoderm from the upper thoracic to the upper lumbar segment (L3) (Fig. 2). Early in the fourth week of development, during regression of the pronephric system, the first excretory tubules appear in the mesonephric system. These tubules elongate rapidly, form an S-shaped loop, and receive a bundle of capillaries that will form a glomerulus in the medial extremity. Around the glomerulus, the tubules form **Bowman's capsule**, and together, these structures **in the cervical andregions** upper thoracic, segmented intermediate mesoderm; in the lower thoracic, lumbar and sacral regions, the mesoderm forms a dense mass of unsegmented tissue, the nephrogenic cord.

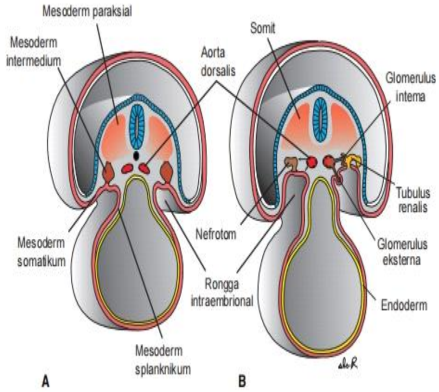

Figure 1. Pronepros

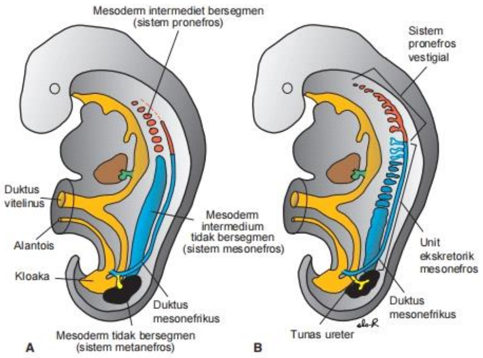

Figure 2. Mesonephros Excretory

tubules of the pronephric and mesonephric systems in a 5-week-old embryo. form the renal corpuscle. Laterally, the tubules enter a*collecting duct*longitudinalknown as the mesonephric duct or Wolffian duct (Fig. 2). In the middle of the second month, the mesonephros forms large ovoid organs on either side of the midline. Because the developing gonads are located on the medial side, the ridge formed by the two organs is known as the *urogenital ridge* . While the caudal tubules are still differentiating, the cranial tubules and glomeruli show degenerative changes, and by the end of the second month, most have disappeared. In males, some of the caudal tubules and mesonephric ducts remain and participate in the formation of the genital system, but these structures disappear in females.

3. Metanephros

The third urinary organ, the metanephros or permanent kidney, appears in the fifth week. Its excretory unit is formed from the metanephric mesoderm (Fig. 3) in the same way as in the mesonephric system. The development of the ductal system differs from that of the other renal systems.

a. Collecting System The collecting

ducts of the permanent kidney are formed from the ureteric bud, an outgrowth from the mesonephric duct near its opening into the cloaca. This bud penetrates the metanephric tissue, the distal end of which forms a cap. Later, this bud dilates, forms the primitive renal pelvis, and divides into cranial and caudal parts, the future major calyx. Each calyx forms two new shoots while penetrating the metanephros tissue. These buds continue to divide until 12 or more generations of tubules are formed (Figure 4). Meanwhile, in the periphery, more tubules were formed until the end of the fifth month. The second-order tubules enlarge and absorb the third and fourth generation tubules, forming the minor calyx of the renal pelvis. During further development, the(*collecting tubulescollecting tubules*) in the fifth and subsequent generations elongate and collect in the minor calyces, forming the renal pyramids. The ureteric bud forms the ureter, renal pelvis, major and minor calyces, and about 1-3 million collecting tubules.

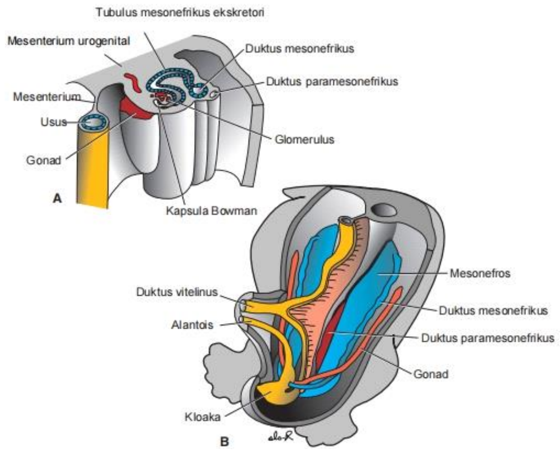

Figure 3. Relationship of hindgut and cloaca.

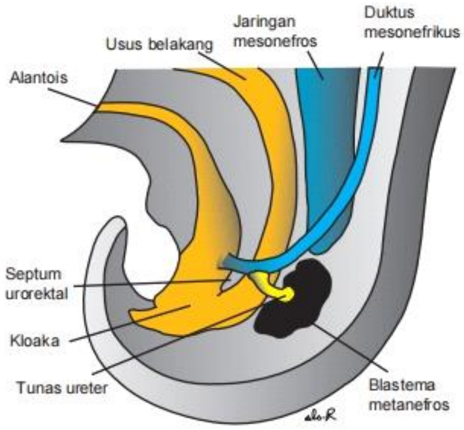

Figure 4. The ureteric bud penetrates the metanephric mesoderm (blastema).

b. The excretory system

Each newly formed collecting tubule is covered distally by a cap of metanephric tissue (Fig. 5). Under the inductive influence of the tubules, the cells of the covering tissue form small vesicles, the renal vesicles, which in turn form small S-shaped tubules.

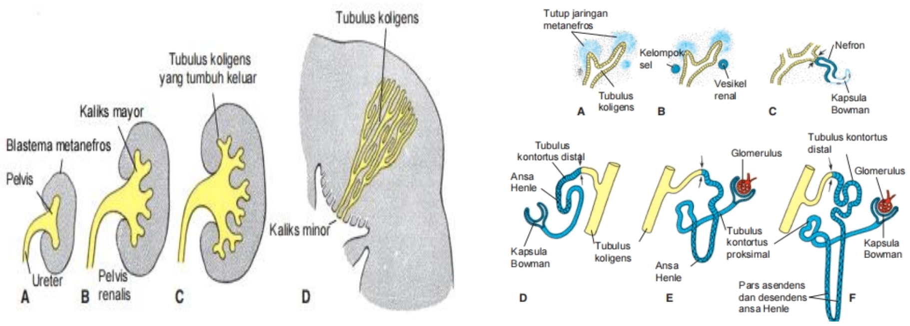

Figure 5. Collecting tubules

Capillary capillaries grow into pockets at one end of the S and differentiate into glomeruli. These tubules, together with their glomeruli, form the nephron, or excretory unit. The proximal end of each nephron forms Bowman's capsule, which is deeply indented by the glomerulus. The distal end forms a direct connection with one of the collecting tubules, which forms a conduit from Bowman's capsule to the collecting unit. Continuous elongation of the excretory tubules leads to the formation of the proximal convoluted tubule, loop of Henle and distal convoluted tubule.

Thus, the kidney is formed from two sources: (1) the metanephric mesoderm, which forms the excretory unit and (2) the ureteral bud, which forms the collecting system. Nephrons continue to form until birth, when there are about 1 million nephrons in each kidney. Urine production begins early in pregnancy, immediately after differentiation of the glomerular capillaries, which begin to form at the 10th week. At birth, the kidneys appear lobed, but this lobed appearance disappears during infancy due to further growth of the nephrons, although their number does not increase.

Molecular Regulation of Kidney Formation

As in most organs, renal differentiation involves mesenchymal epithelial interactions. In this example, the ureteric bud epithelium of the mesonephros interacts with the mesenchyme of the metanephric blastema (Fig. 6). Mesenchyme expresses *WT1*, a transcription factor that makes this tissue competent to respond to induction by the ureteral bud. WT1 also regulates the formation of *glial-derived neurotrophic factor* (GDNF) and *hepatocyte* branching and growth of ureteric buds. The receptor tyrosine kinase RET, for GDNF, and MET, for HGF, are synthesized by the ureteral bud epithelium, which form a signaling pathway between the two tissues. Furthermore, shoots induce mesenchyme through *fibroblast growth factor 2* (FGF2) and *bone morphogenetic protein 7* (BMP7) . These two growth factors inhibit apoptosis and stimulate proliferation in the metanephric mesenchyme while maintainingproduction *WT1*.

The conversion of mesenchyme to epithelium for nephron formation is also mediated by ureteral budding via expression of *WNT9B* and *WNT6*, which increase *PAX2* and *WNT4metanephric* in themesenchyme. *PAX2* promotes compaction of mesenchyme that is preparing to form tubules, whereas *WNT4* causes condensed mesenchyme to epithelialize and form tubules. Because of these interactions, modifications occur in the extracellular matrix. Thus, fibronectin, collagen I, and collagen III are replaced by laminin and type IV collagen, which are typical for the epithelial basal lamina. In addition,cell adhesion moleculesalso synthesized *syndecan* and *E-cadherin* werewhich are important for compaction of mesenchyme into epithelium.

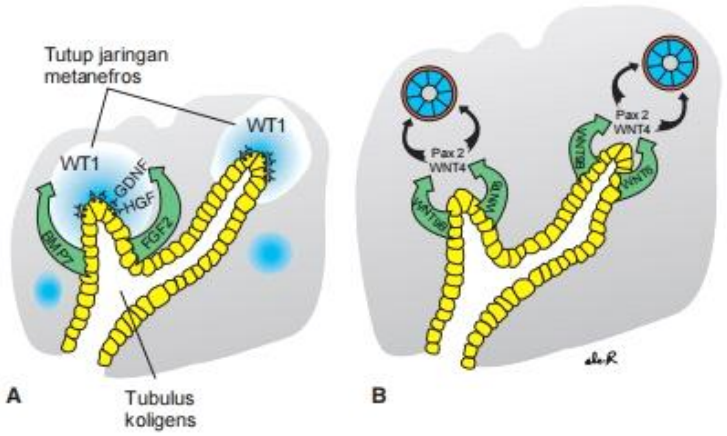

Figure 6 Genes involved in kidney differentiation.

Location of the Kidneys The

kidneys, initially in the pelvic region, then shift to a more cranial position in the abdomen. This elevation of the kidney is due to reduced curvature of the body and by growth of the body in the lumbar and sacral regions (Fig. 7). In the pelvis, the metanephros receives its arterial supply from the pelvic branch of the aorta. During the process of ascending the kidney into the abdominal cavity, the kidney is vascularized by arteries originating from the higher aorta. The veins at the bottom usually degenerate, but some of them may persist.

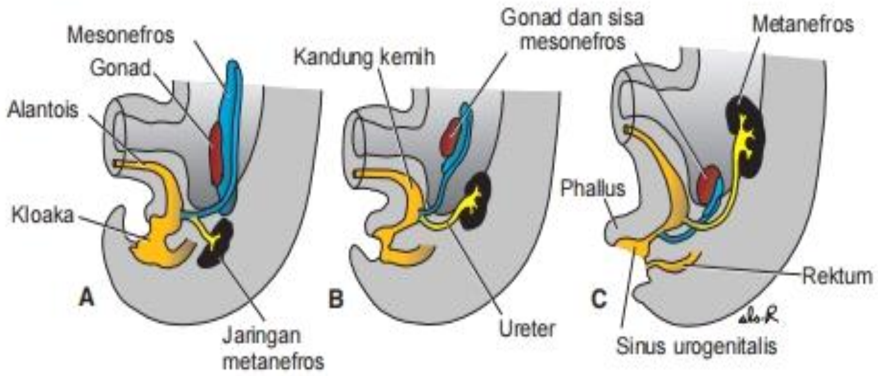

Figure 7. Rising kidney. Note the change in position between the mesonephric and metanephric systems. The mesonephric system is almost completely degenerated, and few remnants remain in close contact with the gonads. In male and female embryos, the gonads descend from their original position to a lower position.

Kidney Function The

definitive kidney formed from the metanephros begins to function near the 12th week. Urine flows into the amniotic cavity and mixes with the amniotic fluid. This fluid is swallowed by the fetus and recycled through the kidneys. During fetal life, the kidneys are not responsible for the excretion of waste substances, since it is the placenta that performs this function.

Bladder and Urethra

During the fourth to seventh week of development, the cloaca divides into the urogenital sinus anteriorly and the anal canal posteriorly (Fig. 8). The urorectal septum is the mesoderm layer between the primitive anal canal and the urogenital sinus. The end of the septum will form the corpus perineale. Three parts of the urogenital sinus can be recognized: the upper and the largest is the bladder. Initially, the bladder is continuous with the allantois, but as the lumen of the allantois obliterates, a thick fibrous cord, the urachus, persists and connects the apex of the bladder to the umbilicus. In adults, the urachus forms the median umbilical ligament. The next part is a rather narrow channel, the pelvic part of the urogenital sinus, which in men forms the prostatic urethra and the membranous part of the urethra.

The last part is the phallus of the urogenital sinus. This section is flattened from one side to the other, and as the genital tubercle grows, this portion of the sinus is pulled ventrally. (The development of the phallic portion of the urogenital sinus is very different in the two sexes.) During cloacal differentiation, the caudal portion of the mesonephric duct is absorbed into the bladder wall. As a result, the two ureters, which initially grow out of the mesonephric ducts, enter the bladder separately. As the kidney ascends, the ureter openings move further cranially. The openings of the mesonephric ducts move closer to each other to enter the prostatic urethra and in men become the ejaculatory ducts

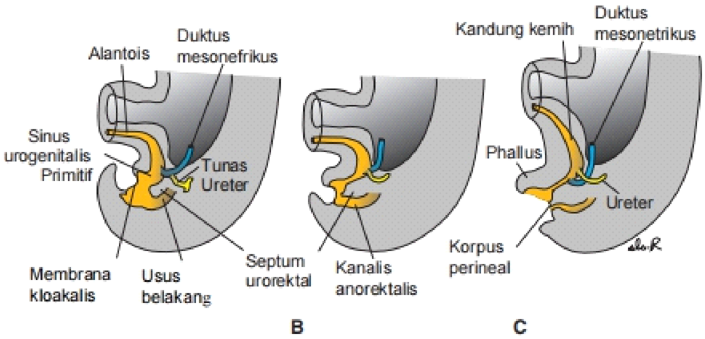

Figure 8. The division of the cloaca into the urogenital sinus and the anorectal canal. The mesonephric ducts are gradually absorbed into the wall of the urogenital sinus, and the ureters enter separately. A. At the end of the fifth week. B. 7 weeks. C. 8 weeks.

Since the mesonephric ducts and ureters are derived from mesoderm, the bladder mucosa formed by the union of these ducts (bladder triangle) is also of mesoderm origin. Over time, the mesoderm layer of the trigone is replaced by endodermal epithelium, so that ultimately, the interior of the bladder is completely lined with endodermal epithelium. The urethral epithelium in both sexes is derived from the endoderm; The surrounding connective tissue and smooth muscle are derived from the visceral mesoderm. At the end of the third month, the prostatic urethral epithelium begins to proliferate and form a number of outgrowths that penetrate the surrounding mesenchyme. In males, these shoots form the prostate gland. In women, the cranial portion of the urethra forms the urethral and paraurethral glands.

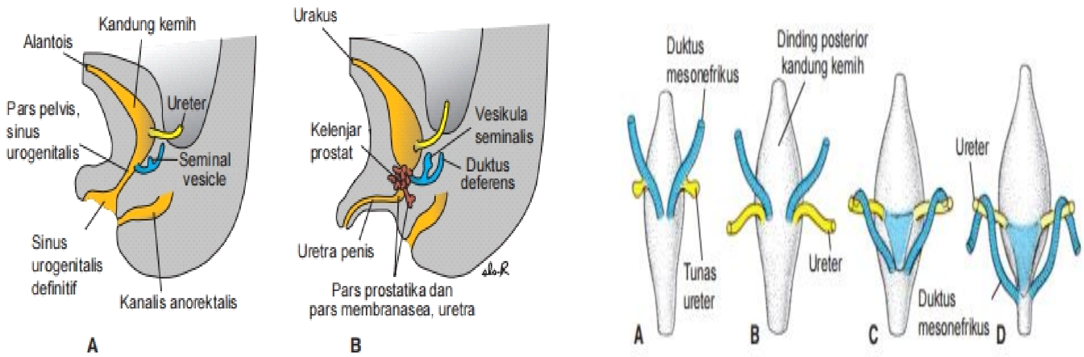

Figure 9. Urogenital Sinus

II. GENITALIAL SYSTEM

Sex differentiation is a complex process involving many genes, including some that are autosomal. The key to sexual dimorphism is the Y chromosome, which contains a testicular-determining gene called thegene *SRY (sex-determining region on Y)* in its short arm (Yp11). The protein product of this gene is a transcription factor that initiates a downstream cascade of genes that determine the fate of rudimentary sexual organs. The SRY protein is a testicular-determining factor; under its influence, development takes place in the male direction; its absence, leads to the development of women.

1. Gonads

The sex of the embryo is determined genetically at fertilization, the gonads do not acquire male or female morphological characteristics until the seventh week of development. The gonads appear first as a pair of longitudinal ridges, theridges *genital* or *gonadal* (Fig. 10). Both are formed by proliferation of the epithelium and compaction of the underlying mesenchyme. Germ cells do not appear in the *genital ridge* until the sixth week of development. The primordial germ cells originate from the epiblast, migrate through the primitive streak, and by the third week, they are located between the endoderm cells in thewall *yolk sac* close to the allantois. During the fourth week, the cells migrate in an amoeba-like motion along the dorsal mesentery of the hindgut reaching the primitive gonads at the beginning of the fifth week and invade the *genital ridge* by the sixth week. If these cells fail to reach the *genital ridge*, the gonads will not develop. Thus, the primordial germ cells have an inductive influence on the development of the gonads into ovaries or testes.

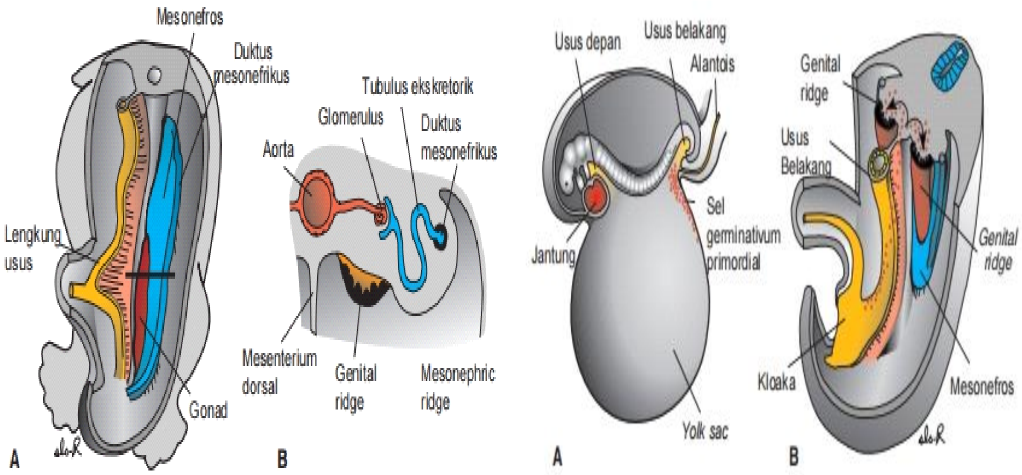

Figure 10. Genital ridge

Just before and during the arrival of the primordial germ cells, the epithelium of the *genital ridge* proliferates, and epithelial cells penetrate the underlying mesenchyme. Here, the cells form a number of irregularly shaped, primitive sex cords. In male and female embryos, these cords are connected by surface epithelium, and it is impossible to distinguish between male and female gonads. Therefore, these gonads are known as indifference gonads.

Ovaries

In female embryos with complementary sex chromosomes XX and without a Y chromosome, the primitive sex cords separate into groups of irregular cells (Fig. 11). These groups, which contain primitive germ cells, occupy the medulla of the ovary. Later, these clusters disappear and are replaced by the vascular stroma that forms the ovarian medulla. The surface epithelium of the female gonads, unlike that of the male, continues to proliferate. By the seventh week, this epithelium forms a second generation of cords, the cortical cords, which penetrate the underlying mesenchyme but remain close to the surface. In the third month, these cords divide into separate cell groups. The cells in this group continue to proliferate and begin to surround each oogonia with a layer of epithelial cells called follicular cells. Together, the oogonia and the follicular cells form the primordial follicle. Therefore, it can be said that the sex of the embryo is genetically determined at the time of fertilization, depending on whether the spermatocyte carries an X or a Y chromosome. In an embryo with an XX sex chromosome configuration, the cord medullary gonad undergoes regression, and a second generation of cortical cords is formed. In embryos with an XY sex chromosome complex, medullary cords develop into testicular cords and secondary cortical cords fail to form.

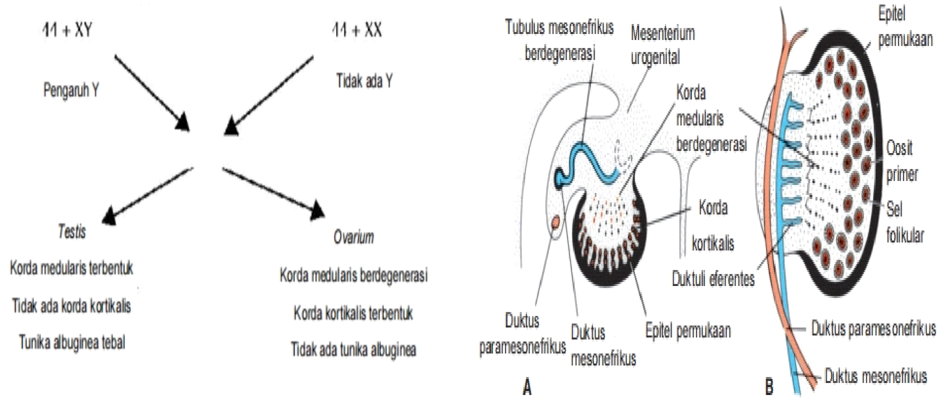

Figure 11. Transverse section of the ovary at the seventh week, showing degeneration of the primitive sex cord (medullary) and formation of the cortical cord. B. Ovaries and genital ducts in the fifth month. Note the degeneration of the medullary cord. The excretory mesonephric tubules (ductuli efferentes) are not associated with the rete testis. The cortical zone of the ovary contains clusters of oogonia surrounded by follicular cells.

2. Genital Duct

a. Indifference Stage

Initially, male and female embryos have two pairs of genital ducts; mesonephric ducts (Wolffii) and paramesonephric ducts (Müller). The paramesonephric ducts appear as a longitudinal invagination of the epithelium on the anterolateral surface of the *urogenital ridge* (Fig. 12). Cranially, the ducts are connected to the abdominal cavity by funnel-shaped structures. Caudally, this duct first runs lateral to the mesonephric duct, then crosses in front of it to grow caudomedially. In the midline, this duct is in close contact with the paramesonephric duct on the opposite side. These two ducts are initially separated by a septum but then merge to form the uterine canal. The caudal end of this combined duct protrudes into the posterior wall of the urogenital sinus, where it gives rise to small thickenings, paramesonephric or muller tubercles. The mesonephric ducts connect with the urogenital sinuses on either side of the tubercles.

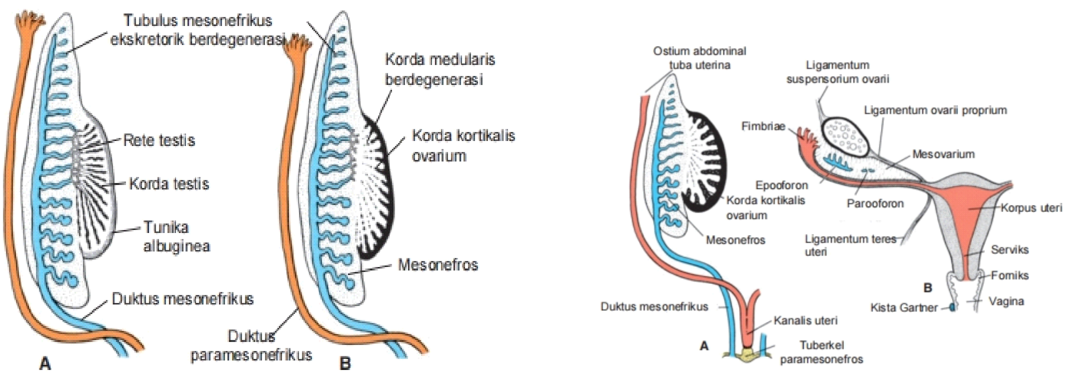

Figure 12 Genital duct 6th week **Figure 13**. Female genital duct end of 2nd month

b. Molecular Regulation of Genital Duct Formation .

SRY is a transcription factor and a major gene for testicular formation. SRY appears to act in concert with the autosomal gene *SOX9*, a transcriptional regulator, which can also induce testicular differentiation (Fig. 13) for possible pathways for these genes. SOX9 is known to bind to the promoter region of the gene for antimulerian hormone (AMH; also called *müllerian inhibiting substance* (MIS) and may regulate the expression of this gene. Initially, *SRY* and/or *SOX9* induce the testes to secrete FGF9 which acts as a chemotactic factor causing tubular from the mesonephric ducts through the *gonadal ridge*. Without penetration by these tubules, testicular differentiation does not continue. Then, SRY either directly or indirectly (via SOX9) increases the production of *steroidogenesis factor 1* (SF1) which stimulates the differentiation of Sertoli and Leydig cells SF1 acting with *SOX9* increases the concentration of AMH thereby causing paramesonephric (Muller) duct regression.In Leydig cells, SF1 increases the expression of genes for enzymes that synthesize testosterone.Testosterone enters target tissue cells where it can remain intact or be converted into dihydrotestosterone by the enzyme 5-α reductase Testosterone and dih Idrotestosterone binds to specific high-affinity intracellular receptors and this hormone receptor complex is transported to the nucleus where it binds to DNA to regulate the transcription of tissue-specific genes and protein products. ***WNT4*** is an ovarian determinant gene. This gene increases DAX1, a member of thereceptor family **nuclear hormone**, which inhibitsfunction *SOX9*. In addition, *WNT4* regulates the expression of other genes that play a role in ovarian differentiation, but these target genes are not yet known. One target is likely thegene *TAFII105*, whose protein product is a subunit for the TATA-binding protein for RNA polymerase in ovarian follicular cells. Female mice that do not synthesize this subunit do not form ovaries. **Estrogen** also plays a role in sex differentiation and under its influence, **the paramesonephric (müller) ducts are** stimulated to form the uterine tubes, uterus, cervix, and upper part of the vagina. In addition, estrogen acts on the external genitalia at an indifference stage to form the labia majora, labia minora, clitoris and the lower part of the vagina (Fig. 14).

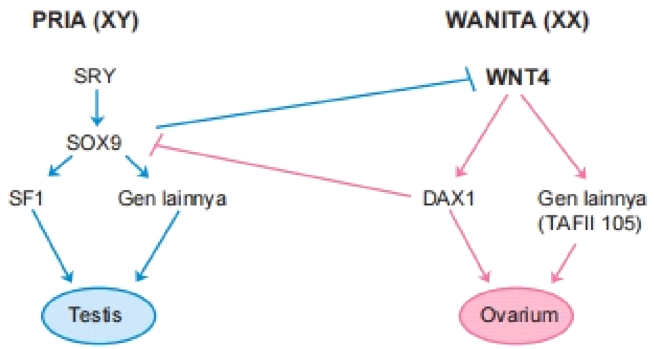

Figure 14. Schematic showing the genes involved in the differentiation of the testes and ovaries.

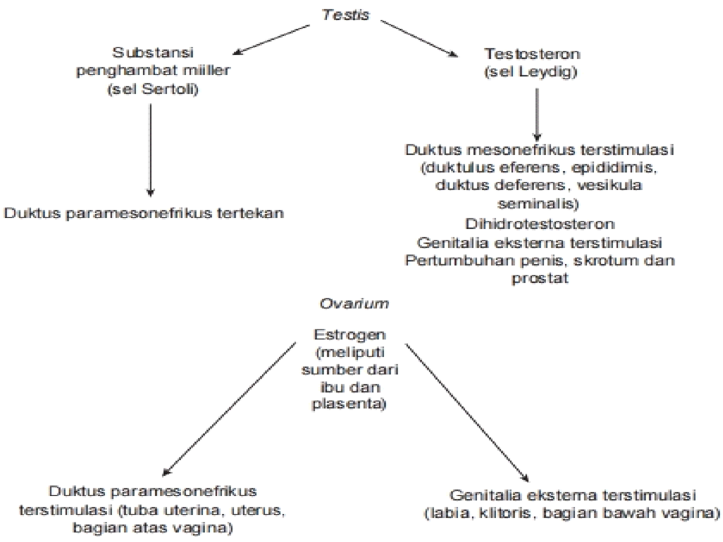

Figure 15. Genital ducts: Mesonephric duct and paramesonephric duct

c. The

Genital ducts in womenparamesonephric ducts develop into the main female genital ducts. Initially, three parts of each duct can be recognized: (1) the vertical cranial portion that opens into the abdominal cavity, (2) the horizontal portion that crosses the mesonephric duct, and (3) the caudal vertical portion that fuses with its partner from the opposite side (Fig. Figure 16.). With descent of the ovary, the first two parts develop into the uterine tube, and the caudal part fuses to form the uterine canal. As the second portion of the paramesonephric duct moves in a mediocaudal direction, the *urogenital ridge* slowly shifts so that it lies in the transverse plane. After the ducts fuse in the midline, a broad transverse pelvic fold is formed. This fold, which extends from the lateral side of the paramesonephric duct to the pelvic wall, is the broad ligament of the uterus. The uterine tube is situated on its upper border, and the ovary is on its posterior surface. The uterus and broad ligaments divide the pelvic cavity into the uterorectal pouch and uterovesical pouch. The fused paramesonephric ducts form the body and cervix of the uterus. Both are lined by a single layer of mesenchyme that forms the muscular sheath of the uterus, the myometrium, and its peritoneal layer, the perimetrium.

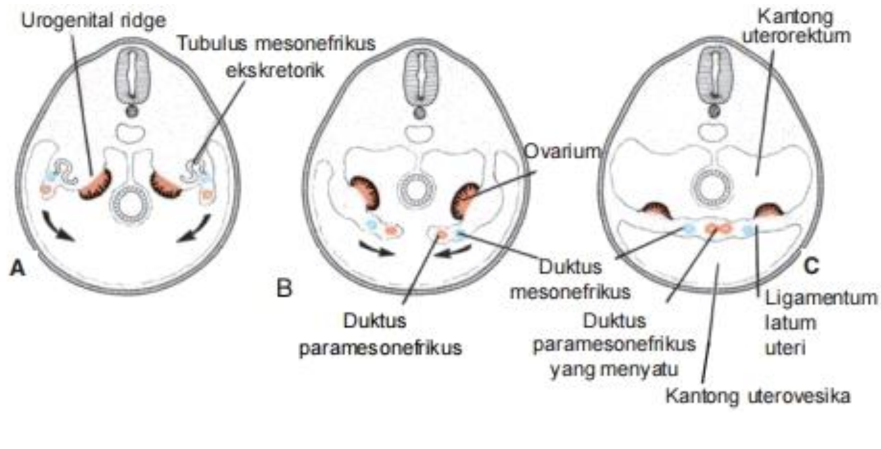

Figure 16. Transverse section through the urogenital ridge at progressively lower levels. **A, B**.

The paramesonephric ducts approach each other in the midline and coalesce. **C**. As a result of fusion a transverse fold is formed, the broad ligament of the uterus in the pelvis. The gonads become located on the posterior aspect of the transverse fold.

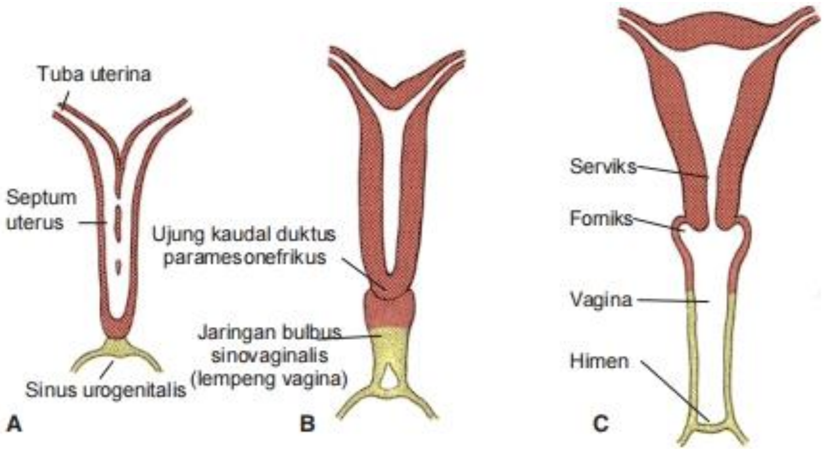

Figure 17. Formation of the uterus and vagina. **A.**9 weeks. Note the disappearance of the uterine septum. **B**. At the end of the third month. Note the sinuvaginal bulb tissue. **C**. Newborn baby. The fornices and the upper part of the vagina are formed by vacuolization of the paramesonephric tissue, and the lower part of the vagina is formed by vacuolization of the bulbus sinuvaginalis.

3. Vagina

As soon as the solid end of the paramesonephric duct reaches the urogenital sinus (Fig. 18), two solid evaginations grow out of the pelvic portion of the sinus. This evagination, the bulbus sinuvaginalis, proliferates and forms a dense vaginal plate. Proliferation continues at the cranial end of the plate, increasing the distance between the uterus and the urogenital sinus. By the fifth month, the vaginal growths have completely canalized. The wing-like extension of the vagina around the end of the uterus, the fornix vaginale, originates in the paramesonephros. Thus, the vagina has a dual origin, with the upper part from the uterine canal and the lower part from the urogenital sinus. The vaginal lumen remains separated from the lumen of the urogenital sinus by a thin plate of tissue, the hymen, which consists of the sinus epithelium and a thin layer of vaginal cells. Usually forms a small opening during perinatal life. In women, there may be remnants of the cranial and caudal excretory tubules in the mesovarium, where these ducts form the epoophoron and paroophoron. The mesonephric duct disappears except for a small cranial portion found in the epoophoron and occasionally a small caudal portion which can be found in the uterine or vaginal walls. In later life, these structures can form Gartner cysts.

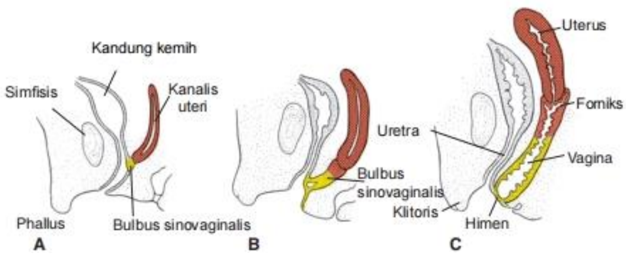

Figure 18. Formation of the uterus and vagina at various stages of development.

4. External Genitalia

a. Indifference Stage

In the third week of development, mesenchymal cells from the primitive streak region migrate around the cloacal membrane to form a pair of slightly elevated cloacal folds (Fig. 19). Cranial to the cloacal membrane, these folds unite to form the genital tubercle. Caudally, these folds divide into the urethral folds anteriorly and the anal folds posteriorly. Meanwhile, a pair of thickenings, genital thickenings, begin to appear on either side of the urethral folds. These thickenings further form a thickening of the scrotum in males and the labia majora in females. However, at the end of the sixth week, the two sexes are still difficult to distinguish.

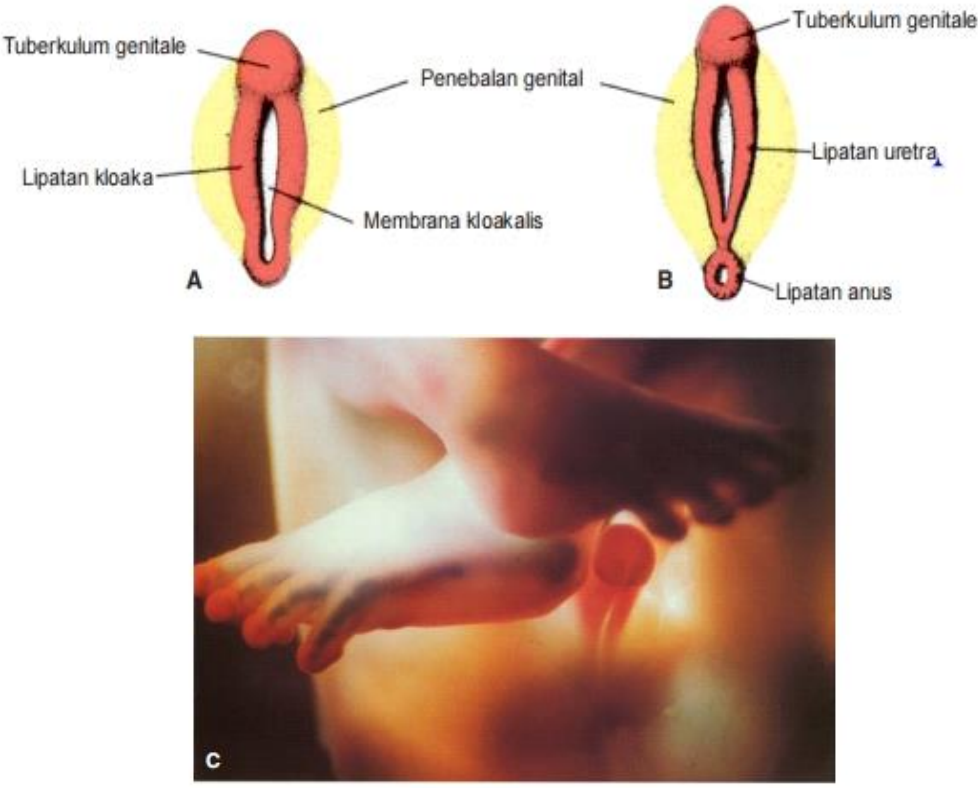

Figure 19 External genitalia indifference stage. **A.**About 4 weeks. **B**. About 6 weeks. **C**. An in utero photograph of a 56-day-old embryo shows continuous growth of the genital tubercle and lengthening of the urethral folds that have not yet begun to fuse. Genital thickening remains unclear.

b. External genitalia in women

Estrogen stimulates the development of female external genitalia. The genital tubercle is only slightly elongated and forms the clitoris; the urethral folds do not fuse, as in men, but develop to form the labia minora. The genital thickening enlarges and forms the labia majora. The urogenital groove opens and forms the vestibule. Although the genital tubercle is not very elongated in women, it is larger than the tubercle in men during the early stages of development. In fact, using tubercle size as a criterion (according to ultrasound monitoring) has led to errors in recognizing sex during the third and fourth months of pregnancy.

5. Ovarian

descent Gonadal descent occurs much less in women than in men, and eventually the ovaries lie just below the true pelvic rim. The cranial genital ligament forms the suspensory ligament of the ovary, while the caudal genital ligament forms the ligamentum ovary and ligamentum teres uteri. The ligamentum teres uteri extends to the labia majora.

Conclusion

The urinary and genital systems develop from mesoderm tissue. The three urinary systems are formed sequentially from the cranial to the caudal segments: The pronephros, which form in the cervical region, are vestigial. The tunica vaginalis Mesonephros, which forms in the thoracic and lumbar regions, is large and characterized by the presence of excretory units (nephrons) and their collecting ducts, mesonephric or Wolffian ducts. In women, this duct regresses. Metanephros or permanent kidney; formed from two sources. This system forms its own excretory tubules or nephrons like the other systems, but its collecting system originates from the ureteric bud, an outgrowth from the mesonephric duct. These buds form the ureters, renal pelvis, calyces and the entire collecting system.

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