Development of the Kidneys and the Efferent Urinary Tract (Weeks 3–6)

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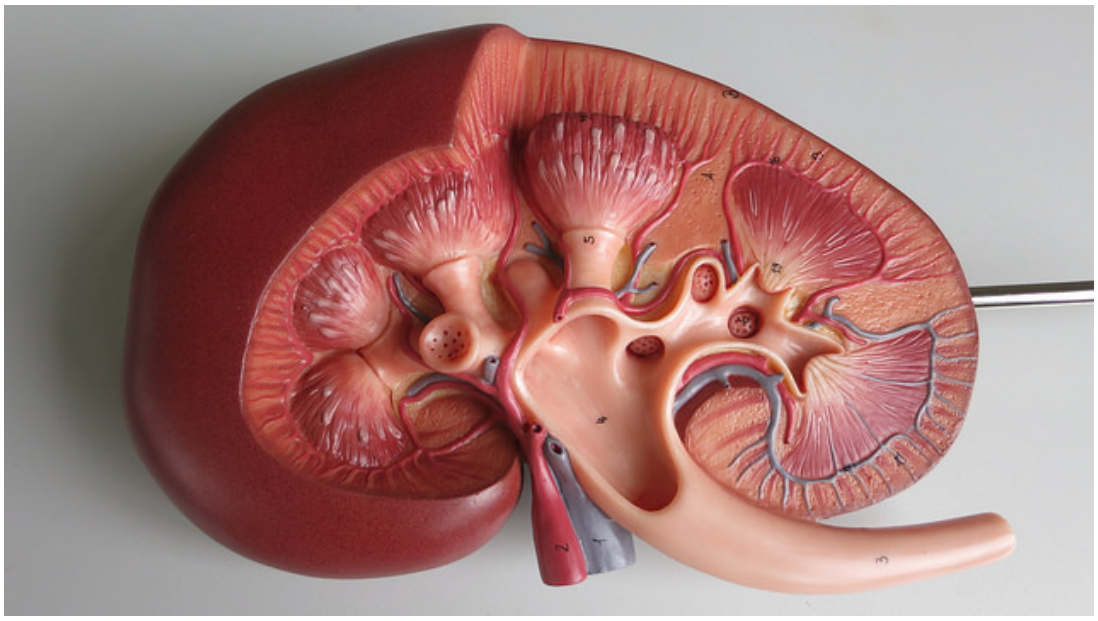
The development of the kidneys and the efferent urinary tract is complex and unalterably interconnected. It is an essential part of embryonic development and closely connected to sexual development. Malformations lead to severe consequences and are often not compatible with postnatal life. In medical studies, this is one of the most important themes in embryology.



Kidney Development over Three Generations of Structures

During their development, the kidneys form with parts from three different structures, as follows:

- **Pronephros**
- **Mesonephros**
- **Metanephros**

What the three structures have in common is that they all form from the **intermediate mesoderm** of the embryo. In the cervical area, this mesoderm is segmented, which then caudally forms the uniform **nephrogenic cord**, whose epithelium protrudes as the kidney ridge next to the gonadal ridge. Together, these two ridges form the **urogenital fold**.

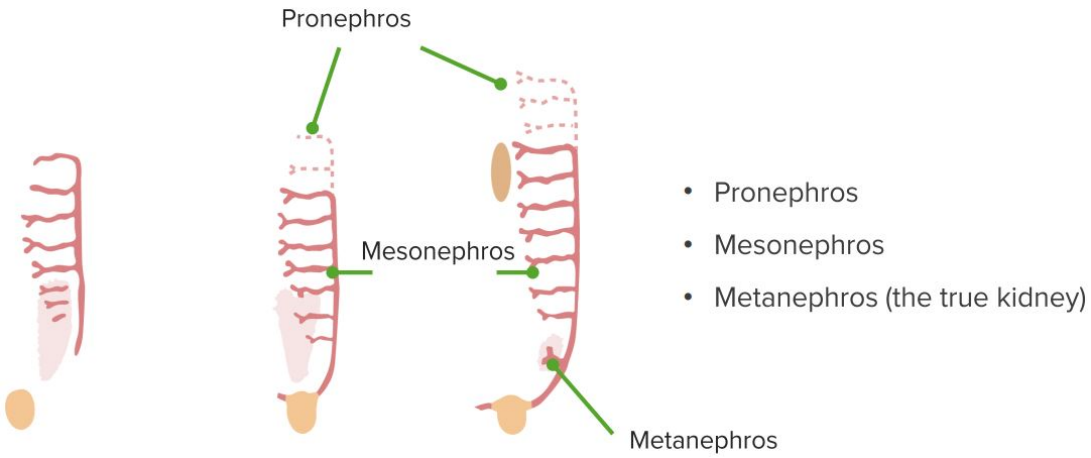


Image: The three stages of kidney development. By Lecturio.

Pronephros

In the **third week of gestation**, the pronephros forms in the **cervical nephrotomes**. The pronephros is a **functionless, segmented structure** made out of a duct from which a series of tubules branch off toward the midline of the embryo, one on each side. The pronephros does not develop beyond a **rudimentary state** and regresses without ever having produced urine. The two **pronephric ducts (ducti pronephrici)** that form at the lateral edge of the intermediate mesoderm remain in part.

Mesonephros

Immediately caudal to the pronephros—that is, in the thoracic and lumbar area—a tubular structure called the ‘mesonephros’ begins to form **starting at the end of the fourth week**, while the pronephros is still regressing. The mesonephros is an elongated organ; in contrast to the pronephros, it is no longer segmented and it has renal corpuscles or nephrons, which, for a short period, are able to produce urine.

The mesonephros is connected to the pronephric duct via the mesonephric duct. Caudally, it continues as the **mesonephric duct (ductus mesonephricus**, or **Wolffian duct)**. **It connects to the cloaca.** The Wolffian duct plays an essential role in the sexual development of men. The functionless remains of the mesonephric anlage are also found in women.

The mesonephros is functional for roughly 4 weeks, and then it regresses. A few tubules remain, later becoming the **efferent ducts of the epididymis** in men (see the article ‘Cryptorchidism (Undescended Testicle)—Diagnosis and Treatment’). This shows how closely this aspect of development is connected to sexual development, leading to its often being called **urogenital development**.

Metanephros

The development of the metanephros, which constitutes the final urine-producing organ, is more complex. It develops starting at the **fifth week** and is caudal to the mesonephros. It forms in the lumbar area from projections that originate from the mesonephric tubule near its attachment to the cloaca, called the ‘ureteric buds.’ At this time, the mesonephros is still regressing. Initially, the function of the metanephros is primarily for fluid and pressure balance rather than metabolism, because in embryos the placenta performs this function.

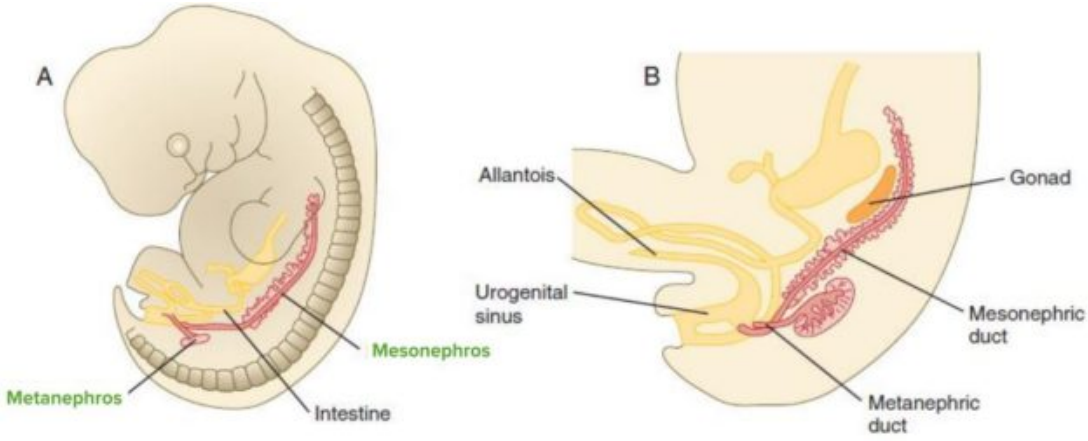


Image: The metanephros. By Lecturio.

The **ureteric bud**, also called the **metanephrogenic diverticulum**, grows posteriorly and toward the head of the embryo. The elongated stalk of the ureteric bud, called the **metanephric duct**, later forms the ureter. As the cranial end of the bud extends **into the intermediate mesoderm**, it undergoes a series of branchings to form the collecting duct system of the kidney. It also forms the major and minor calyces and the renal pelvis.

The portion of undifferentiated intermediate mesoderm in contact with the tips of the branching ureteric bud is known as the **metanephrogenic blastema.** Signals released from the ureteric bud induce the differentiation of the metanephrogenic blastema into the renal tubules.

As the renal tubules grow, they come into contact and join with connecting tubules of the collecting duct system, forming a continuous passage for flow from the renal tubule to the collecting duct. Simultaneously, precursors of vascular endothelial cells begin to take their position at the tips of the renal tubules. These cells differentiate into the cells of the definitive glomerulus.

The following structures form out of the stem of the ureteric bud, which has sprouted, by means of widening and branching:

- Ureter
- Renal pelvis
- Five major calyces
- Minor calyces
- Collecting ducts

The following structures form out of the metanephrogenic blastema:

- Bowman’s capsule
- Proximal and distal tubules
- Loop of Henle

At the end of the collecting ducts, mesenchymal cells condense to become the **metanephric vesicle** in the metanephrogenic blastema. This forms metanephric tubules, to which capillary loops attach. The epithelium at the capillaries alters to become **podocytes**, forming the visceral sheet of **Bowman’s capsule**, the overlying cohesive epithelium covering the parietal sheet of the podocytes.

The superior section of the metanephric vesicle further elongates to connect to the collecting ducts. Thus, the nephron, the smallest unit of the kidney, is completed. Starting in the **fourth month**, the **definitive kidney** (the term for the completed metanephros)

produces urine, which is directed into the amniotic cavity of the embryo and is then swallowed by the embryo.

Ascension of the Kidney

In contrast to the more superficially located mesonephros, the metanephros is, from the outset, located in the **retroperitoneum**. Growth of the embryo in the lumbar and sacral area is accompanied by the **ascension of the kidney**; the kidneys move into the abdomen, underneath the adrenal glands. The left kidney completes the ascension at the level of Th11–L2 and the right one slightly lower, at the level of Th12–L2/3.

The ureter must grow in length during the ascension because it is connected to both the kidneys and the urinary bladder. This movement is completed at about the ninth week. Sometimes the process is referred to as **relative ascension**. This means that only an apparent movement into the abdomen occurs because the embryo just grows away from the kidneys, underneath them.

Development of the Ureters

In the fifth week, the ureteric bud arises from the mesonephric duct, close to where the mesonephric duct attaches to the cloaca. This grows into the metanephrogenic blastema in a dorsocranial direction. There it branches into additional structures. The stem of the ureteric bud is then called the ‘ureter.’

In the course of the development of the urinary bladder, there is a widening of the Wolffian duct as far as the separation of the ureter so that, eventually, the ureter is directly connected to the bladder. During the ascension of the kidneys, the ureters are stretched not only in length but also laterally, so that they discharge into the urinary bladder inferiorly and laterally.

Blood Supply to the Kidneys

The kidneys are initially supplied by the **common iliac arteries**, in keeping with their location in the pelvis. On ascension, new vessels form on the respective levels of the aorta. These vessels normally disappear completely because they become unnecessary on further ascension. The final **renal arteries** form when the kidneys arrive at their destination underneath the adrenal glands.

Development of the Urinary Bladder

During embryonic development, the urinary bladder is formed out of the cloaca, which constitutes the caudal end of the hindgut. At first, both the urogenital tract and the intestine end in the cloaca. The cloaca originates from the endoderm and is connected to the navel via the **allantois** in a ventrocranial direction. The so-called cloacal membrane, which originates from both the ectoderm and the endoderm, seals the cloaca.

Starting in the fourth week of development, an epithelial transverse fold, with the adjacent mesenchyme, grows from a cranial direction toward the cloacal membrane: the **urorectal septum**. This septum separates the cloaca into two parts, the dorsal **anorectal canal** and the **ventral urogenital sinus**. The part between the two sections of the cloacal membrane is referred to as the **perineum**.

The **urogenital sinus** can be divided into the following three sections or levels:

- Cranial vesicular part
- Medial pelvic part
- Caudal phallic part

The cranial vesicular part merges with the allantois, which is later obliterated and, along with the **urachus**, takes no part in the formation of the bladder. In adults, the urachus remains as the **median umbilical ligament**. The two mesonephric ducts lead to the cranial part of the urogenital sinus and then widen so that the ureteric buds and subsequently the ureters lead directly into the urinary bladder. The **bladder trigone** is thereby formed.

The bladder trigone constitutes the connective-tissue elements of the bladder; it develops out of the widened mesonephric ducts and is located between the openings of the two ureters and the mesonephric ducts, which almost fuse caudally. This section, therefore, originates from the mesoderm. However, during its further development, it is also covered by endodermal epithelium.

Development of the Urethra

In a female fetus, the middle part (the pelvic part) forms the complete urethra. In a male fetus, this accounts for only the proximal parts of the urethra, i.e. the intramural part, the prostatic part, and the membranous part of the male urethra as far as the seminal colliculus.

Also in a female fetus, the vaginal vestibule develops from the caudal phallic part, which later grows together with the uterovaginal canal. In male fetuses, this section of the urogenital sinus forms the spongy part of the urethra. The external genitals develop from the folds attached to the urogenital sinus.

The whole female urethra, therefore, originates from the endoderm. The male urethra is also mainly of endodermal origin. However, it has a small part in the glans penis, which is ectodermal and grows together with the spongy part out of the urogenital sinus.

Normal and Abnormal Amniotic Fluid Circulation

Amniotic fluid is produced by the cells (amnioblasts) lining the amniotic cavity. The embryo and fetus swallow this fluid, and a corresponding amount of fluid is excreted via the kidneys. This is not urine; true waste products are handled by the mother’s body via the placenta.

If there is something wrong with the swallowing process (e.g., blockage of the gut at some level), then excess amniotic fluid builds up, resulting in polyhydramnios (> 25 cm total depth on four ultrasound measurements). A problem with fluid excretion (blocked urethra, kidneys not functioning) results in a deficiency of amniotic fluid (oligohydramnios; < 5 cm total depth on four ultrasound measurements). These measurements are the amniotic fluid index (AFI).

About 8% of women have oligohydramnios, which may resolve spontaneously. Among the possible courses of action are the following:

- Monitoring of the baby and consideration given to delivering early
- Administering saline

About 2% of women have polyhydramnios, which leads to discomfort and problems with breathing. Amniocentesis may help.

Pathology of the Kidneys and the Efferent Urinary Tract

Malformations in development can, in principle, occur at each stage. About 3–4% of newborns have abnormalities in kidney or ureter development. Higher familial incidences have been observed. Such incidences can often be found prior to birth by using ultrasonography.

Malformations of the kidney

Cystic Kidney Diseases

Cystic kidney diseases can be divided into two types:

- **Polycystic kidney disease**, Potter type I
- **Multicystic dysplastic kidney disease**, Potter type IIA

In both of these diseases, the occurrence of cysts impairs the development of renal tissue. Polycystic kidney disease is inherited as an autosomal recessive trait and is indicative of poor progress and poor postnatal chances of survival. Multicystic dysplastic kidney disease is often limited to one side. It generally contains fewer cysts, leading to a better chance of survival.

Renal agenesis

Renal agenesis is the absence of one or both kidneys. This can be traced back to either an absent metanephrogenic blastema or to a nondeveloped ureteric bud. Although the absence of one kidney is not problematic because the other kidney hypertrophies to compensate, the absence of both kidneys is not compatible with postnatal life.

Before birth, renal agenesis on both sides presents itself as **oligohydramnios**, the absence of amniotic fluid. The reason for this is that too little or no urine is excreted into the amniotic cavity. If the electrolyte balance of the fetus has not been disrupted—as the exchange occurs via the placenta—children with two-sided agenesis die shortly after birth.

Renal aplasia

Renal aplasia is the incorrect development of one or both kidneys. As with renal agenesis, a two-sided occurrence is not compatible with life. Incorrect anlage of metanephrogenic blastema or mesonephric ducts can be the cause of this malformation. Inoperable cysts or tubules often develop.

Double kidneys

Double kidneys develop from either complete division of the ureteric bud or a double anlage. The development of double kidneys is rare as compared to the development of a double ureter. In this case, the ureter of the superior kidney ends caudomedially and the ureter of the inferior kidney anlage ends cranially in the urinary bladder.

Renal dystopia

Abnormalities in kidney location often develop when there has been incorrect ascension. This can affect either one or both kidneys. In general, patients with dystopic kidneys are asymptomatic and are usually not treated. Examples of dystopic kidneys are as follows:

- Pelvic kidneys: ascension halts
- Clump kidneys: disk-shaped fusion of the two kidneys
- Horseshoe kidneys: fusion of the two kidneys at their poles
- Crossed kidney ectopia: a kidney reaching to the other side (with or without fusion)

Malformations of the ureter

Double ureter (ureter duplex) and blind ureter (ureter fissus)

A double ureter forms by the division of the ureteric bud or a double anlage. In this case, the ureter fissus is only partially split. This can result in a divided or double kidney with only one junction to the urinary bladder. The ureter duplex is completely separated. This usually leads to a double kidney with two separated junctions to the urinary bladder.

Ectopic ureter

An atypical junction to the efferent urinary system is referred to as an ‘ectopic ureter.’ This often results in incontinence because sealing of the urinary bladder occurs only with sphincters. In boys, the ureters often open into the prostatic urethra or the neck of the urinary bladder. In girls, they open in the vagina or the vaginal vestibule. The cause is incorrect alignment of the ureter in relation to the Wolffian duct.

Malformations of the bladder

Bladder agenesis

If the urogenital septum fails to separate the cloaca or separates it only partially, a so-called **persistent cloaca** results. In this case, the intestinal and urinary tracts both end in a common canal. The genital tract is often also included.

Bladder exstrophy

Bladder exstrophy can be traced back to the failed migration of mesenchymal cells into the space between the abdominal wall and the bladder wall, resulting in absence of the muscular layer. The posterior wall of the bladder and the openings of the ureters are exposed. Incontinence occurs because of the protrusion of the wall of the bladder into the anterior abdominal wall.

Malformations of the urethra

Hypospadias and epispadias

Hypospadias is the formation of a ventral fissure of the urethra, whereas epispadias is a dorsal fissure. Incorrect fusion of the urethral folds is the cause of both of these malformations. Both variations result in an incorrect junction of the external urethral meatus and are treated surgically. In both cases, boys are affected more frequently than girls.

Incorrect regression of the urachus

Urachal cysts

If the urachus does not completely regress during embryonic development, small hollow cavities, which are called ‘urachal cysts,’ remain in the previously extant duct. Normally, they are rather discrete clinically. However, they can become inflamed, and if they do, they must be treated surgically.

Urachal fistula

If the urachus does not close completely, urine can further pass through the duct. Distinctions are drawn between an **inner urachal fistula**, which contains an opening in the section close to the bladder, an **outer urachal fistula**, which contains an opening at the navel, and a **complete urachal fistula**, which contains a passage from bladder to the navel. The final variation permits urine to exit through the navel.

Exam Questions Related to Kidney Development

The answers can be found below the references.

1. Which statement is true with respect to the development of the kidneys?

A. The pronephros performs the same task as the mesonephros and the metanephros.
B. The mesonephros is the only segmented structure.
C. The metanephros is the final urine-producing organ.
D. The collecting ducts consist of minor calyces.
E. The pronephros is nonfunctional and completely regresses.

2. Which statement is true concerning the development of the urinary bladder?

A. The urinary bladder originates solely from the endoderm.
B. In the fetus, the urinary bladder is connected to the navel via the allantois.
C. The urorectal septum separates the urogenital sinus into xxxxx parts.
D. The bladder trigone is bordered by the urachus.
E. The urinary bladder consists of the phallic part of the urogenital sinus.

3. The relative ascension of the kidneys indicates

A. An incomplete ascension of the kidneys.
B. A relatively marginal ascension of the kidneys as compared with that of the ureter.
C. An actual descent of the kidneys as compared with the other organs of the abdomen.
D. An ascension of the kidneys caused by the growth of the embryo caudal to the kidneys.
E. The ascension of one kidney and the descent of the other.

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Correct answers: 1. D; 2. B; 3. D

Notes