Chapter 1
Abnormal Development of the Female Genital Tract

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1.1 The Development of the Female Genital System

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1.1.1 Anatomy of the Female Reproductive System

The female reproductive system is composed of the internal and external genitalia depending on their anatomical positions along the genital tract. The internal genitalia consist of ovaries, fallopian tubes, uterus, and vagina; the external genitalia include the mons pubis, labia majora and minora, clitoris, vestibule, and perineum. The development of these organs prior to puberty is very slow; after puberty, the follicle-stimulating hormone (FSH), luteinizing hormone (LH), and other sex hormones actively promote a rapid development of both internal and external genitalia. The uterus starts to enlarge at the age of 10, and it reaches adult size at the age of 18. The endometrium undergoes cyclical changes and sheds as menstruation under the influence of ovarian hormones. The vagina becomes long and wide and changes to gray in color. The vulva becomes swollen with pubic hairs appearing and undergoes transition to the adult appearance. The labia become hypertrophied and pigmented.

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1.1.1.1 Internal Genitalia

Ovaries

Ovaries are the most important female sex glands. They are white, flat oval bodies of 4×3×1 cm in size, situated on both sides of the uterus. They produce ova and female hormones. They are small and smooth before 8 years old, but they begin to develop at the age of 8–10; thereafter they increase in a linear fashion. At menarche, the weight of an ovary is only 30 % of its adult's weight. It continues to increase in size and is mature at the age of 17–18. There are two aspects of ovarian development: (a) it produces germ cells and then ova, and (b) it produces sex hormones including estrogen and progesterone. Therefore, ovaries are both female reproductive organs and endocrine organs.

Fallopian Tubes

They are a pair of elongated hollow tubes lined with smooth muscles. The medial end communicates with the corner uteri and its lateral end is free lying next to the ovary. The outer end is funnel shaped with many fingerlike projections called tubal fimbria, stretching over the ovary. The fimbria helps to pick up the ovum into the fallopian tube where fertilization takes place when the sperm meets the ovum. The fertilized ovum then travels down into the uterine cavity, and then egg implantation takes place in the uterus.

Uterus

The uterus situates at the center of the pelvic cavity like an inverted pear. It measures about 7–8 cm long, 4–5 cm wide, and 2–3 cm thick. The uterus lay in an anteverted position suspended by its ligaments. Its lower one-third is the narrow cervix, which connects to the vagina. Its upper two-thirds is wider and is the uterine body. The top of the uterine body is the fundus with uterine corners on both sides and connects with a fallopian tube on each side. The cervical canal is a narrow tube-like, leading to the uterine cavity. The uterus is the breeding ground of the fetus, where pregnancy takes place. The uterus composes of three layers of tissues: (1) The inner endometrial layer is rich in glands and blood supply; the endometrium continues to change following each menstrual cycle and the woman's age. During menstruation, the shedding of the endometrium is a major component of the menses; (2) the middle layer is a very thick muscle layer. It can produce strong contractions during labor and at orgasms. It is resilient and can stretch sufficiently to accommodate a mature fetus; (3) the outermost layer is a serosal layer which is a part of the peritoneum.

Vagina

It is a soft elastic hollow tube which tilts backward. It is the female organ of sexual intercourse. It also serves as the passage of menstrual blood and the birth channel. It has a strong stretching property. With advancing age, the vaginal wall gets thinner with reducing vaginal wrinkles and weakened elasticity. Vaginal nerve endings mainly distribute in the outer 1/3 of the vagina, with no nerve endings at the upper 2/3. Therefore, the sex-sensitive area is located at the outer ½ of the vagina.

1.1.1.2 External Genitalia

Female external genitalia consist of the mons pubis, labia, and vaginal opening. All together, they are labeled as the vulva.

Mons Pubis

It is the swelling in front of the pubic symphysis, with the labia majora on adjacent sides. There are pubic hairs on the mons pubis, mostly trapezoid, inverted triangle, or rectangle in distribution. It regulates the local temperature and buffers the body impact of collision. The subcutaneous fat tissue underneath the mons pubis possesses shock-cushioning effect.

Clitoris

The clitoris is homologous to the male penis, both evolved from the same embryonic tissue. It is the only organ without reproductive function in the female genitalia, but it is related to sexual arousal and sexual function in humans. The clitoris is rich in nerve endings, which are very sensitive to touch, and it is the most important sex-sensitive zone.

Labia

There are two pairs of female labia – the labia majora and labia minora. The labia majora are the fat pads on both sides of the vaginal opening, with its skin covering with pubic hairs. Both the labia majora and minora have thin mucosal layers with no pubic hairs on its inner side. The sizes of labia and their thickness vary widely which are not directly related to sexual function. However, the labia are rich in nerve fibers and can have an important role in sexual stimulation and sexual arousal.

Vaginal Vestibule

It is a diamond-shaped area between the two labia minora. Its anterior end has the urethra where urine can pass out; its posterior has the vaginal opening with vestibular bulbs on its sides.

Bartholin Gland

Bartholin glands are located in the lower part of the labia minora as a small pair of glands, with its glandular opening between the labia minora and the hymen. If infected with inflammation, they can be significantly enlarged.

Hymen

Covering the vaginal opening is a layer of thin membrane, called "hymen." The hymen has a central hole, which varies in sizes depending on individuals. Some are too small in size, which will not allow even a finger to pass through, but others may accommodate two fingers through it. The hymen thickness is generally about 2 mm. But individuals may have very thin hymen, which may rupture during strenuous exercise or inadvertent collision to the vulva. It usually tears open at the time of first sexual intercourse and is accompanied by a small amount of bleeding.

1.1.2 The Development of the Female Reproductive System

The genetic sex of an embryo is determined by the sperm type (23X or 23Y) which fertilizes the ovum, but before 6 weeks of life, both male and female embryos have the same undifferentiated gonads, known as the undifferentiated genital phase. At the 7th week, gonads begin to have gender-related morphological changes. In the 8th to 9th weeks, internal genital differentiation begins. The external genital differentiation can only be identified at the 12th week. Therefore, the reproductive system including the gonads, reproductive tract, and external genitalia has an undifferentiated and differentiated phases of development.

1.1.2.1 The Undifferentiated Sex Phase

The Formation of the Undifferentiated Gonads

When the embryo is at 3–4 weeks' gestation, there are many reproductive cells which are larger and more round than the somatic cells lying at the posterior wall of the yolk sac near the allantoic endoderm. These are the primordial germ cells. When the embryo is at the 4th week, the sides of the embryo body start to have fold formation;

the ventral mesoderm gradually moves toward the body separated from intermediate body, forming into the left and right cord-like structure, known as nephrogenic cords. At the end of the 4th week, the volume of the nephrogenic cords continues to increase, and from the posterior wall of the embryo, it bulges to form a body cavity. At this time, at the back of the body cavity, the epithelial hyperplasia of each side of the body forms two longitudinal ridges, known as the urogenital ridges, which are the origins of kidneys, gonads, and primitive reproductive tract. In its further development, a central longitudinal groove forms in this urogenital ridge, dividing it into inner and outer parts. The outer part is longer and thicker and known as the mesonephric ridge; the inner part is shorter and thinner known as the genital ridge. When the embryo is at the 5th week, the genital ridge is covered with a layer of columnar epithelium, also called the germinal epithelium. When the embryo is at the 6th week, the germinal epithelium will hollow down and grow rapidly forming multiple cords with vertical extensions stretching between the gonadal tissues. It is also known as primary sex cord. In a 6-week embryo, primordial germ cells along the hindgut mesentery move to the genital stroma at the 10th thoracic vertebral level. The migration takes 1 week to complete. Some of these sex cord cells will surround each primordial germ cell. The larger primordial germ cells, the smaller primitive sex cord cells and the surrounding stromal tissues will form the undifferentiated gonadal tissue. At this time, whether it is a testis or an ovary cannot be distinguished. Thus, the gonads mainly come from the genital ridge of the coelomic cavity epithelium. But the epithelium, the underneath mesenchymal tissue, and the primordial germ cells are from three different origins.

The Formation of the Primitive Reproductive Tract

The development of the primitive reproductive tract is slightly later than the undifferentiated gonads. At a 6-week embryo, both male and female embryos consist of mesonephric ducts and paramesonephric ducts which are two different reproductive tracts. Both develop from the mesonephric ridge lateral to the genital ridge. One is called the mesonephric duct (also known as Wolffian duct), which originates from the mesonephros of the pronephros and gradually moves downward and ends into the primitive cloaca. This is the primitive male reproductive tract. The other is the paramesonephric duct, also called the Müllerian duct. This is the female primitive reproductive tract which forms at the time of mesonephric duct formation, at the inner aspect of mesonephric duct. It is formed by invagination of the coelomic epithelium. The upper part of the duct is located at the outer aspect of the mesonephric duct, lying parallel to each other. The middle part of the duct turns to the inner aspect and crosses the back of the mesonephric duct and lies in the inner aspect of it. In the lower end, the right and left paramesonephric ducts merge at the midline. The upper part of the paramesonephric duct has a funnel-shaped opening to the coelomic cavity forming the fimbrial end of the fallopian tube. The lower ends are blind ends merging into the sides of the back wall of the urogenital sinus. At the sinus, it forms a protrusion, called sinus tubercle, also known as the Müllerian tubercle or Müllerian nodules.

Embryonic Formation of the External Genitalia

When the embryo is at 9 weeks old, its external genitalia does not show any sex differentiation. At about the 5th week, both sides of the primordial urogenital sinus organize into folds and merge at the cephalic end forming a genital tubercle. A urorectal septum separates the cloacal opening from the primordial urogenital sinus in front and the anus at the back. Lateral to the urogenital fold, a pair of large uplift develops, forming the labia or scrotum. Urogenital fold forms a depression for a urethral groove covered by a urogenital membrane. At the 7th week, the urogenital membrane ruptures.

1.1.2.2 The Differentiated Sex Phase

Differentiation and Descending of the Gonad

The undifferentiated gonad has the potential to differentiate into the testes or ovaries. The sex differentiation depends on whether there is any testis-determining factor – TDF in the Y chromosome. At current knowledge, the Y chromosome sex-determining region Y gene – SRY – is the best candidate gene for TDF. It is situated at the short arm of the Y chromosome near the centromere in the IAIA District (Yp11.32). It contains an exon, is of a non-intron structure, and harbors the histocompatibility Y antigen – H-Y antigen.

If the membranes of body cells and primordial germ cells do not contain the H-Y antigen, the undifferentiated gonad will develop into an ovary. When the embryo is 10 weeks old, the embryonic sex cord will grow deeper, forming an incomplete ovarian network. Later, these embryonic sex cord and ovarian network will degenerate and be replaced by blood vessels and stroma forming the ovarian medulla. Thereafter, the genital surface epithelium (also known as primitive cortical cells) continues to grow thicker. It also penetrates into the deep layer, forming new cell cords, known as secondary sex cord or cortical cord. They are shorter and scatter in the cortex. In a 16th-week human embryo, cortical cord will break into many isolated cell groups that are primitive follicles, also known as primordial follicles. At this time, the ovaries are formed. Each primordial follicle has a primitive germ cell which will differentiate into a cell called oogonium.

The oogonium is surrounded by a layer of cortical cells which differentiate into small and flat follicular cells, also known as granular cells. Between the follicles mesenchymal cells differentiate into ovarian stroma. In the embryonic stage, the oogonium can split, divide, and proliferate into oocytes. There are up to six million oogonia in both ovaries. After the embryo is at the 20th week, these oogonia will no longer divide and a large number of them undergo degradation. Only some grow up and differentiate into primary oocytes. At birth, all oogonia within the ovaries disappeared, leaving about 70–200 million primary oocytes. All cells enter the first meiosis and stop dividing at their early stage. Not until after puberty, they complete their meiotic division before ovulation. Primary oocyte cannot self-replicate. After birth the primary oocytes within the ovary no longer grow, instead many of them

gradually degenerate and undergo atresia. At adolescence, there are about four million remaining oocytes. After the embryo reaches 16 weeks, the ovarian cortex and medulla continue to develop. The cortical surface has a layer of connective tissue called the tunica albuginea. Outside the albuginea, it is covered by a layer of cuboidal epithelium arising from the body cavity called the ectodermal epithelia.

The ovary is initially located in the upper part of the posterior coelomic wall between the end of gonadal cord to the labia majora along a cord-like structure called ovarian gubernaculum. With the proliferation and differentiation of the gonadal cord, the gubernaculum gradually rises to the coelomic cavity and position the ovaries in the abdominal cavity. As the embryo gradually grows up, the ligament continues to shorten. The ovaries come down to a pelvic location slightly below the pelvic rim at the 12th week of gestation.

The Evolution of the Internal Genitalia

If the undifferentiated gonads differentiate into ovaries, in the absence of testes to produce androgens and no influence from any Müllerian inhibiting factor (MIF), the mesonephric ducts (Wolffian) will degenerate. The paramesonephric ducts differentiate and develop into the internal female genitalia. It is noteworthy that about 1/4 of the women may have the residual remnant of the mesonephric ducts or tubules. For example, they form the epoophoron and paroophoron in the mesovarium and the Gartner's duct cyst alongside the uterus and vagina.

But in the process of paramesonephric duct differentiation into the internal female genitalia, the mesonephric ducts and ovaries played a leading induction role. The mesonephric ducts induce the fusion and resorption of the bilateral Müllerian ducts. The ovarian tissue attached to the Müllerian duct is composed of muscle fibers from non-Müllerian and mesonephric duct origin and promotes the integration and development of the uterus.

Uterus and Fallopian Tubes

When the fetus is at about the 9th week of gestation, the upper part of the paramesonephric ducts becomes the fallopian tubes. The middle part to the lower part merges at the midline to form the uterus, the cervix, and the vaginal dome. At the beginning of the merger, there is a septum to divide into two ductal cavities. Toward the end of 12 weeks, the septum disappeared into a single cavity to form the uterus and the vaginal tube. The endometrial cavity is lined with columnar epithelium, and in the part of the uterus formed by the paramesonephric duct, the mesenchymal tissue surrounding it will proliferate actively, and the uterine wall will become thickened. The tissue at the uterine cervix will form the vaginal dome. At the 16th week, the muscular and serosal layers of the uterus will form. At the 24th week, glandular buds will form in the endometrial cavity. In the last 12 weeks, by the influence of the placental hormones, there is a rapid development of the uterus, and the endometrium will thicken and be congested with blood. At birth, the development of endometrial glands has been more mature and complete. At birth, the uterus surface is

flat. The ratio of the uterine body and uterine cervix is about 1:2, until after puberty, the ratio starts to change. The uterus will further develop and mature.

The Vagina

The vagina comes from two origins. The upper 3/4 to 4/5 of the vagina is from the paramesonephric duct and the lower 1/5 to 1/4 from the urogenital sinus. At the 9th week of gestation, the caudal end of the paramesonephric duct and the back of urogenital sinus will form the paramesonephric duct tubercle (Müllerian tubercle), which is also known as the sinus tubercle. The urogenital sinus epithelial cells and cells at the caudal ends of the paramesonephric duct proliferate together and form a solid sinovaginal bulk and further develop into a vaginal plate. The vaginal plate is initially a solid tubular structure called sinovaginal bulk. It gradually expands and increases the distance between the uterus and the urogenital sinus.

From the 11th week onward, the cells in the central part of the vaginal plate gradually degenerate, forming a cavity. At the 20th week, a vagina is formed, which links the uterus internally and externally with the urogenital sinus, separated by a hymen.

In recent years, many embryologists believe that the whole vagina is from the sinovaginal bulk. The belief is that when the paramesonephric duct reaches the urogenital sinus surface and becomes surrounded by the sinovaginal bulk, the sinovaginal bulk will grow cranially and develop into the vaginal plate, as the prototype of the future vagina. After that, the vaginal plate cavitates from a top-down direction to make the vagina a top-down funnel-shaped cavity. The top forms a vaginal dome, and the bottom separates from the urogenital sinus by a thin tissue. The central part of this thin tissue will be absorbed, and it forms a hole in the vaginal hymen. Although the paramesonephric ducts do not involve in the formation of the vagina, it plays an inducing role in the evolutionary development of the sinovaginal bulk. One side of the paramesonephric duct will induce the vagina formation from the ipsilateral side. However, this belief requires future validation. Another theory is that the mesonephric duct degenerates from top downward; its end at the level of the external cervical opening enlarges to form the sinovaginal bulk and integrates with Müllerian tubercle of the paramesonephric duct. Their further proliferation will form the vaginal plate.

The Development of the External Genitalia

At the 7th to 8th week of fetal development, the external genitalia start to differentiate into male or female. When the gonad is an ovary, the body produces no testosterone. The genital tubercle gradually enlarges slowly and forms the clitoris. The urogenital folds on both sides will not merge and form the labia minora. The right and left labia fuse with the scrotal bulge in the front of the clitoris, forming the mons pubis. The posterior labia fuse together and form the posterior commissure. The rest of the non-fused labia become the labia majora. At this time, the urethral groove expands with the lower end of the urogenital sinus to form the front of the vagina. When the fetus is at the 12th week, the female external genitalia begin to take shape, and they gradually further developed.

1.2 Abnormal Development of Female Reproductive Organs

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The development and differentiation processes of the female reproductive organs are influenced by both endogenous factors (nondisjunction of the germ cell chromosomes, chimera, karyotype abnormalities, etc.) and exogenous factors (use of hormone, drugs, etc.). The differentiation of the primitive gonad, its development and fusions within the reproductive system, and cavity development and formation of the external genitalia may be affected by these factors resulting in a variety of developmental anomalies.

Abnormal development of the female reproductive organs includes the developmental and morphological anomalies in the fallopian tubes, uterus, vagina, and vulva. These anomalies can be associated with abnormal ovaries, kidney, or other organs. Most of the female genital tract anomalies arise from the developmental anomalies of the paramesonephric ducts (Müllerian duct); however, these Müllerian anomalies originate from the abnormal development of the Gartner's duct. Genital tract anomalies have different clinical manifestations. Some do not present with any clinical symptoms, others have different symptoms at different times and different ages, and the impact on fertility is also widely variable. The management of these genital anomalies varies widely from observation to surgery. Therefore, a correct diagnosis within a clear classification of these congenital anomalies is very important.

1.2.1 The Classification of Female Reproductive Tract Anomalies

There are many classifications of female reproductive tract anomalies. The early classification began in 1842; it is based on the embryology and Müllerian duct development, since then there are many other classifications. Before 1950, all classifications are based on embryonic developments: the Müllerian duct fusion and its abnormal developments. After 1950, the classifications take into account many other factors. This chapter describes three types of classifications for reproductive tract anomalies.

1.2.1.1 American Fertility Society (AFS) Classification of Reproductive Tract Anomalies

American Fertility Society (AFS) developed this classification in 1988 [1]. The classification is as follows [6]: (1) Anomaly caused by developmental anomaly of the Müllerian duct including the agenesis of the uterus and vagina and is a defect characterized by no reproductive potential, e.g., in the case of congenital absence of

the vagina [7]. (2) Anomaly caused by the developmental anomaly of the genitourinary sinus: The urogenital sinus was not involved in the formation of the lower vagina; it is mainly responsible for the different degrees of vaginal atresia [8]. (3) Anomaly caused by abnormal fusion of the Müllerian ducts. The anomalies are divided into vertical fusion and lateral fusion anomalies. Vertical fusion anomaly presents as transverse vaginal septum and lateral fusion anomaly as longitudinal vaginal septum and oblique vaginal septum syndrome.

AFS classification is mainly based on Müllerian anomalies and their effects on fertility; it includes seven categories (Fig. 1.1): (1) Müllerian agenesis (absent uterus) or hypoplasias, (2) unicornuate uterus (a one-sided uterus), (3) uterus didelphys (double uterus), (4) bicornuate uterus (uterus with two horns), (5) septated uterus (uterine septum or partition), (6) arcuate uterus, and(7) DES uterus as a result of fetal exposure to diethylstilbestrol. This classification is simple and clear; therefore, it has been widely adopted in the past 20 years. This classification defines different levels of uterine anomalies, and its prognosis has a good clinical correlation with the pregnancy outcome. However, this classification has its limitations: Many complex reproductive tract anomalies are not covered. Category 1 includes all patients with dysplasia or congenital absence of the vagina, cervix, uterus, and/or gonads as a single class which would be too vague and generalized.

Figure 1.1 [2]

A type: bilateral developmental anomalies. (1) Vaginal agenesis, complete; (2) vaginal agenesis, partial (upper or lower); (3) cervical aplasia; (4) cervical hypoplasia; (5) tubal aplasia; (6) uterine aplasia; (7) uterine hypoplasia (with or without uterine cavity); (8) combined dysplasia

B type: unilateral developmental anomalies. (1) Unicornuate, no horn; (2) unicornuate, non-fused, non-cavitary horn; (3) unicornuate, fused, non-cavitary horn; (4) unicornuate, cavitary, non-fused horn; (5) unicornuate, cavitary, fused, noncommunicating horn; (6) unicornuate, cavitary, fused, communicating horn.

C type: fusion anomalies. (1) Vaginal septum; (2) arcuate uterus; (3) septate uterus, partial; (4) septate uterus, complete to external os of the cervix; (5) septate uterus, complete, up to internal os of the cervix; (6) complete septate, vagina, and uterus; (7) bicornuate uterus, complete to internal os of cervix; (8) bicornuate uterus, partial; (9) uterus didelphys bicollis; (10) uterus didelphys with the vaginal septum; (11) uterus didelphys with the vaginal septum, with unilateral vaginal obstruction; (12) uterus didelphys with the vaginal septum with bilateral obstructed vagina

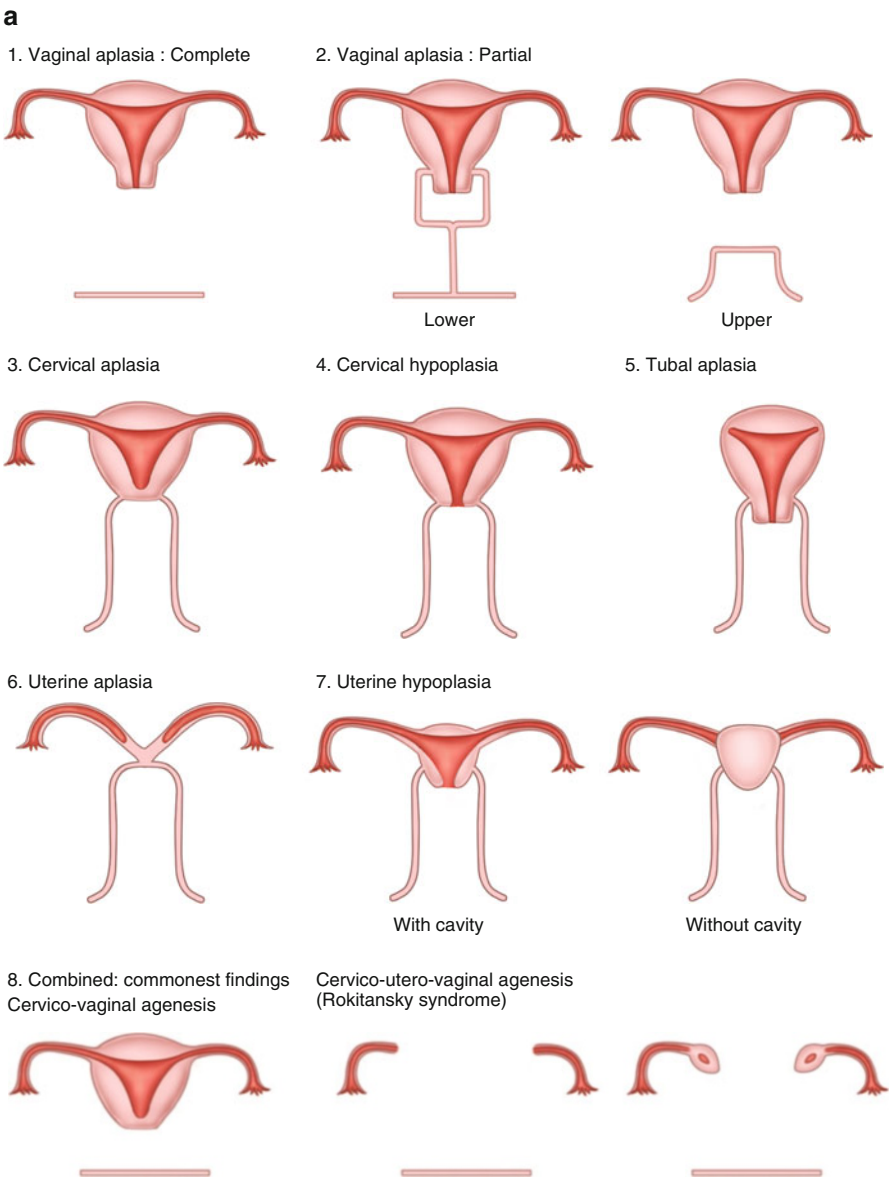


Fig. 1.1 AFS classification based on Müllerian anomalies

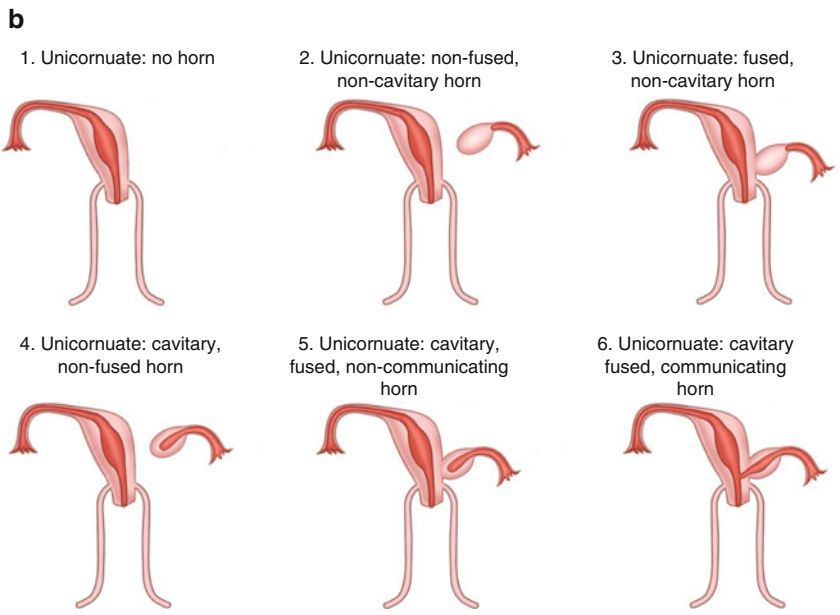


Fig. 1.1 (continued)

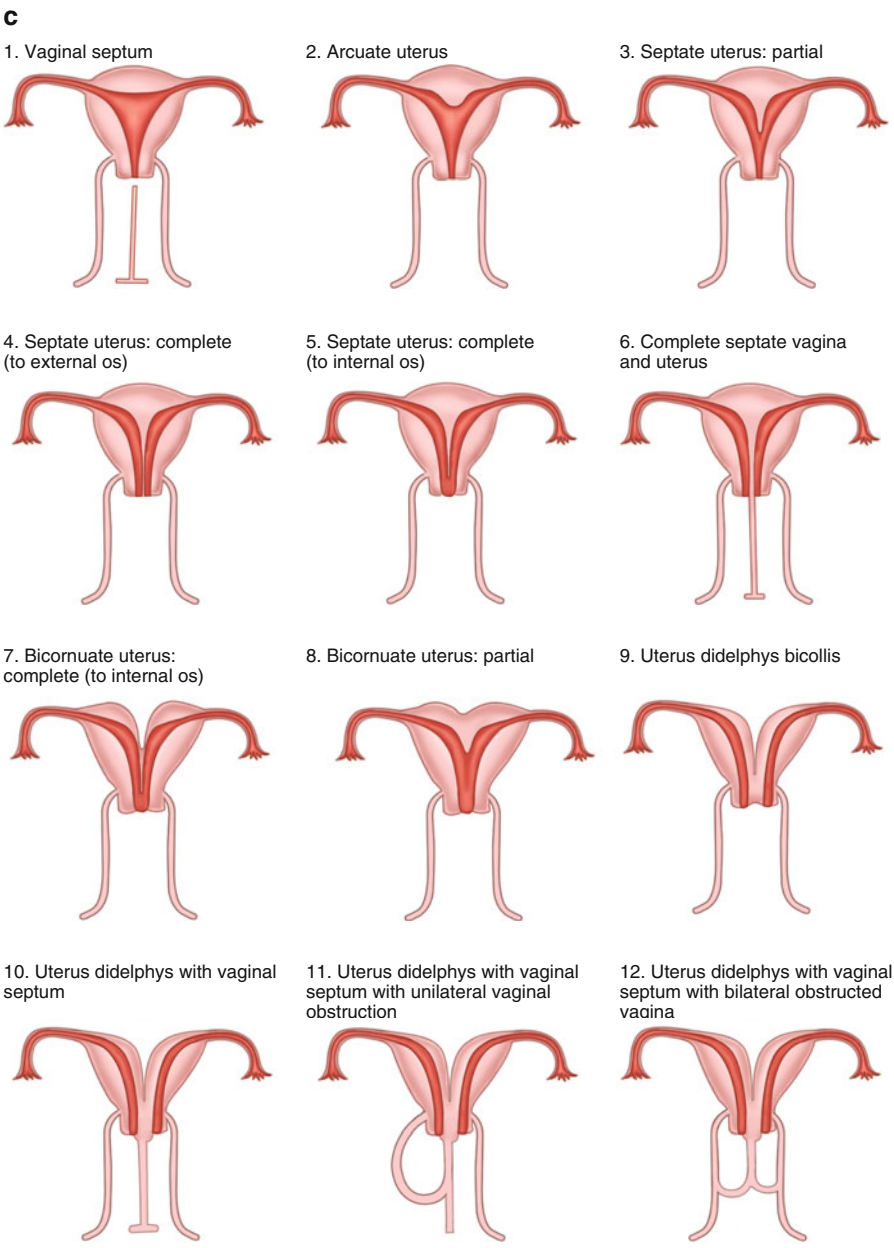


Fig. 1.1 (continued)

1.2.1.2 Acién Classification of Reproductive Tract Anomalies

In 2011, Acién [3] conducted a systematic review of relevant articles of reproductive tract anomalies from 64 full-text articles and more than 300 related clinical papers in the literature. Based on the experience gained from the application of the current classification systems and the appropriate treatment, he updated the female urogenital tract anomalies in accordance with the etiopathogenesis and proposed a new embryological-clinical classification of female reproductive tract anomalies. The system also considers both Müllerian and renal tubular developmental anomalies (Fig. 1.2), but his classification system has only been published for a short time and has not been widely used.

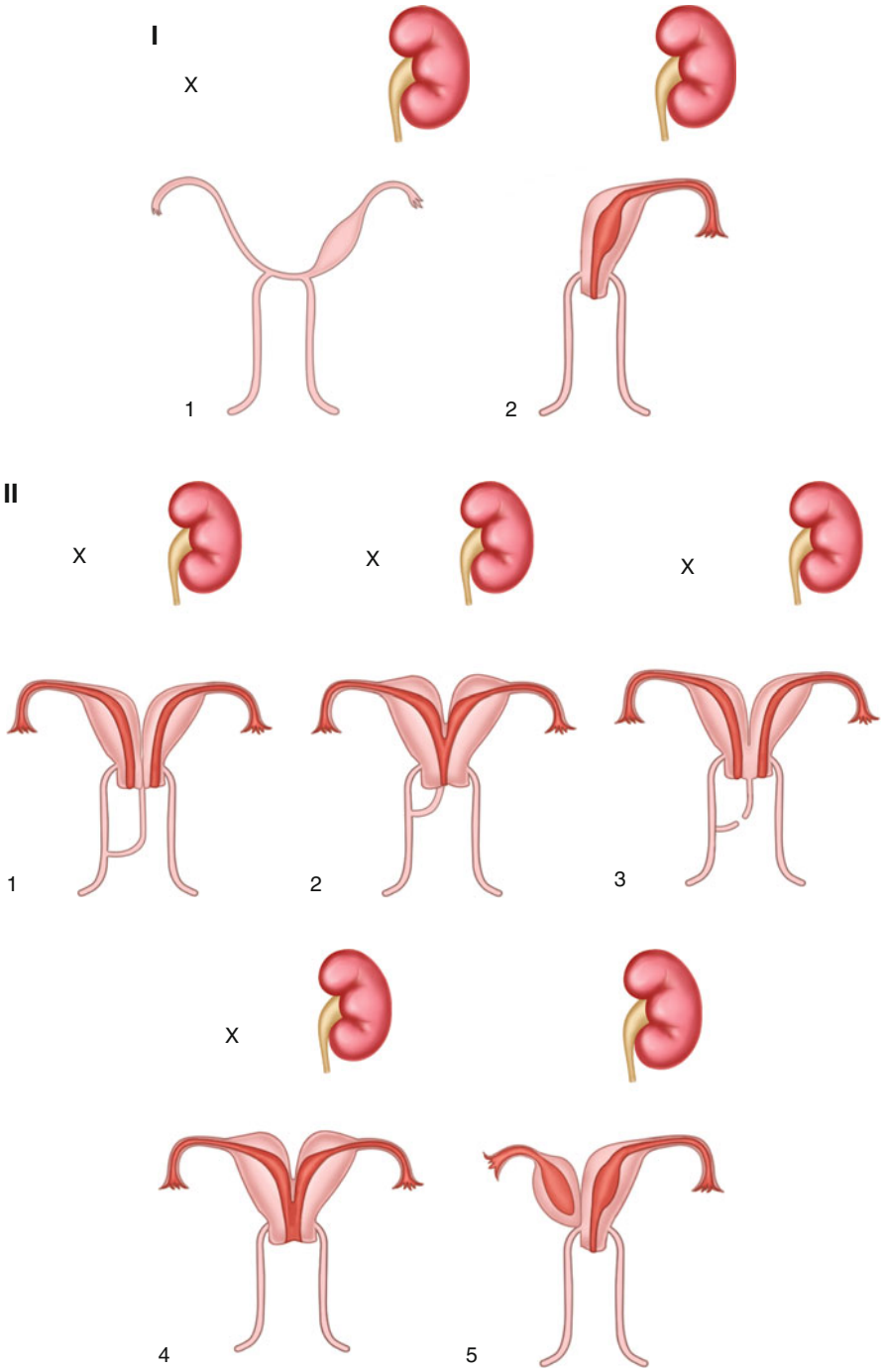


Fig. 1.2 Acién classification of reproductive tract anomalies

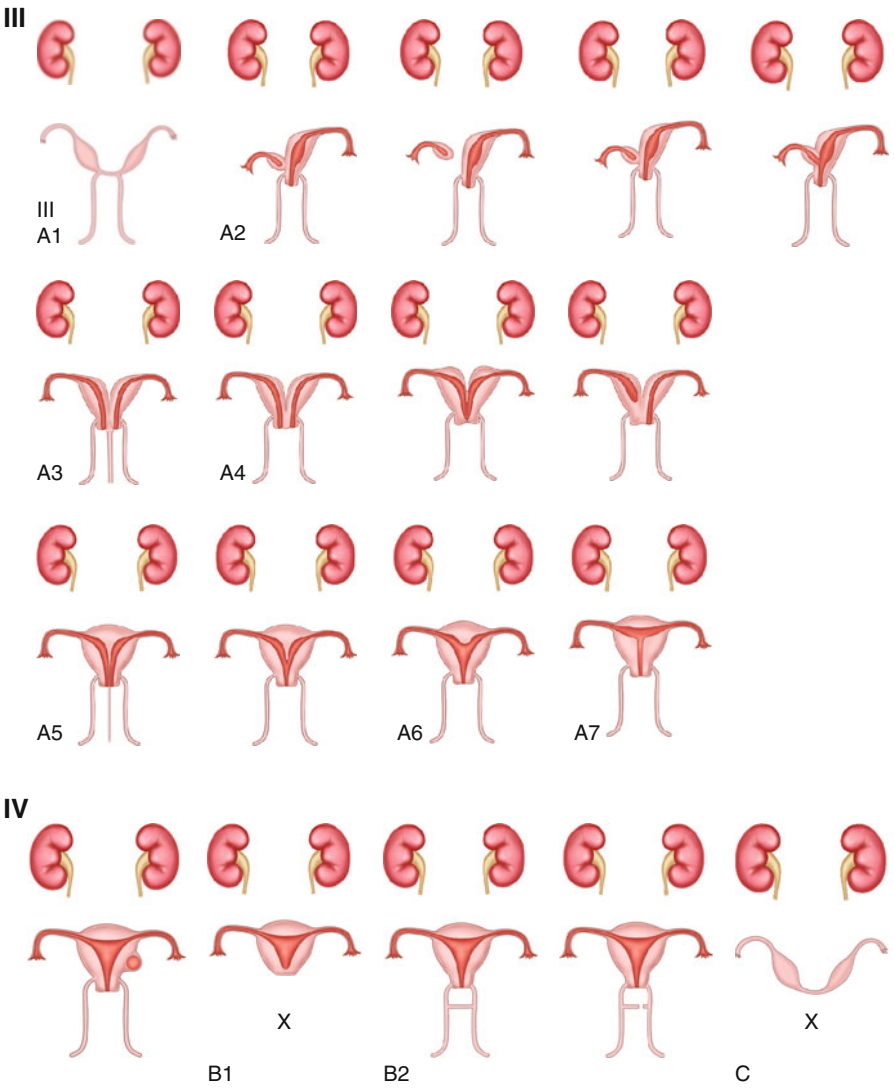


Fig. 1.2 (continued)

1.2.1.3 The European Society of Human Reproduction and Embryology (ESHRE) and the European Association for Gynaecological Endoscopy (ESGE) Classification of Female Reproductive Tract Anomalies

In 2013 the European Society of Human Reproduction and Embryology (ESHRE) and the European Association for Gynaecological Endoscopy (ESGE) proposed a new classification system based on anatomy. Anomalies are classified into the following main classes from the same embryological origin: the uterus, cervix, and vagina [4]: (Fig. 1.3).

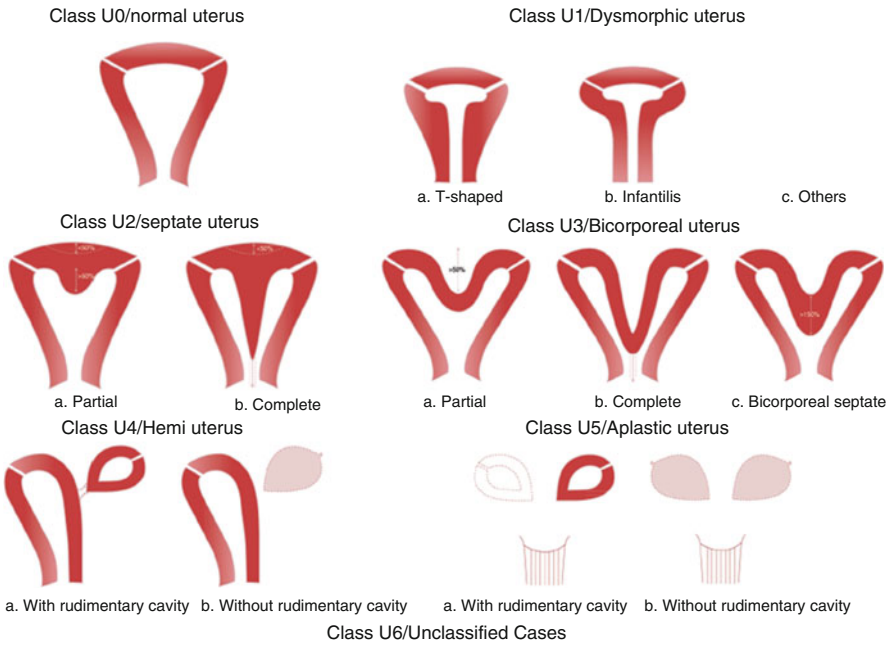


Fig. 1.3 ESHRE/ESGE – uterine anomalies

1.2.2 Common Reproductive Tract Anomalies

The current classifications of reproductive tract anomalies vary with advantages and disadvantages for each classification. Among them, there are many various nomenclatures, leading to a lot of confusion and overlapping. Hereby we describe some common reproductive tract anomalies and their clinical manifestations as follows.

1.2.2.1 External Genital Anomalies

The most common female external genital anomaly is the congenital hymen anomaly.

Congenital Hymen Anomaly

The hymen is a layer of mucosal membrane located at the vaginal opening, with squamous epithelium covering on its outer and inner surfaces. In between these surfaces it contains connective tissue, blood vessels, and nerve endings. During its development, abnormal cavity formation at the urogenital sinus will develop into various anomalies which include the imperforate hymen, microperforate hymen, septate hymen, cribriform hymen, etc. (Fig. 1.4).

Imperforate hymen is a rare genital anomaly, also known as nonporous hymen. The incidence of imperforate hymen is about 0.015 %. Imperforate hymen mainly obstructs the discharge of vaginal secretions. It may be asymptomatic at childhood due to minimal vaginal secretions, but at puberty, as both the vaginal and cervical secretions gradually increase, they accumulate in the vagina and lead to a sense of heaviness in the lower abdomen. After menarche, as the menstrual blood cannot drain out, it accumulates in the vagina forming a vaginal hematoma after several menstruations. Subsequently, it may lead to uterine and tubal hematomas, and eventually retrograde menstrual flow will enter into the pelvic cavity forming pelvic hematomas. Clinical symptoms are cyclical lower abdominal pains which progressively increase in intensity. On gynecological examination a bulging hymen can be seen, with a purple blue surface; on rectal examination, a vaginal mass bulging into the rectum is felt as a palpable pelvic mass. With a finger in the rectum, the pressing on the vaginal mass will make the bulging hymen more obvious. Ultrasound scan may show accumulated fluid in the vagina and even in the uterine cavity.

The clinical manifestations in patients with imperforate hymen or micropore hymen would vary according to the absence or sizes of the pore holes in the hymen. Some patients have periodic menstruations with moderate amount of menstrual blood outflow, but a lot of blood still accumulates in the vagina; sometimes these periods are irregular; some patients present with delayed menarche, with complaints of periodic abdominal pain, dyspareunia, and smelly vaginal discharge due to poor vaginal drainage. Similar to imperforate hymen, micropore hymen can cause the reflux of vaginal secretions and blood into the peritoneal cavity forming a pelvic mass. The micropore openings in the hymen may serve as communicating channels between the vagina and the outside, through which bacteria will enter and exit, leading to recurrent urinary tract infection and more commonly pelvic infection or abscess.

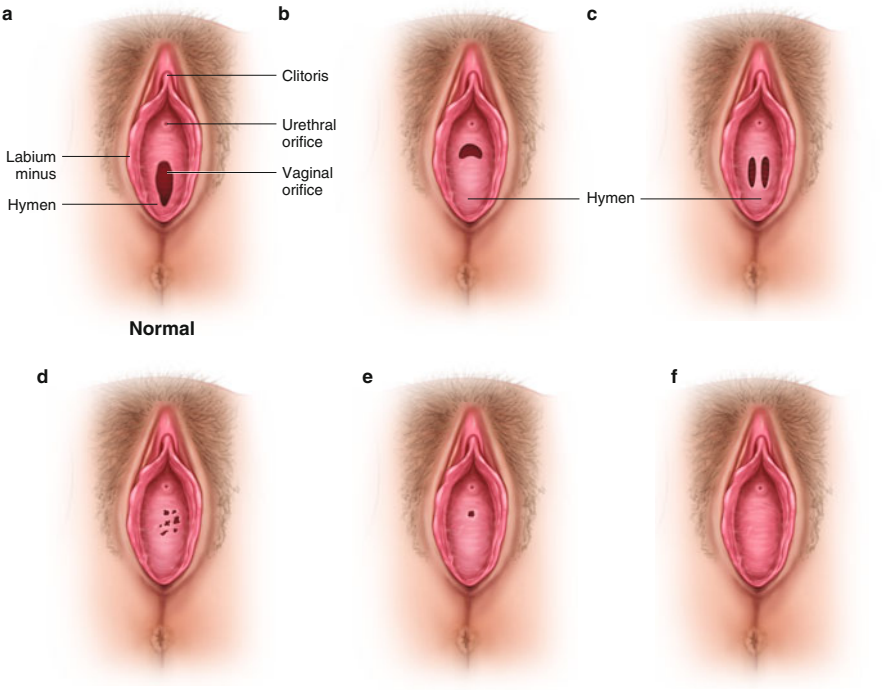


Fig. 1.4 Congenital anomalies of the hymen

1.2.2.2 Vagina Anomalies

Vaginal Agenesis

Vaginal agenesis is also known as MRKHs (Mayer-Rokitansky-Küster-Hauser) syndrome which includes congenital absence of the uterus and vagina. It is a kind of functional defect in the reproductive tract characterized by no reproductive ability. At present, the etiology is unclear. In animal models, it could be demonstrated that WNT4 gene suppresses male gonadal differentiation and ovarian androgen secretion; the absence of this gene might be related to this disorder [5].

Congenital vaginal agenesis is often accompanied by cervical or uterine abnormalities; 7–10 % of these patients have rudimentary uterine horn or cervical aplasia (Fig. 1.5), while the majorities have normal ovarian function. Seventy-eight percent of patients have normal uterus, 16 % with ovaries outside the pelvis, and 6 % with unilateral abnormal ovarian development [11]. These patients are often associated with other nongenital anomalies. Twenty-five to fifty percent of patients have urinary tract anomalies, including pelvic kidney or unilateral renal agenesis; 10–15 % also have skeletal anomalies mainly spinal deformities. Other rare anomalies include congenital heart disease, hand anomalies, deafness, cleft palate, and inguinal hernia.

Clinical manifestations are primary amenorrhea and sexual difficulties. Generally the patient has only a primitive uterus without periodic abdominal pain. Physical examination shows normal physical appearance, with normal secondary sexual characteristics and external genitalia, but there is no vaginal opening or only a shallow concave at the posterior part of vestibule. Occasionally there is a short vagina with a closed end.

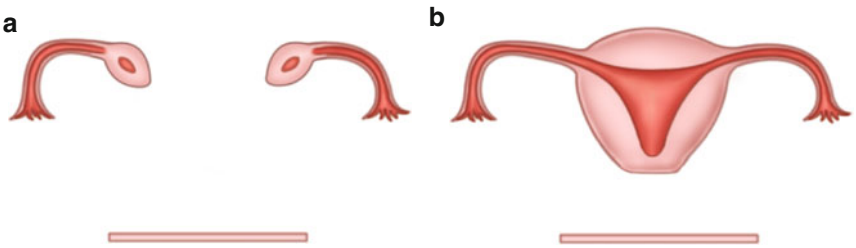


Fig. 1.5 Vaginal agenesis. (**a**) With rudimentary horns. (**b**) With cervical aplasia

Agenesis of the Lower Vagina

In the lower vaginal agenesis (Fig. 1.2 2), the upper vagina, cervix, and uterus are normal, but it is often associated with external genital anomalies. The clinical manifestations are primary amenorrhea, periodic abdominal pain, etc. Because the endometrium functions normally, these symptoms can occur early. Pelvic examination reveals a low-positioned pelvic mass, located in front of the rectum. Often treatment can be offered timely, because their symptoms present early similar to the imperforate hymen. On examination, there is no vaginal opening and the mucosal surface of the posterior vestibule shows normal color without any outward bulging. Digital rectal examination shows a palpable mass protruding into the rectum, but at a higher position than that in the imperforate hymen. It is also associated with lesser blood reflux into the peritoneal cavity causing pelvic endometriosis.

Transverse Vaginal Septum

It is caused by the failure to the fusion of the end the paramesonephric ducts which either do not open up or only partially open together with the urogenital sinus. The incidence rate is about 1/30,000 to 1/80,000 [7]. This condition is rarely associated with urinary tract and other organ abnormalities. The septum can be located in any part of the vagina; 46 % occurred at the upper part, 35–40 % at the middle, and 15–20 % at the lower part of the vagina. The septal thickness is usually less than 1 cm. If there is no hole in the septum, it is a complete transverse septum. If there are some small holes, it is an incomplete transverse septum (Figs. 1.2 (IIIB2) and 1.6). Transverse vaginal septum at the upper end of the vagina is often an incomplete septum, while the one at the lower end is often a complete septum.

Incomplete transverse septa at the upper vagina are often asymptomatic, while those at lower positions can affect sex life and also affect the descent of fetal presenting part at vaginal delivery. A patient with complete septum will present with primary amenorrhea and periodic abdominal pain which is progressively severe. Vaginal gynecological examination reveals a short vagina with a blind end or with a small pore across the center of the septum. On rectal examination, the cervix and uterus are palpable. Because a complete septum causes retention of menstrual blood, a mass can be palpable above the septum.

Transverse vaginal septum, at various positions of the vagina, can be a complete or incomplete transverse vaginal septum.

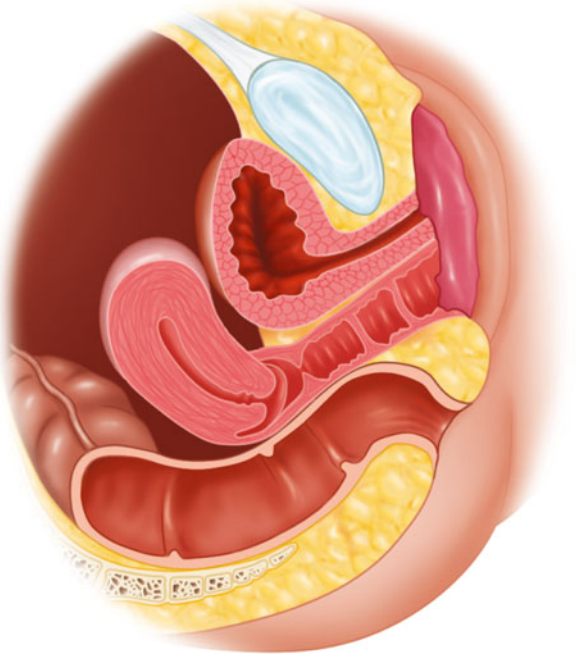


Fig. 1.6 Transverse vaginal septum

Longitudinal Vaginal Septum

It is caused by the partial fusion failure of the paramesonephric ducts with the lower ends of their wall persisted or only partially disappeared. They can be either a complete or an incomplete longitudinal septum. As a result, the vagina is divided into two longitudinal tunnels lined by mucosal wall and separated by a septum. A complete longitudinal septum extends from the cervix at the top and down to the vaginal opening at the lower end. An incomplete septum extends from the top, but does not reach the vaginal opening. A complete septum is often associated with a didelphic uterus, double cervices, and underdevelopment of a kidney on one side.

A complete longitudinal vaginal septum is often asymptomatic, with no impact on sex life and vaginal delivery. An incomplete longitudinal septum may have sex problems or discomfort. During labor, the descent of the fetal presenting part can be obstructed by the septum. Vaginal examination can reveal a longitudinal vaginal septum dividing the vagina into two longitudinal tunnels, with the top end of the septal mucosal wall close to the cervix, and for a complete longitudinal septum, the lower part of the septum reaches the vaginal opening, while for the incomplete longitudinal septum, it fails to reach the vaginal opening.

Oblique Vaginal Septum

The etiology is yet unclear and it may be that the paramesonephric ducts in the process extending downward do not reach the urogenital sinus and form a dead end. Oblique vaginal septum is often accompanied by ipsilateral urinary tract anomalies, often presenting with uterus didelphys, double cervices, and ipsilateral renal agenesis.

There are three types of oblique vaginal septum (Fig. 1.7).

Type I: Oblique septum without holes. The uterus behind the septum is completely separated from the uterus on the other side and also with the outside. The menstrual blood accumulates in the uterine cavity and the vaginal cavity behind the septum.

Type II: Oblique septum with a hole. The hole is a few millimeters in size. The uterus behind the septum is completely separated from the uterus on the other side. The menstrual blood can be discharged through the hole, but with poor drainage.

Type III: Oblique septum without holes combined with a cervical fistula. There is a small fistula between the two adjacent cervices or between a cervix and the adjacent vaginal cavity behind the septum on the other side. The menstrual blood in the uterine cavity on the side of the septum can be discharged via the small fistula to the cervix on the other side, but it is also with poor drainage.

In younger patients, their menstrual periods are regular and normal. All three types of vaginal septum will present with dysmenorrhea. Type I has more severe dysmenorrhea, usually with lower abdominal pain on one side. Type II has a small amount of vaginal discharge or intermenstrual brownish spotting or even smelly

purulent discharge. Type III has prolonged menstrual period with spotting, but also may have purulent discharge. Gynecological examination of the side of the closed vaginal end may show a cystic tumor. For type I, the mass is harder and the retained uterine blood can lead to an enlarged uterus. For type II and III, the cystic masses are less distended, and old blood can flow out when pressed.

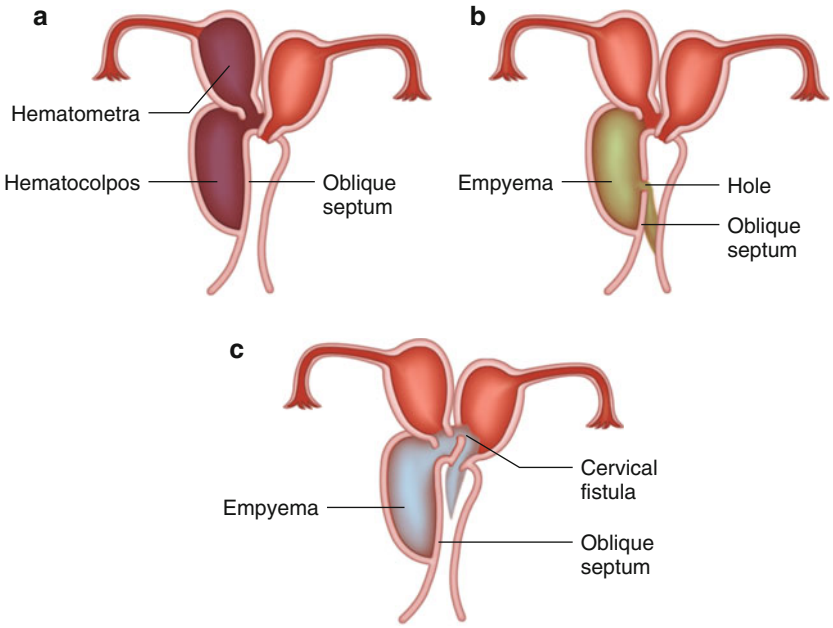
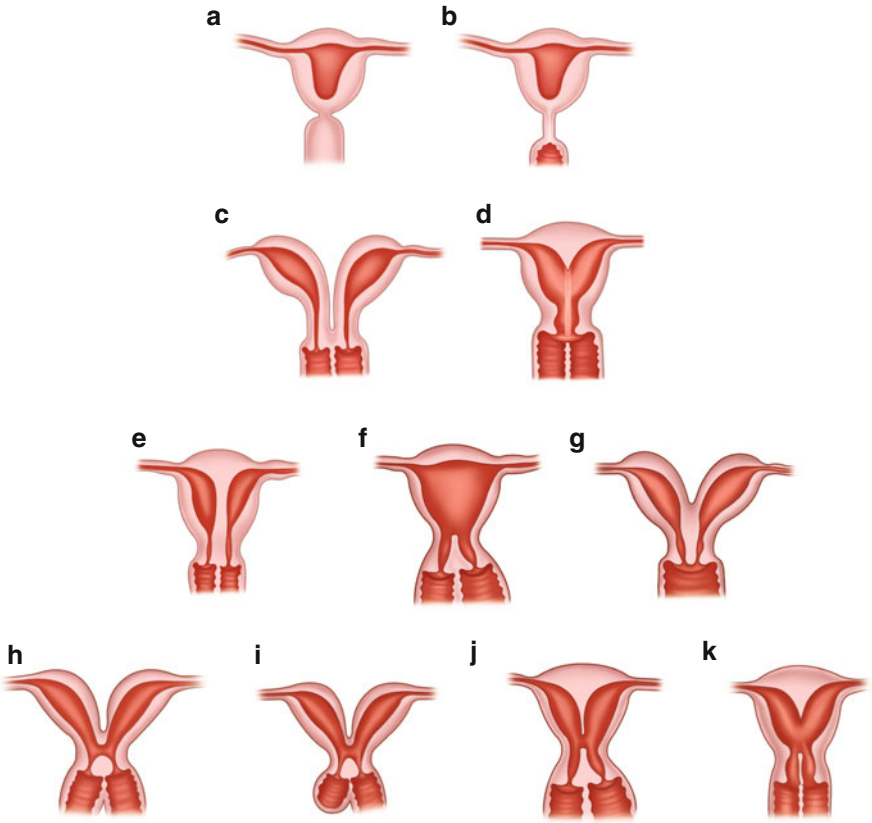


Fig. 1.7 Three types of oblique vaginal septum. (**a**) Septum without holes. (**b**) Septum with a hole. (**c**) Oblique septum without holes, but with a cervical fistula

Fig. 1.8 Congenital cervical anomalies. (**a**) Cervical agenesis; (**b**) cervical hypoplasia; (**c**) double cervices, double vaginas and bicornuate uterus; (**d**) septate uterus and longitudinal septa of cervix and vagina; (**e**) double cervices, double vaginas and complete septate uterus; (**f**) double cervices, double vaginas and single uterus; (**g**) septate cervix with double uteri; (**h**) double cervices, double vaginas, double uteri with low fistula; (**i**) as in H with type III oblique vaginal septum; (**j**) double cervices, double vaginas, incomplete septate uterus; (**k**) cervical septum with longitudinal vaginal septum and incomplete septate uterus

1.2.2.3 Cervical Aplasia or Hypoplasia

The new hypothesis is that the cervix is developed at about the 10th week of gestation. At the time of fusion, the lower ends of both Müllerian ducts fuse with the urogenital sinus isthmus beginning at the cervix. After the completion of Müllerian ducts fusion, reabsorption of the septum between both Müllerian ducts will form the body of the uterus with the upper segment of the cervix forming the internal os and the lower end forming the external os. Fusion and subsequent reabsorption progress toward the tip and tail of the fused Müllerian tubercle, while the tail end of the Müllerian tubercle forms the vagina. Both upper and lower ends of the Müllerian ducts fuse and reabsorb at different points in time. Any error in the development will lead to cervical agenesis, hypoplasia, or double cervices, sometimes associated with various vaginal, uterine, and urinary anomalies. Isolated cervical agenesis or hypoplasia is rare. The cervical agenesis is usually associated with upper vaginal anomaly, while cervical hypoplasia can have a normal vagina. Double cervices and cervical septum can be difficult to distinguish from their external appearance, and they are asymptomatic when there is no outflow obstruction. Some rare cervical anomalies cannot fall in line with the recommended American Society for Reproductive Medicine classification system of female reproductive tract anomalies (Fig. 1.8).



1.2.2.4 Uterine Anomalies

Congenital uterine anomalies often do not present with any symptoms and not being noticed. Therefore, it is difficult to determine its exact incidence. In women with normal childbirth, 2–4 % may be associated with uterine anomalies. The most common anomalies are uterine septum (90 %), double uterine horns (5 %), and double uteri (5 %). For women with adverse obstetrical history and recurrent miscarriages, the incidence of uterine anomalies is 10–25 % [8]. In the general population, the incidences of various uterine anomalies are [9] septate uterus (35 %), double uterine horns (26 %), arcuate uterus (18 %), single uterine horn (10 %), double uteri (8 %), and uterine agenesis (3 %).

Uterine Agenesis or Uterine Hypoplasia

The cause is due to the failure of fusion and reabsorption at the uterine end of both paramesonephric ducts. It is often associated with absence of the vagina as described previously as the MRKH syndrome.

Unilateral Uterine Anomalies

It is usually due to abnormal Müllerian duct development, which results in the following common uterine anomalies:

Septate Uterus and Arcuate Uterus

Septate uterus has a normal uterine shape, but with two uterine cavities (Figs. 1.1 C4, C5, and 1.2 III-A5). A septate uterus is a result of failure to reabsorb the longitudinal uterine septum after the fusion of the paramesonephric ducts. There are two types of septate uterus: (1) complete septate uterus, the longitudinal septum extends from the fundus of the uterus to the internal cervical os, and (2) incomplete septate uterus, the longitudinal septum extends to a level above the internal cervical os. Usually they are asymptomatic.

Arcuate uterus (Fig. 1.2 III-A6) is due to the abnormal development at the fundus of the uterus. There is a depression in the middle of the uterine fundus with the uterine wall slightly protruding into the uterine cavity. It is usually asymptomatic. On examination, there is a palpable depression at the fundus of the uterus which may suggest an arcuate uterus. The clinical manifestations of an arcuate uterus are their possible impacts on the pregnancy outcome; these include recurrent miscarriages, premature delivery, and premature rupture of membranes. But these are still controversial [10]. Among patients with adverse pregnancy outcomes, there are 21–44 % spontaneous abortions, 12–33 % premature delivery, and the remaining 50–72 % normal delivery.

Unicornuate Uterus

Only one of the paramesonephric ducts develops normally, forming a single uterine horn (Figs. 1.1b, 1.2 III-A2 and 1.3 U4), with a normal functioning ipsilateral ovary. The other paramesonephric duct becomes agenesis, tubular, or hypoplasia, with an undeveloped ovary. Both the fallopian tube and kidney on the same side are often absent. A part of the paramesonephric duct may form a rudimentary uterine horn. Single uterine horn has an incidence of 1: 4020, particularly higher in infertile women. Approximately 65 % of single uterine horn is associated with rudimentary uterine horn. The rudimentary uterine horn may be with or without a uterine cavity which may or may not connect with the single uterine horn. Forty percent of the single uterine horn is associated with renal abnormality. This anomaly is often related to some obstetric complications, e.g., ectopic pregnancy 2.7 %, early trimester miscarriage 24.3 %, mid-trimester miscarriage 9.7 %, premature birth 20.1 %, and intrauterine fetal death 10.5 %. Only 49.9 % of these patients can have live births [11].

A unicornuate uterus is asymptomatic. If its associated rudimentary uterine horn has functional endometrium and its cavity does not communicate with that of the unicornuate uterus, this will lead to retrograde blood flow into the pelvic cavity, and this can cause dysmenorrhea and pelvic endometriosis. Vaginal examination may show a small, spindle-shaped unicornuate uterus deviated from the midline. If it is accompanied by a rudimentary horn, a smaller lump can be palpable next to the uterus. This may be misdiagnosed as an ovarian cyst or tumor. If there is menstrual bleeding inside the cavity of the rudimentary horn, a tender lump can be palpable due to a uterine hematoma.

Bicornuate Uterus

Bicornuate uterus has a significant depression at the fundus with its appearance quite different from a septate uterus (Figs. 1.1 C7, C8, and 1.2 III-A4). It is due to a failure of the fusion of bilateral paramesonephric ducts. Depending the separation of uterine cavity, it can be a complete double uterus (separation begins from the internal cervical os) or an incomplete double uterus (separation from above the internal cervical os) and the arcuate uterus (this latter is in dispute). Patients usually do not have any clinical symptom. But sometimes there can be heavy menstrual bleeding, associated with various degrees of dysmenorrhea. On examination, a depression can be palpable at the fundus of the uterus.

Didelphic Uterus

Didelphic uterus is formed when both paramesonephric ducts did not fuse together, and they separately develop into two uteri and two cervices. The two cervices can be separated or connected with a communicating fistula. Most didelphic uteri have favorable pregnancy outcome. However, one of the cervices may not develop normally or even absent, but there may be a small fistula connecting it with the adjacent vagina. A didelphic uterus can be associated with a longitudinal vaginal septum or an oblique septum, but patients usually do not have any symptoms if there is no outflow obstruction.

Abnormal Vertical Fusion of the Uterus

Abnormal Müllerian ducts fusion with the urogenital tubercle or abnormal vaginal recanalization will lead to cervical agenesis, hypoplasia, or vaginal septum.

Diethylstilbestrol-Related Uterine Anomalies

Diethylstilbestrol, a synthetic estrogen, had been used from 1949 to 1971. The in vivo exposure to diethylstilbestrol can cause developmental defects of the paramesonephric ducts associated with various fetal malformations, including (1) female fetus that can have uterine anomalies like a small T-shaped uterine cavity, a narrow uterine cavity, or a uterus with widened lower uterine segment and irregular uterine wall (the T- shaped uterine cavity is the most common diethylstilbestrol-related uterine anomaly (42–62 %)); (2) vaginal adenosis, vaginal ridges, and transverse vaginal septum; and (3) cervical anomalies with hypoplasia.

1.2.2.5 Fallopian Tubes Anomalies

Tubal developmental abnormality is rare. It is caused by developmental blockage at the top end of the paramesonephric ducts, and it often coexists with uterine anomalies. Almost all are discovered incidentally at surgery because of other diseases.

Absence or Remnant of Fallopian Tubes

The absence and remnant of the fallopian tube is the result of an undeveloped ipsilateral paramesonephric duct, often accompanied with ipsilateral abnormal development of the ureter and kidney. There is yet no reported case of a simple absence of both fallopian tubes. Absence of fallopian tube is often accompanied with severe abnormalities of other internal organs, and as such the fetus cannot survive.

Abnormal Development of Fallopian Tubes

It is a common genital anomaly. The fallopian tubes can be small, slender, and curving, with various degree of abnormal tubal wall development, tubes without lumen, and partly obliterated lumen. All these can result in infertility. Tubal diverticulum or abnormal tubal orifice can be a cause of ectopic pregnancy.

Supernumerary Fallopian Tube(s)

Attaching to one or both of the fallopian tubes, there is another smaller tube with fimbrial end. In some cases, there is a communication between the normal fallopian tube and this smaller tube and some do not.

Supernumerary Normal Fallopian Tube(s)

There is/are normally developed fallopian tube(s) either unilateral or bilateral. They are all communicated with the uterine cavity.

1.2.2.6 Ovarian Anomalies

Ovarian anomaly is due to the blockage of primordial germ cell migration or the abnormal shift in location at the formation of gonads.

Ovarian Agenesis or Ovarian Anomalies

Unilateral or bilateral agenesis of ovaries is extremely rare. Unilateral or bilateral hypoplastic ovaries are white in appearance, as slender cords. They are also known as streak ovaries. Sectioning of a hypoplastic ovary shows only fibrous tissue without follicles. The clinical manifestations include primary amenorrhea or delayed menarche, scanty menstruation, and poor secondary sexual characteristics. It is often accompanied by abnormal development of genital or urinary organs and more commonly seen in patients with Turner's syndrome.

Ectopic Ovaries

After the formation of ovaries, they remain in the primitive genital ridge area, without descent to the pelvis. Patients with ectopic ovaries have normal ovarian functions and are asymptomatic.

Supernumerary Ovaries

The supernumerary ovary is rare. It is generally far away from the normal position of the ovary and in a retroperitoneal position. It is asymptomatic and more often found incidentally during surgery for other diseases.

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