CHAPTER 3: Congenital Genitourinary Abnormalities

Abnormalities in the development or fusion of one or both Müllerian ducts may result in malformations which sometimes possess an obstetrical significance. Pregnancy may be associated with any one of these malformations, provided an ovum be cast off from the ovaries and no serious obstacle be opposed to the upward passage of the spermatozoa and their subsequent union with it.

—J. Whitridge Williams (1903)

GENITOURINARY TRACT DEVELOPMENT

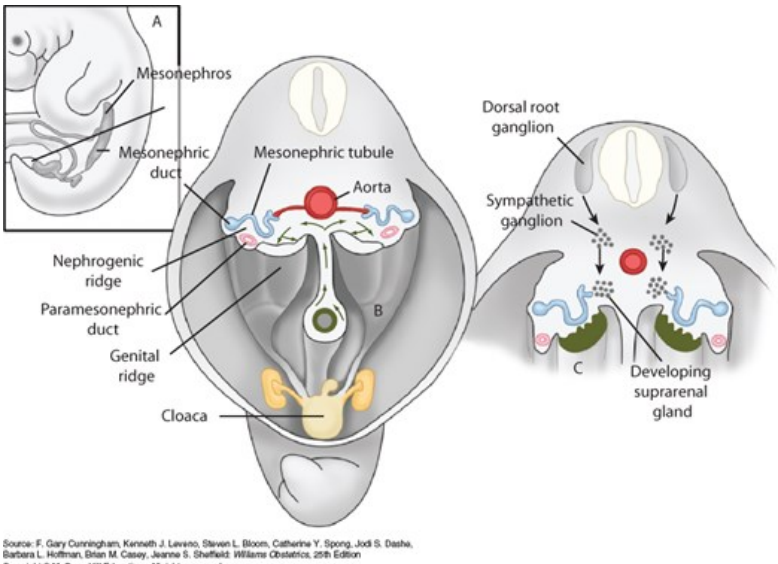
In females, the external genitalia, gonads, and müllerian ducts each derive from different primordia and in close association with the urinary tract and hindgut. Abnormal embryogenesis during this process is thought to be multifactorial and can create sporadic anomalies. Several of these can lead to infertility, subfertility, miscarriage, or preterm delivery. Thus, knowledge of genitourinary system development is essential.

Embryology of the Urinary System

Between the 3rd and 5th gestational weeks, an elevation of intermediate mesoderm on each side of the fetus—the urogenital ridge—begins development into the urogenital tract. Subsequently, the urogenital ridge divides into the genital ridge, destined to become the ovary, and into the nephrogenic ridge (Fig. 3-1). The nephrogenic ridges develop into the mesonephros (mesonephric kidney) and paired mesonephric ducts, also termed wolffian ducts, which connect to the cloaca.

FIGURE 3-1

A. Cross-section of an embryo at 4 to 6 weeks. **B.** Large ameboid primordial germ cells migrate (*arrows*) from the yolk sac to the area of germinal epithelium, within the genital ridge. **C.** Migration of sympathetic cells from the spinal ganglia to a region above the developing kidney.

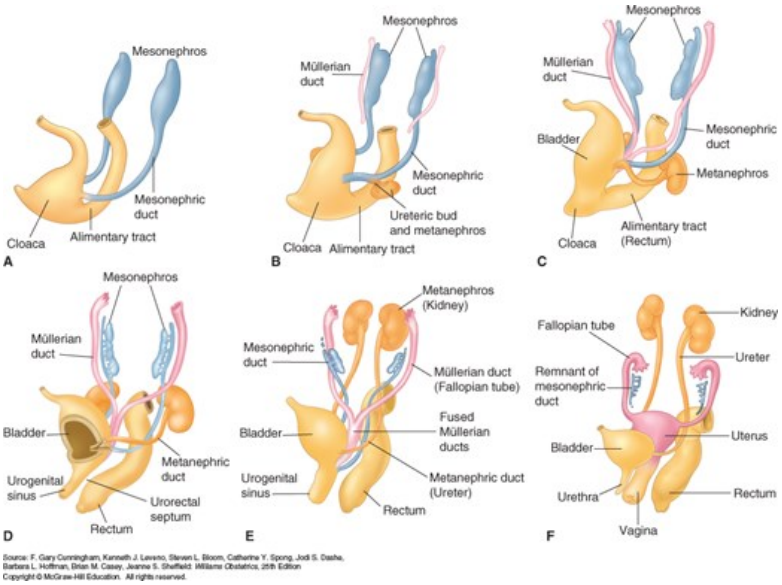


The early urinary tract develops from the mesonephros and its mesonephric ducts (Fig. 3-2A). Recall that evolution of the renal system passes sequentially through the pronephric and mesonephric stages to reach the permanent metanephric system. Between the 4th and 5th weeks, each mesonephric duct gives rise to a ureteric bud, which grows cephalad toward its respective mesonephros (Fig. 3-2B). As each bud lengthens, it induces differentiation of the metanephros, which will become the final kidney (Fig. 3-2C). Each mesonephros degenerates near the end of the first trimester,

and without testosterone, the mesonephric ducts regress as well.

FIGURE 3-2

Embryonic development of the female genitourinary tract **(A-F)**. (Reproduced with permission from Shatzkes DR, Haller JO, Velcek FT: Imaging of uterovaginal anomalies in the pediatric patient, Urol Radiol 1991;13(1):58–66.)



The cloaca begins as a common opening for the embryonic urinary, genital, and alimentary tracts. By the 7th week it becomes divided by the urorectal septum to create the rectum and the urogenital sinus (Fig. 3-2D). The urogenital sinus is considered in three parts: (1) the cephalad or vesicle portion, which forms the urinary bladder; (2) the middle or pelvic portion, which creates the female urethra; and (3) the caudal or phallic part, which gives rise to the distal vagina and to the greater vestibular (Bartholin) and paraurethral glands.

Embryology of the Genital Tract

The fallopian tubes, uterus, and upper vagina derive from the müllerian ducts, also termed paramesonephric ducts, which form adjacent to each mesonephros (see Fig. 3-2B). These ducts extend downward and then turn medially to meet and fuse together in the midline. The uterus is formed by this union of the two müllerian ducts at approximately the 10th week (Fig. 3-2E). Fusion to create the uterus begins in the middle and then extends both caudally and cephalad. With cellular proliferation at the upper portion, a thick wedge of tissue creates the characteristic piriform uterine shape. At the same time, dissolution of cells at the lower pole forms the first uterine cavity (Fig. 3-2F). As the upper wedge-shaped septum is slowly reabsorbed, the final uterine cavity is usually formed by the 20th week. If the two müllerian ducts fail to fuse, then two separate uterine horns remain. In contrast, resorption failure of the common tissue between them results in various degrees of persistent uterine septum.

As the distal end of the fused müllerian ducts contacts the urogenital sinus, this induces endodermal outgrowths from the sinus termed the sinovaginal bulbs. These bulbs proliferate and fuse to form the vaginal plate, which later resorbs to form the vaginal lumen. This vaginal canalization is generally completed by the 20th week. However, the lumen remains separated from the urogenital sinus by the hymeneal membrane. This membrane further degenerates to leave only the hymeneal ring.

The close association of the mesonephric (wolffian) and paramesonephric (müllerian) ducts explains the simultaneous abnormalities in their end organs. Kenney and colleagues (1984) showed that up to half of females with uterovaginal malformations have associated urinary tract defects. Anomalies most frequently associated with renal defects are unicornuate uterus, uterine didelphys, and agenesis syndromes, whereas arcuate and bicornuate are less commonly linked (Reichman, 2010). When müllerian anomalies are identified, the urinary system can be evaluated with magnetic resonance (MR) imaging, sonography, or intravenous pyelography (Hall-Craggs, 2013). With müllerian anomalies, ovaries are functionally normal but have a higher incidence of anatomical maldescent into the pelvis (Allen, 2012; Dabirashrafi, 1994).

As discussed, the mesonephric ducts usually degenerate, however, persistent remnants may become clinically apparent. Mesonephric or wolffian

vestiges can persist as Gartner duct cysts. These are typically located in the proximal anterolateral vaginal wall but may be found at other sites along the vaginal length. They can be further characterized by MR imaging, which provides excellent image resolution at soft tissue interfaces. Most cysts are asymptomatic and benign and usually do not require surgical excision.

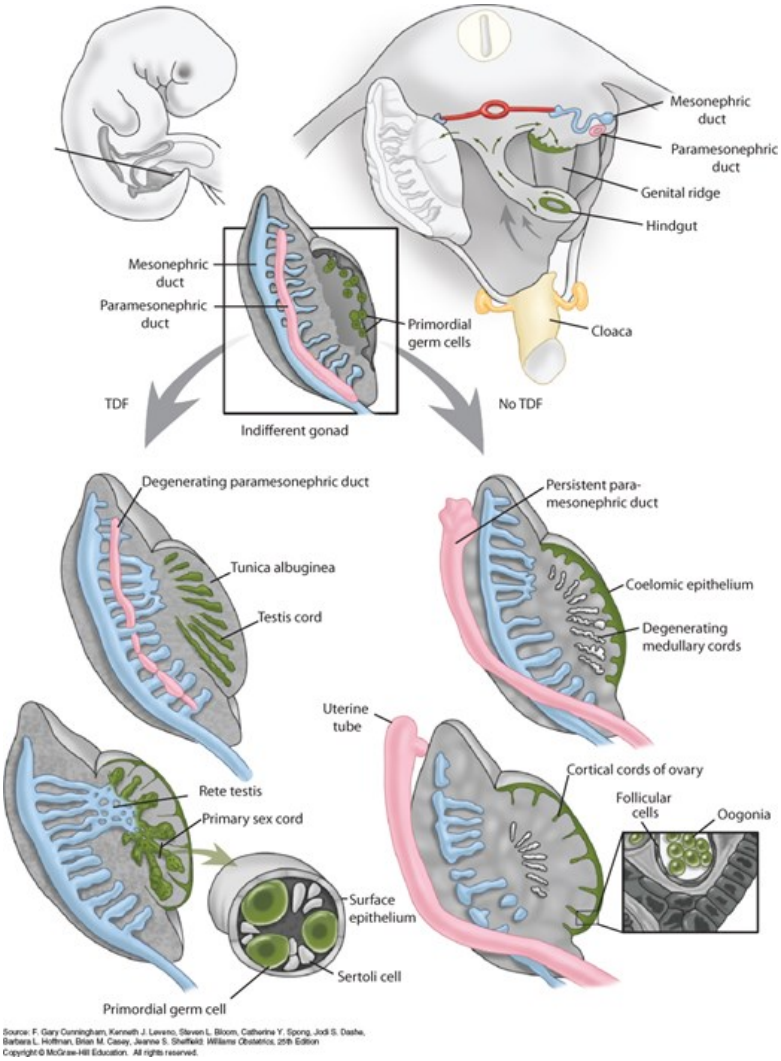
Intraabdominal wolffian remnants in the female include a few blind tubules in the mesovarium—the epoöphoron—and similar ones adjacent to the uterus—paroöphoron (see Fig. 3-2F) (Moore, 2013). The epoöphoron or paroöphoron may develop into clinically identifiable cysts in the adult.

Embryology of the Gonads

At approximately 4 weeks, gonads derive from coelomic epithelium covering the medial and ventral surface of the nephrogenic cord at a site between the eighth thoracic and fourth lumbar segments. Because of this separate gonadal and müllerian derivation, women with müllerian defects typically have functionally normal ovaries and are phenotypic females. The coelomic epithelium thickens to form the genital ridge, also known as the gonadal ridge. Strands of these epithelial cells extend into the underlying mesenchyme as the primary sex cords. By the sixth week, primordial germ cells have migrated from the yolk sac to enter the genital ridge mesenchyme (Fig. 3-3). The primordial germ cells are then incorporated into the primary sex cords.

FIGURE 3-3

Embryonic gonad differentiation. TDF = testis-determining factor.



In the seventh week, the sexes can be distinguished, and testes are recognized during microscopic sectioning by their well-defined radiating testis

cords. These cords are separated from the coelomic epithelium by mesenchyme that is to become the tunica albuginea. The testis cords develop into the seminiferous tubules and rete testis. The rete testis establishes connection with small tubes arising off the mesonephric duct. These small tubes become the efferent ducts that drain into the epididymis and then into the vas deferens, which are main mesonephric duct derivatives.

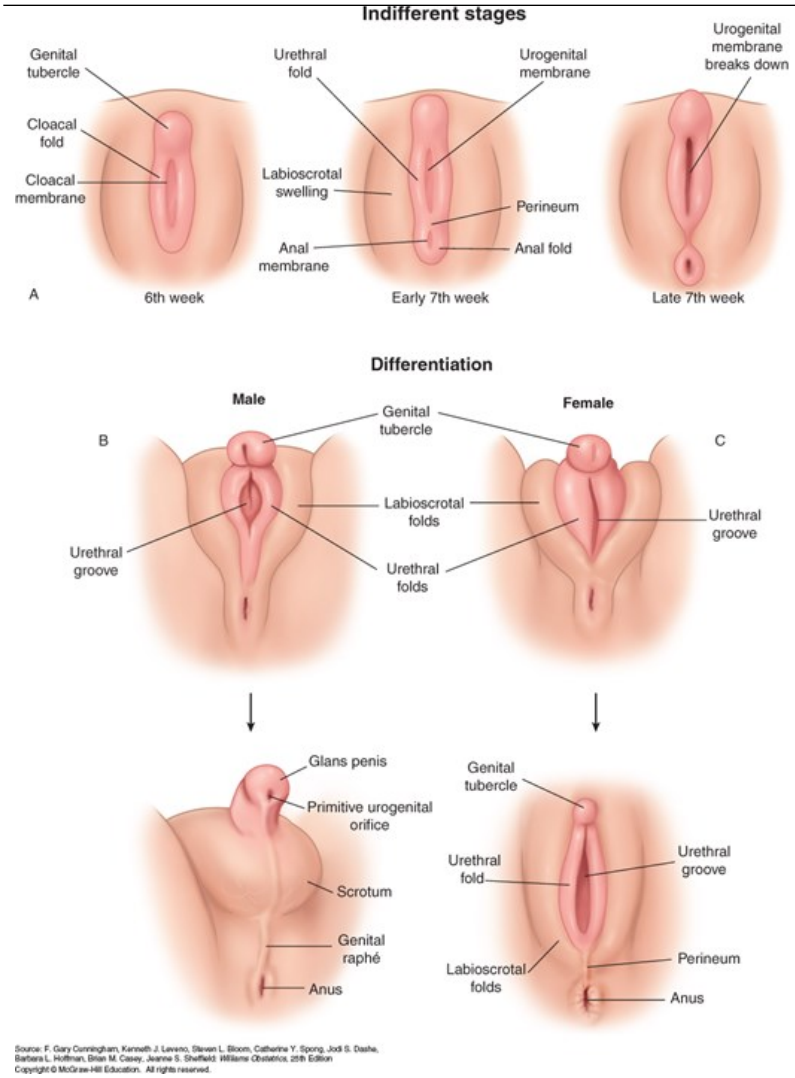
In the female embryo, the primary sex cords give rise to the medullary cords, which persist only for a short time. The coelomic epithelium again proliferates into the underlying mesenchyme, and these strands are the cortical cords. By the fourth month, the cortical cords begin to form isolated cell clusters called primordial follicles. These follicles contain the oogonia, which derive from primordial germ cells and are surrounded by a single layer of flattened follicular cells derived from the cortical cords. Follicular cells serve as supporting nutrient cells. By 8 months, the ovary has become a long, narrow, lobulated structure that is attached to the body wall by the mesovarium. The coelomic epithelium has been separated by a band of connective tissue—tunica albuginea—from the cortex. At this stage, the cortex contains follicles and is well defined from the inner medulla, which is composed of abundant blood vessels, lymphatic vessels, and nerve fibers.

Embryology of the External Genitalia

Early development of the external genitalia is similar in both sexes. By 6 weeks' gestation, three external protuberances have developed surrounding the cloacal membrane. These are the left and right cloacal folds, which meet ventrally to form the genital tubercle (Fig. 3-4). With division of the cloacal membrane into anal and urogenital membranes, the cloacal folds become the anal and urethral folds, respectively. Lateral to the urethral folds, genital swellings arise, and these become the labioscrotal folds. Between the urethral folds, the urogenital sinus extends onto the surface of the enlarging genital tubercle to form the urethral groove. By week 7, the urogenital membrane ruptures, exposing the cavity of the urogenital sinus to amnionic fluid.

FIGURE 3-4

Development of the external genitalia. **A.** Indifferent stage. **B.** Virilization of external genitalia. **C.** Feminization. (Reproduced with permission from Bradshaw KD: Anatomical disorders. In Hoffman BL, Schorge JO, Bradshaw KD, et al (eds): Williams Gynecology, 3rd ed. New York, McGraw Hill Education, 2016.)



Source: F. Gary Cunningham, Kenneth J. Leveno, Steven L. Bloom, Catherine Y. Spong, Jodi S. Dashe, Barbara L. Hoffman, Brian M. Casey, Jeanne S. Sheffield: *Williams Obstetrics*, 25th Edition

The genital tubercle elongates to form the phallus in males and the clitoris in females. Still, it is not possible to visually differentiate between male and female external genitalia until week 12. In the male fetus, dihydrotestosterone (DHT) forms locally by the 5-α reduction of testosterone. DHT prompts the anogenital distance to lengthen, the phallus to enlarge, and the labioscrotal folds to fuse and form the scrotum.

In the female fetus, without DHT, the anogenital distance does not lengthen, and the labioscrotal and urethral folds do not fuse (Fig. 3-4C). The genital tubercle bends caudally to become the clitoris, and the urogenital sinus forms the vestibule of the vagina. The labioscrotal folds create the labia majora, whereas the urethral folds persist as the labia minora. Female external genital differentiation is complete by 11 weeks, whereas male external genital differentiation is complete by 14 weeks.

SEXUAL DIFFERENTIATION

Defining gender incorporates genetic gender, gonadal gender, and phenotypic gender. *Genetic gender*—XX or XY—is established at fertilization. However, for the first 6 weeks, development of male and female embryos is morphologically indistinguishable.

Gonadal gender is heralded by the differentiation of the primordial gonad into a testis or an ovary. If a Y chromosome is present, the gonad begins developing into a testis. Testis development is directed by a protein called the *testis-determining factor (TDF)*, which modulates the transcription of several genes involved in gonadal differentiation. TDF is encoded by the *sex-determining region (SRY) gene,* located on the short arm of the Y chromosome. But testis development is much more complex and requires other autosomal genes (Nistal, 2015a).

The importance of the *SRY* gene is demonstrated in several paradoxical conditions. First, 46,XX phenotypic males can result from translocation of the Y

chromosome fragment containing *SRY* to the X chromosome during meiosis of male germ cells (Wu, 2014). Similarly, 46,XY individuals can appear phenotypically female if they carry a mutation in the *SRY* gene (Helszer, 2013).

Last, *phenotypic gender* begins at 8 weeks' gestation. Before this, urogenital tract development in both sexes is indistinguishable. Thereafter, differentiation of the internal and external genitalia to the male phenotype is dependent on testicular function. In the absence of a testis, female differentiation ensues irrespective of genetic gender (Table 3-1).

TABLE 3-1

Embryonic Urogenital Structures and Their Adult Homologues

Indifferent Structure	Female	Male
Genital ridge	Ovary	Testis
Primordial germ cells	Ova	Spermatozoa
Sex cords	Granulosa cells	Seminiferous tubules, Sertoli cells
Gubernaculum	Uteroovarian and round ligaments	Gubernaculum testis
Mesonephric tubules	Epoöphoron, paroöphoron	Efferent ductules, paradidymis
Mesonephric ducts	Gartner duct	Epididymis, ductus deferens, ejaculatory duct
Paramesonephric ducts	Uterus, fallopian tubes, upper vagina	Prostatic utricle, appendix of testis
Urogenital sinus	Bladder, urethra Vagina Paraurethral glands Greater (Bartholin) and lesser vestibular glands	Bladder, urethra Prostatic utricle Prostate glands Bulbourethral glands
Genital tubercle	Clitoris	Glans penis
Urogenital folds	Labia minora	Floor of penile urethra
Labioscrotal swellings	Labia majora	Scrotum

In males, the fetal testis secretes a protein called müllerian-inhibiting substance (MIS), also called antimüllerian hormone (AMH). It acts locally as a paracrine factor to cause müllerian duct regression. Thus, it prevents the development of uterus, fallopian tube, and upper vagina. AMH is produced by the Sertoli cells of the seminiferous tubules. Importantly, these tubules appear in fetal gonads and secrete AMH before differentiation of Leydig cells, which are the cellular site of testosterone synthesis. AMH is secreted as early as 7 weeks, and müllerian duct regression is completed by 9 to 10 weeks. Because AMH acts locally near its site of formation, if a testis were absent on one side, the müllerian duct on that side would persist, and the uterus and fallopian tube would develop on that side.

Apparently through stimulation initially by human chorionic gonadotropin (hCG), and later by fetal pituitary luteinizing hormone (LH), the fetal testes secrete testosterone. This hormone acts directly on the wolffian duct to effect the development of the vas deferens, epididymis, and seminal vesicles. Testosterone also enters fetal blood and acts on the external genitalia anlage. In these tissues, testosterone is converted to 5α-DHT to cause virilization of the external genitalia.

DISORDERS OF SEX DEVELOPMENT

Definitions

As evident from the prior discussion, abnormal sex development may involve the gonads, internal duct system, or external genitalia. Rates vary and approximate 1 in every 1000 to 4500 births (Murphy, 2011; Ocal, 2011). The nomenclature used to describe disorders of sex development (DSDs) has evolved. Current classification of these disorders include: (1) sex chromosome DSDs, (2) 46,XY DSDs, and (3) 46,XX DSDs (Table 3-2) (Hughes, 2006).

TABLE 3-2

Disorders of Sex Development (DSD) Classification

Sex Chromosome DSD
45,X Turner[a]
47,XXY Klinefelter[a]
45,X/46,XY Mixed gonadal dysgenesis
46,XX/46,XY Ovotesticular DSD
46,XY DSD
Testicular development
Pure gonadal dysgenesis
Partial gonadal dysgenesis
Ovotesticular
Testis regression
Androgen production or action
Androgen synthesis
Androgen receptor
LH/hCG receptor
AMH
46,XX DSD
Ovary development
Ovotesticular
Testicular
Gonadal dysgenesis
Androgen excess
Fetal
Maternal
Placental

[a]And syndrome variants.

AMH = antimüllerian hormone; hCG = human chorionic gonadotropin; LH = luteinizing hormone.

Adapted with permission from Hughes IA, Houk C, Ahmed SF, et al: Consensus statement on management of intersex disorders. J Pediatr Urol 2:148, 2006.

Other important terms describe the abnormal phenotypic findings that can be found. First, some disorders of sexual development are associated with abnormal, underdeveloped gonads, that is, *gonadal dysgenesis*. With this, if a testis is poorly formed, it is called a *dysgenetic testis*, and if an ovary is poorly formed, it is called a *streak gonad*. In affected patients, the underdeveloped gonad ultimately fails, which is indicated by elevated gonadotropin levels. Another important clinical sequela is that patients bearing a Y chromosome are at high risk of developing a germ cell tumor in the dysgenetic gonad.

A second term, *ambiguous genitalia*, describes genitalia that do not appear clearly male or female. Abnormalities may include hypospadias, undescended testes, micropenis or enlarged clitoris, labial fusion, and labial mass.

Last, *ovotesticular* defines states characterized by ovarian and testicular tissue in the same individual. It was formerly termed true hermaphroditism. In these cases, different types of gonads can be paired. The types of gonads that may be paired include a normal testis, a normal ovary, a streak gonad, dysgenetic testis, or an ovotestis. In the latter, both ovarian and testicular elements are combined within the same gonad. With ovotesticular DSDs, the internal ductal system structure depends on the ipsilateral gonad and its degree of determination. Specifically, the amount of AMH and testosterone determines the degree to which the internal ductal system is masculinized or feminized. External genitalia are usually ambiguous and undermasculinized due to inadequate testosterone.

Sex Chromosome Disorders of Sex Development

Turner and Klinefelter Syndromes

Sex chromosome disorders of sexual development typically arise from an abnormal number of sex chromosomes. Of these, Turner and Klinefelter syndromes are most frequently encountered (Nielsen, 1990).

Turner syndrome is caused by de novo loss or severe structural abnormality of one X chromosome in a phenotypic female. Most affected fetuses are spontaneously aborted. However, in girls with Turner syndrome who survive, phenotype varies widely, but nearly all affected patients have short stature. Associated problems include cardiac anomalies (especially coarctation of the aorta), renal anomalies, hearing impairment, otitis media and mastoiditis, and an increased incidence of hypertension, achlorhydria, diabetes mellitus, and Hashimoto thyroiditis. It is the most common form of gonadal dysgenesis that leads to primary ovarian failure. In these cases, the uterus and vagina are normal and capable of responding to exogenous hormones (Matthews, 2017).

Another sex chromosome disorder is *Klinefelter syndrome* (47,XXY). These individuals tend to be tall, undervirilized males with gynecomastia and small, firm testes. They have significantly reduced fertility from hypogonadism due to gradual testicular cell failure. These men are at increased risk for germ cell tumors, osteoporosis, hypothyroidism, diabetes mellitus, breast cancer, cardiovascular abnormalities, and cognitive and psychosocial problems (Aksglaede, 2013; Calogero, 2017).

Chromosomal Ovotesticular DSD

Several karyotypes can create a coexistent ovary and testis, and thus ovotesticular DSD is found in all three DSD categories (see Table 3-2). In the sex chromosome group, ovotesticular DSD may arise from a 46,XX/46,XY karyotype. Here, an ovary, testis, or ovotestis may be paired. The phenotype in general mirrors that for ovotesticular disorders, which are described earlier on this page.

For others in the sex chromosome DSD group, ovotesticular disorder arises from a chromosomal mosaic such as 45,X/46,XY. With this karyotype, a picture of *mixed gonadal dysgenesis* shows a streak gonad on one side and a dysgenetic or normal testis on the other. The phenotypical appearance ranges from undervirilized male to ambiguous genitalia to Turner stigmata.

46,XY Disorders of Sex Development

Insufficient androgen exposure of a fetus destined to be a male leads to 46,XY DSD—formerly called male pseudohermaphroditism. The karyotype is 46,XY and testes are frequently present. The uterus is generally absent as a result of normal embryonic AMH production by Sertoli cells. These subjects are most often sterile from abnormal spermatogenesis and have a small phallus that is inadequate for sexual function. As seen in Table 3-2, etiology of 46,XY DSD may stem from abnormal testis development or from abnormal androgen production or action.

46,XY Gonadal Dysgenesis

This spectrum of abnormal gonad underdevelopment includes pure or complete, partial, or mixed 46,XY gonadal dysgenesis. These are defined by the amount of normal testicular tissue and by karyotype. Because of the potential for germ cell tumors in dysgenetic testes and intraabdominal testes, affected patients routinely have been advised to undergo gonadectomy (Jiang, 2016).

Of these, *pure gonadal dysgenesis* results from a mutation in the *SRY* gene or in other genes with testis-determining effects (Hutson, 2014). This leads to underdeveloped dysgenetic gonads that fail to produce androgens or AMH. Formerly named Swyer syndrome, the condition creates a normal prepubertal female phenotype and a normal müllerian system due to absent AMH.

Partial gonadal dysgenesis defines those with gonad development intermediate between normal and dysgenetic testes. Depending on the percentage of underdeveloped testis, wolffian and müllerian structures and genital ambiguity are variably expressed.

Mixed gonadal dysgenesis is one type of ovotesticular disorder of sexual differentiation. As discussed in Sex Chromosome Disorders of Sex Development, one gonad is streak, and the other is a normal or a dysgenetic testis. Of affected individuals, 15 percent have a 46,XY karyotype (Nistal, 2015b). The phenotype is wide ranging as with partial gonadal dysgenesis.

Last, *testicular regression* can follow initial testis development. A broad phenotypic spectrum is possible and depends on the timing of testis failure.

Abnormal Androgen Production or Action

In some cases, 46,XY disorders of sexual differentiation stem from abnormalities in: (1) testosterone biosynthesis, (2) LH receptor function, (3) AMH function, or (4) androgen receptor action. First, the sex steroid biosynthesis pathway can suffer enzymatic defects that block testosterone production. Depending on the timing and degree of blockade, undervirilized males or phenotypic females may result. In contrast to these central enzymatic defects, peripheral defects may be causative. Namely, abnormal 5-α reductase type 2 enzyme action leads to impaired conversion of testosterone to DHT and thus to undervirilization.

Second, hCG/LH receptor abnormalities within the testes can lead to Leydig cell aplasia/hypoplasia and impaired testosterone production. In contrast, disorders of AMH and AMH receptors result in persistent müllerian duct syndrome (PMDS). Affected patients appear as males but have a persistent uterus and fallopian tubes due to failed AMH action.

Last, the androgen receptor may be defective and result in androgen-insensitivity syndrome (AIS). Resistance to androgens may be incomplete and associated with varying degrees of virilization and genital ambiguity. Milder forms have been described in men with severe male factor infertility and poor virilization.

Females with complete androgen-insensitivity syndrome (CAIS) appear as phenotypically normal females at birth. They often present at puberty with primary amenorrhea. External genitalia appear normal; scant or absent pubic and axillary hair are noted; the vagina is shortened or blind ending; and the uterus and fallopian tubes are absent. However, these individuals develop breasts during pubertal maturation due to abundant androgen to estrogen conversion. Testes may be palpable in the labia or inguinal area or may be found intraabdominally. Surgical excision of the testes after puberty is recommended to decrease the associated risk of germ cell tumors, which may be as high as 20 to 30 percent.

46,XX Disorders of Sex Development

As seen in Table 3-2, etiology of 46,XX disorders of sexual differentiation may stem from abnormal ovarian development or from excess androgen exposure.

Abnormal Ovarian Development

Disorders of ovarian development of those with a 46,XX complement include: (1) gonadal dysgenesis, (2) testicular DSD, and (3) ovotesticular DSD.

With *46,XX gonadal dysgenesis*, similar to Turner syndrome, streak gonads develop. These lead to hypogonadism, prepubertal normal female genitalia, and normal müllerian structures, but other Turner stigmata are absent.

With *46,XX testicular DSD*, several possible genetic mutations lead to testis-like formation within the ovary—streak gonad, dysgenetic testis, or ovotestis. Defects may stem from *SRY* translocation onto one X chromosome. In individuals without *SRY* translocation, other genes with testis-determining effects are most likely activated. Regardless, production of AMH prompts müllerian system regression, and androgens promote wolffian system development and external genitalia masculinization. Spermatogenesis, however, is absent due to a lack of needed genes on the long arm of the Y chromosome. These individuals are not usually diagnosed until puberty or during infertility evaluation.

With *46,XX ovotesticular DSD*, individuals possess a unilateral ovotestis with a contralateral ovary or testis, or bilateral ovotestes. Phenotypic findings depend on the degree of androgen exposures and mirror those for other ovotesticular DSDs discussed in Sex Chromosome Disorders of Sex Development.

Androgen Excess

Discordance between gonadal sex (46,XX) and the phenotypic appearance of external genitalia (masculinized) may also result from excessive fetal androgen exposure. This was previously termed female pseudohermaphroditism. In affected individuals, the ovaries and female internal ductal structures such as the uterus, cervix, and upper vagina are present. Thus, patients are potentially fertile. The external genitalia, however, are virilized to a varying degree depending on the amount and timing of androgen exposure. The three embryonic structures that are commonly affected by elevated androgen levels or ovarian development disorders are the clitoris, labioscrotal folds, and urogenital sinus. As a result, virilization may range from modest clitoromegaly to posterior labial fusion and development of a phallus with a penile urethra. Degrees of virilization can be described by the Prader score, which ranges from 0 for a normal-appearing female to 5 for a normal, virilized male.

Fetal, placental, or maternal sources can provide the excessive androgen levels. Maternally derived androgen excess may come from virilizing ovarian tumors such as luteoma and Sertoli-Leydig cell tumor or from virilizing adrenal tumors. Fortunately, these neoplasms infrequently cause fetal effects because of the tremendous ability of placental syncytiotrophoblast to convert C_{19} steroids—androstenedione and testosterone—to estradiol via the enzyme aromatase (Chap. 5, Placental Estrogen Production). As another source, drugs such as testosterone, danazol, and other androgen derivatives may cause fetal virilization.

Of fetal sources, exposure can arise from fetal congenital adrenal hyperplasia (CAH). This stems from a fetal enzyme deficiency in the steroidogenic pathway that leads to androgen accumulation. The most common defect is 21-hydroxylase deficiency. CAH is a frequent cause of virilization and has an incidence approximating 1 in 10,000 to 20,000 live births (Speiser, 2010).

With CAH, phenotypes depend on the location of the enzyme defect in the steroidogenic pathway and on the severity of the resulting enzymatic deficiency (Miller, 2011). With severe enzymatic deficiency, affected newborns have life-threatening salt wasting and virilization. Other mutations may prompt virilization alone (Auchus, 2015). The mildest abnormalities present later and are described as “nonclassic,” “late-onset,” or “adult-onset” CAH. In these patients, activation of the adrenal axis at puberty increases steroidogenesis and unmasks a mild enzymatic deficiency. Excess androgen provides negative feedback to gonadotropin-releasing hormone (GnRH) receptors in the hypothalamus. These patients often present with hirsutism, acne, and anovulation. Thus, late-onset CAH may mimic polycystic ovarian syndrome (McCann-Crosby, 2014). In some instances, CAH can be diagnosed antenatally. Early maternal dexamethasone therapy can dampen androgen excess to minimize virilization (Chap. 16, Congenital Adrenal Hyperplasia).

Of rare placental sources, placental aromatase deficiency from a fetal *CYP19* gene mutation causes an accumulation of placental androgen and underproduction of placental estrogens (Chap. 5, Placental Estriol Synthesis) (Jones, 2007). Consequently, both the mother and the 46,XX fetus are virilized.

Gender Assignment

Delivery of a newborn with a disorder of sexual differentiation is a potential medical emergency and can create possible long-lasting psychosexual and social ramifications for the individual and family. Ideally, as soon as the affected neonate is stable, parents are encouraged to hold the child. The newborn is referred to as “your baby,” and suggested terms include “phallus,” “gonads,” “folds,” and “urogenital sinus” to reference underdeveloped

structures. The obstetrician explains that the genitalia are incompletely formed and emphasizes the seriousness of the situation and the need for rapid consultation and laboratory testing.

Because similar or identical phenotypes may have several etiologies, identification of a specific DSD may require several diagnostic tools (McCann-Crosby, 2015). Relevant neonatal physical examination evaluates: (1) ability to palpate gonads in the labioscrotal or inguinal regions, (2) ability to palpate uterus during rectal examination, (3) phallus size, (4) genitalia pigmentation, and (5) presence of other syndromic features. The newborn metabolic condition is assessed, as hyperkalemia, hyponatremia, and hypoglycemia may indicate CAH. The mother is examined for signs of hyperandrogenism. Other neonatal tests include genetic studies, hormone measurements, imaging, and in some cases endoscopic, laparoscopic, and gonadal biopsy. Sonography shows the presence or absence of müllerian/wolffian structures, can locate the gonads, and can identify associated malformations such as renal anomalies.

BLADDER AND PERINEAL ABNORMALITIES

Very early during embryo formation, a bilaminar cloacal membrane lies at the caudal end of the germinal disc and forms the infraumbilical abdominal wall. Normally, an ingrowth of mesoderm between the ectodermal and endodermal layers of the cloacal membrane leads to formation of the lower abdominal musculature and pelvic bones. Without this reinforcement, the cloacal membrane may prematurely rupture, and depending on the extent of the infraumbilical defect, cloacal exstrophy, bladder exstrophy, or epispadias may result.

Of these, *cloacal exstrophy* is rare. It includes the triad of omphalocele, bladder exstrophy, and imperforate anus.

Bladder exstrophy is uncommon and is characterized by an exposed bladder lying outside the abdomen. Associated findings often include abnormal external genitalia and a widened symphysis pubis. At the same time, however, the uterus, fallopian tubes, and ovaries are typically normal except for occasional müllerian duct fusion defects. Pregnancy with bladder exstrophy is associated with greater risk for antepartum pyelonephritis, urinary retention, ureteral obstruction, pelvic organ prolapse, preterm birth, and breech presentation. The American Urological Association has published management guidelines for pregnancy (Eswara, 2016). Due to the extensive adhesions from prior repair and altered anatomy typically encountered, some recommend planned cesarean delivery at a tertiary center (Deans, 2012; Dy, 2015; Greenwell, 2003).

Epispadias without bladder exstrophy is rare and develops in association with other anomalies such as a widened, patulous urethra; absent or bifid clitoris; nonfused labial folds; and flattened mons pubis. Vertebral abnormalities and pubic symphysis diathesis are also common.

Clitoral anomalies are unusual. One is clitoral duplication or bifid clitoris, which is rare and usually develops in association with bladder exstrophy or epispadias. With female phallic urethra, the urethra opens at the clitoral tip. Last, clitoromegaly noted at birth suggests fetal exposure to excessive androgens (46,XX Disorders of Sex Development). In other cases, congenital clitoromegaly in females born extremely premature is a rare but well-recognized finding thought to be due to transient androgen levels in these neonates (Greaves, 2008).

As noted, the hymen marks the embryological boundary between structures derived from the müllerian and urogenital sinus. *Hymeneal anomalies* include imperforate, microperforate, cribriform (sievelike), navicular (boat-shaped), and septate hymens. They result from failure of the inferior end of the vaginal plate—the hymeneal membrane—to canalize. Their incidences approximate 1 in 1000 to 2000 females (American College of Obstetricians and Gynecologists, 2016). During the neonatal period, significant amounts of mucus can be secreted due to maternal estrogen stimulation. With an imperforate hymen, secretions collect to form a bulging, translucent yellow-gray mass, termed hydro- or mucocolpos, at the vaginal introitus. Most are asymptomatic and resolve as mucus is reabsorbed and estrogen levels decrease, but rarely can cause perinatal urinary retention from their mass effects (Johal, 2009).

MÜLLERIAN ABNORMALITIES

Four principal deformities arise from defective müllerian duct embryological steps: (1) agenesis of both ducts, either focally or along the entire duct length; (2) unilateral maturation of one müllerian duct with incomplete or absent development of the opposite side; (3) absent or faulty midline fusion of the ducts; or (4) defective canalization. Various classifications have been proposed, and Table 3-3 shows the one from the American Fertility Society (1988). It separates anomalies into groups with similar clinical characteristics, prognosis for pregnancy, and treatment. It also includes one for abnormalities associated with fetal exposure to diethylstilbestrol (DES). Several other classification systems have been crafted, but this one is the most widely used (Acién, 2011; Di Spiezio Sardo, 2015; Oppelt, 2005).

TABLE 3-3

Classification of Müllerian Anomalies

I.	**Segmental müllerian hypoplasia or agenesis** a. Vaginal b. Cervical c. Uterine fundal d. Tubal e. Combined anomalies
II.	**Unicornuate uterus** a. Communicating rudimentary horn b. Noncommunicating horn c. No endometrial cavity d. No rudimentary horn
III.	**Uterine didelphys**
IV.	**Bicornuate uterus** a. Complete—division to internal os b. Partial
V.	**Septate uterus** a. Complete—septum to internal os b. Partial
VI.	**Arcuate**
VII.	**Diethylstilbestrol related**

Data from American Fertility Society: The American Fertility Society classifications of adnexal adhesions, distal tubal occlusion, tubal occlusion secondary to tubal ligation, tubal pregnancies, Müllerian anomalies and intrauterine adhesions, Fertil Steril 1988 Jun;49(6):944–955.

Müllerian anomalies may be suspected by symptoms or physical findings such as vaginal septa, blind-ending vagina, or duplicated cervix. Amenorrhea may be an initial complaint for those with agenesis of a müllerian component. In those with outlet obstruction, pelvic pain from occult blood that accumulates and distends the vagina, uterus, or fallopian tubes may arise from functioning endometrium. Endometriosis and its associated dysmenorrhea, dyspareunia, and chronic pain are also frequent with outlet obstruction.

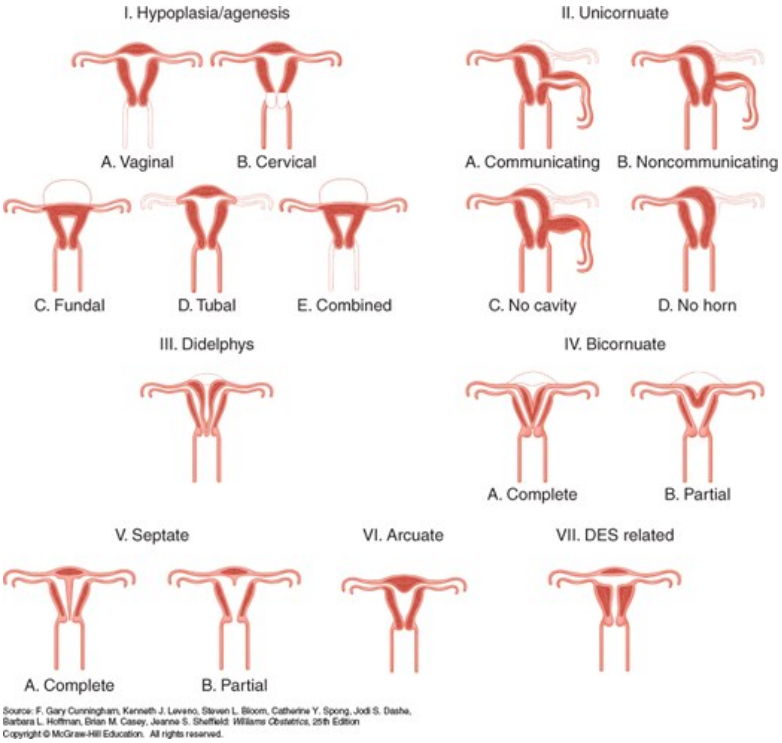
Müllerian Agenesis

Class I segmental defects are caused by müllerian hypoplasia or agenesis as shown in Figure 3-5. These developmental defects can affect the vagina, cervix, uterus, or fallopian tubes and may be isolated or may coexist with other müllerian defects.

FIGURE 3-5

Classification of müllerian anomalies. DES = diethylstilbestrol. (Modified with permission from American Fertility Society: The American Fertility Society classifications of adnexal adhesions, distal tubal occlusion, tubal occlusion secondary to tubal ligation, tubal pregnancies, Müllerian anomalies and

intrauterine adhesions, Fertil Steril 1988 Jun;49(6):944–55.)



Source: F. Gary Cunningham, Kenneth J. Leveno, Steven L. Bloom, Catherine Y. Spong, Jodi S. Dashe, Barbara L. Hoffman, Brian M. Casey, Jeanne S. Sheffield: *Williams Obstetrics*, 25th Edition

Vaginal Abnormalities

Of all vaginal anomalies, vaginal agenesis is the most profound and may be isolated or associated with other müllerian anomalies. One example is the Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome, in which upper vaginal agenesis is typically associated with uterine hypoplasia or agenesis. Less often, this syndrome also displays abnormalities of the renal, skeletal, and auditory systems. This triad is known by the acronym MURCS, which reflects müllerian duct aplasia, renal aplasia, and cervicothoracic somite dysplasia (Rall, 2015).

The obstetrical significance of vaginal anomalies depends greatly on the degree of obstruction. Complete vaginal agenesis, unless corrected operatively, precludes pregnancy by vaginal intercourse. With MRKH syndrome, a functional vagina can be created, but uterine agenesis proscribes childbearing. In these women, however, ova can be retrieved for in vitro fertilization (IVF) in a surrogate mother (Friedler, 2016). Uterine transplantation is currently experimental but holds future promise for these women (Johannesson, 2016).

Of other vaginal anomalies, congenital septa may form longitudinally or transversely, and each can arise from a fusion or resorption defect. Longitudinal septa divide the vagina into right and left portions. They may be complete and extend the entire vaginal length. Partial septa usually form high in the vagina but may develop at lower levels. Septa are typically associated with other müllerian anomalies (Haddad, 1997). During labor, a complete longitudinal vaginal septum usually does not cause dystocia because the vaginal side through which the fetus descends dilates satisfactorily. An incomplete or partially obstructed longitudinal septum, however, may interfere with descent. Occasionally, a woman with a distal longitudinal septum presents in labor. During second-stage labor, this septum usually becomes attenuated by pressure from the fetal head. After ensuring adequate analgesia, the inferior attachment of the septum is isolated, clamped, transected, and ligated. Following placenta delivery, the superior attachment can be transected while carefully avoiding urethral injury.

A transverse septum poses an obstruction of variable thickness. It may develop at any depth within the vagina, but most are in the lower third (Williams, 2014). These may or may not be perforate, and thus obstruction or infertility is variably present. In labor, perforate strictures may be mistaken for the upper limit of the vaginal vault, and the septal opening is misidentified as an undilated cervical os (Kumar, 2014). If encountered during labor, and after the external os has dilated completely, the head impinges on the septum and causes it to bulge downward. If the septum does not yield, slight stretching pressure on its opening usually leads to further dilatation, but occasionally cruciate incisions are required to permit delivery (Blanton, 2003). If there is a thick transverse septum, however, cesarean delivery may be necessary.

Cervical Abnormalities

Developmental abnormalities of the cervix include partial or complete agenesis, duplication, and longitudinal septa. Uncorrected complete agenesis is incompatible with pregnancy, and in vitro fertilization with gestational surrogacy is an option. Surgical correction by uterovaginal anastomosis has resulted in successful pregnancy (Kriplani, 2012). Significant complications accompany this corrective surgery, and the need for clear preoperative anatomy delineation has been emphasized by Rock (2010) and Roberts (2011) and their colleagues. For this reason, they recommend hysterectomy for complete cervical agenesis and reserve reconstruction attempts for carefully selected patients with cervical dysgenesis.

Uterine Abnormalities

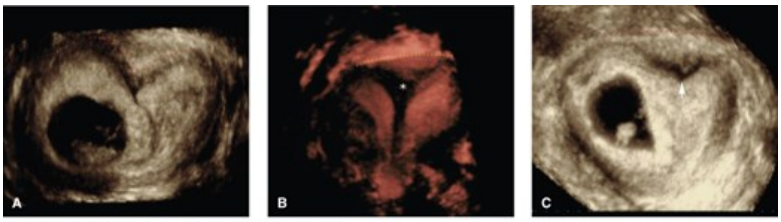
From a large variety, a few of the more common congenital uterine malformations are shown in Table 3-3. An accurate population prevalence of these is difficult to assess because the best diagnostic techniques are invasive. That said, the prevalence found with imaging ranges from 0.4 to 10 percent, and rates in women with recurrent miscarriage are significantly higher (Byrne, 2000; Dreisler, 2014; Saravelos, 2008). In a general population, the most common finding is arcuate uterus, followed in descending order by septate, bicornuate, didelphic, and unicornuate classes (Chan, 2011b).

Müllerian anomalies may be discovered during pelvic examination, cesarean delivery, tubal sterilization, or infertility evaluation. Depending on clinical presentation, diagnostic tools may include sonography, hysterosalpingography, magnetic-resonance imaging, laparoscopy, and hysteroscopy. Each has limitations, and these may be used in combination to completely define anatomy. In women undergoing fertility evaluation, hysterosalpingography (HSG) is commonly selected for uterine cavity and tubal patency assessment. It is contraindicated during pregnancy. HSG poorly defines the external uterine contour and can delineate only patent cavities. Regarding patency, remember that some unicornuate rudimentary horns lack a cavity. Also, outlet obstructions will preclude dye filling.

In most clinical settings, two-dimensional transvaginal sonography (2-D TVS) is initially performed. For this indication, the pooled accuracy for TVS is 90 to 92 percent (Pellerito, 1992). Saline infusion sonography (SIS) improves delineation of the endometrium and internal uterine morphology, but only with a patent endometrial cavity. It also is contraindicated in pregnancy. Three-dimensional (3-D) sonography is more accurate than 2-D sonography because it provides uterine images from virtually any angle. Thus, coronal images can be constructed as shown in Figure 3-6, and these are essential in evaluating both internal and external uterine contours (Grimbizis, 2016). Both 2-D and 3-D sonography are suitable for use in pregnancy.

FIGURE 3-6

Three-dimensional transvaginal sonographic images. **A.** Bicornuate uterus with an 8-week gestation. The external fundal contour (*red dotted line*) dips centrally below the intercornual line, and the endometrial cavities communicate. **B.** Septate uterus with a 5-week gestation. The external fundal contour is normal and convex (*yellow dotted line*), and the long septum (*asterisk*) extends caudad in the midline. **C.** Arcuate uterus with an 8-week gestation. The external fundal contour is normal and convex (*red dotted line*), but the fundal endometrial cavity is slightly indented (*arrow*).



Several studies have reported very good concordance between 3-D TVS and MR imaging of müllerian anomalies (Deutch, 2008; Graupera, 2015). MR imaging is often preferred for complex anatomy, especially cases for which corrective surgery is planned. MR imaging provides clear delineation of both the internal and external uterine anatomy and has a reported accuracy of up to 100 percent for müllerian anomaly evaluation (Bermejo, 2010; Pellerito, 1992). In addition, complex anomalies and commonly associated secondary diagnoses such as renal or skeletal anomalies can be concurrently evaluated. Precautions with MR imaging in pregnancy are discussed in Chapter 46 (Safety).

In some women undergoing an infertility evaluation, hysteroscopy and laparoscopy may be selected to assess for müllerian anomalies; screen for endometriosis, which is often coexistent; and exclude other tubal or uterine cavity pathologies (Puscheck, 2008; Saravelos, 2008). In pregnancy, these

approaches are rarely used to diagnose müllerian anomalies, and hysteroscopy is contraindicated.

Unicornuate Uterus (Class II)

With this abnormality, the underdeveloped or rudimentary horn may be absent. If present, it may or may not communicate with the dominant horn and may or may not contain an endometrium-lined cavity (see Fig. 3-5). General population estimates cite an incidence of 1 in 4000 women (Reichman, 2009). This anomaly may be detected during fertility evaluation by HSG. But as noted, noncommunicating or noncavitary rudimentary horns may not fill with dye. If this anomaly is suspected, 3-D sonography increases diagnostic accuracy, but again MR imaging may be preferred. Importantly, 40 percent of affected women will have renal anomalies (Fedele, 1996).

This müllerian anomaly carries significant obstetrical risks, including first- and second-trimester miscarriage, malpresentation, fetal-growth restriction, fetal demise, prematurely ruptured membranes, and preterm delivery (Chan, 2011a; Hua, 2011; Reichman, 2009). Abnormal uterine blood flow, cervical incompetence, and diminished cavity size and muscle mass of the hemiuterus are postulated to underlie these risks (Donderwinkel, 1992).

Rudimentary horns also increase the risk for an ectopic pregnancy within the remnant, which may be disastrous. This risk includes noncommunicating cavitary rudiments, for which transperitoneal sperm migration permits ovum fertilization and pregnancy (Nahum, 2004). In a report of 70 such pregnancies, Rolen and associates (1966) found that the rudimentary uterine horn ruptured prior to 20 weeks in most. Nahum (2002) reviewed the literature from 1900 to 1999 and identified 588 rudimentary horn pregnancies. Half had uterine rupture, and 80 percent did so before the third trimester. Of the total 588, the neonatal survival rate was only 6 percent.

Imaging allows an earlier diagnosis of rudimentary horn pregnancy so that it can be treated either medically with methotrexate or surgically before rupture (Dove, 2017; Edelman, 2003; Khati, 2012; Worley, 2008). Although not emphasized in Figure 3-5, the attachment site between the rudimentary horn at times can be broad and vascular.

If diagnosed in a nonpregnant woman, most recommend prophylactic excision of a horn that has a cavity (Fedele, 2005; Rackow, 2007). Data regarding subsequent pregnancy after excision are scarce. In one series of eight women, all had a preterm cesarean delivery (Pados, 2014).

Uterine Didelphys (Class III)

This müllerian anomaly arises from a complete lack of fusion that results in two entirely separate hemiuteri, cervices, and usually two vaginas (see Fig. 3-5). It is common among marsupials, for example, the American possum—*Didelphys virginiana*. Most women have a double vagina or a longitudinal vaginal septum. Uterine didelphys may be isolated. Or, it may compose a triad with an obstructed hemivagina and with ipsilateral renal agenesis (OHVIRA), also known as Herlyn- Werner-Wunderlich syndrome (Tong, 2013).

These anomalies are suspected on pelvic examination by identification of a longitudinal vaginal septum and two cervices. During HSG for fertility evaluation, contrast shows two separate endocervical canals. These open into separate noncommunicating fusiform endometrial cavities that each ends with a solitary fallopian tube. In women without fertility issues, 2- or 3-D TVS is a logical initial imaging tool, and separate divergent uterine horns with a large intervening fundal cleft are seen. Endometrial cavities are uniformly separate. MR imaging may be valuable in cases without classic findings.

Adverse obstetrical outcomes associated with uterine didelphys are similar but less frequent than those seen with unicornuate uterus. Increased risks include miscarriage, preterm birth, and malpresentation (Chan, 2011a; Grimbizis, 2001; Hua, 2011).

Metroplasty for either uterine didelphys or bicornuate uterus involves resection of intervening myometrium and fundal recombination (Alborzi, 2015). These rarely performed surgeries are chosen for highly selected patients with otherwise unexplained miscarriages. Moreover, no evidence-based data confirm the efficacy of such surgical repair.

Bicornuate Uterus (Class IV)

This fusion anomaly results in two hemiuteri. As shown in Figure 3-5, the central myometrium runs either partially or completely to the cervix. A complete bicornuate uterus may extend to the internal cervical os and have a single cervix (bicornuate unicollis) or reach the external os (bicornuate bicollis). As with uterine didelphys, a coexistent longitudinal vaginal septum is not uncommon.

Radiological discrimination of a bicornuate uterus from a septate uterus can be challenging. This distinction, however, is important because septate uterus can be treated with hysteroscopic septal resection. HSG or 2-D TVS may initially suggest an anomaly, but further distinction is provided by 3-D TVS or MR imaging (see Fig. 3-6). With these, an intercornual angle greater than 105 degrees typifies a bicornuate uterus, whereas one less than 75 degrees indicates a septate uterus. Fundal contour also assists, and a straight line drawn between the imaged tubal ostia serves as the defining threshold. Referent to this, an intrafundal downward cleft measuring ≥1 cm or more is indicative of bicornuate uterus. A septate uterus shows a cleft depth <1 cm, or it may have a normal fundal contour.

Bicornuate uterus carries increased risks for adverse obstetrical outcomes that include miscarriage, preterm birth, and malpresentation. As discussed in the prior section, rare surgical correction by metroplasty is reserved for highly selected patients.

Septate Uterus (Class V)

With this anomaly, a resorption defect leads to a persistent complete or partial longitudinal uterine septum (see Fig. 3-5). Less often, a complete vaginocervicouterine septum is found (Ludwin, 2013). Many septate uteri are identified during evaluation of infertility or recurrent pregnancy loss. Although an abnormality may be identified with HSG or 2-D TVS, typically 3-D TVS or MR imaging is required to differentiate this from a bicornuate uterus (see Fig. 3-6).

Septate anomalies are associated with diminished fertility and increased risks for adverse pregnancy outcomes that include miscarriage, preterm delivery, and malpresentation (Chan, 2011a; Ghi, 2012). Hysteroscopic septal resection has been shown to improve pregnancy rates and outcomes (Mollo, 2009; Pabuçcu, 2004). From their metaanalysis, Valle and colleagues (2013) reported a 63-percent pregnancy rate and 50-percent live birth rate following resection.

Arcuate Uterus (Class VI)

This malformation is a mild deviation from the normally developed uterus. Although some studies report no increased adverse associated outcomes, others have found excessive second-trimester losses, preterm labor, and malpresentation (Chan, 2011a; Mucowski, 2010; Woelfer, 2001).

Treatment with Cerclage

Some women with uterine anomalies and repetitive pregnancy losses may benefit from transvaginal or transabdominal cervical cerclage (Golan, 1992; Groom, 2004). Others with partial cervical atresia or hypoplasia may also benefit (Hampton, 1990; Ludmir, 1991). Candidacy for cerclage is determined by the same criteria used for women without such defects, which is discussed in Chapter 18 (Management).

Diethylstilbestrol Reproductive Tract Abnormalities (Class VII)

During the 1960s, a synthetic nonsteroidal estrogen—diethylstilbestrol (DES)—was used to treat pregnant women for threatened abortion, preterm labor, preeclampsia, and diabetes. The treatment was remarkably ineffective. Later, it was also discovered that women exposed as fetuses had increased risks of developing several specific reproductive-tract abnormalities. These included vaginal clear cell adenocarcinoma, cervical intraepithelial neoplasia, small-cell cervical carcinoma, and vaginal adenosis. Affected women had identifiable structural variations in the cervix and vagina that include transverse septa, circumferential ridges, and cervical collars. Uteri potentially had smaller cavities, shortened upper uterine segments, or T-shaped and other irregular cavities (see Fig. 3-5) (Kaufman, 1984).

These women suffer impaired conception rates and higher rates of miscarriage, ectopic pregnancy, and preterm delivery, especially in those with structural abnormalities (Kaufman, 2000; Palmer, 2001). Now, more than 50 years after DES use was proscribed, most affected women are past childbearing age, but higher rates of earlier menopause, cervical intraepithelial neoplasia, and breast cancer are reported in exposed women (Hatch, 2006; Hoover, 2011; Troisi, 2016).

Fallopian Tube Abnormalities

The fallopian tubes develop from the unpaired distal ends of the müllerian ducts. Congenital anomalies include accessory ostia, complete or segmental tubal agenesis, and several embryonic cystic remnants. The most common is a small, benign cyst attached by a pedicle to the distal end of

the fallopian tube—the hydatid of Morgagni. In other cases, benign paratubal cysts may be of mesonephric or mesothelial origin. Last, in utero exposure to DES is associated with various tubal abnormalities. Of these, short, tortuous tubes or ones with shriveled fimbria and small ostia are linked to infertility (DeCherney, 1981).

UTERINE FLEXION

The pregnant uterus may infrequently show exaggerated flexion. Mild or moderate flexion is typically inconsequential, but congenital or acquired extremes may lead to pregnancy complications.

Anteflexion describes forward angling of the uterine fundus in the sagittal plane relative to the cervix. Exaggerated degrees usually pose no problem in early pregnancy. Later, however, particularly when the abdominal wall is lax such as with diastasis recti or ventral hernia, the uterus may fall forward. In extreme cases, the fundus lies below the lower margin of the symphysis. Sometimes, this abnormal uterine position prevents proper transmission of labor contractions, but this is usually overcome by repositioning and application of an abdominal binder.

Retroflexion describes posterior uterine fundal angling in the sagittal plane. A growing retroflexed uterus will occasionally become incarcerated in the hollow of the sacrum. Symptoms include abdominal discomfort, pelvic pressure, and voiding dysfunction or retention. During bimanual pelvic examination, the cervix will be anterior and behind the symphysis pubis, whereas the uterus is appreciated as a mass wedged in the pelvis. Sonography or MR imaging can aid the clinical diagnosis (Gardner, 2013; Grossenburg, 2011; van Beekhuizen, 2003).

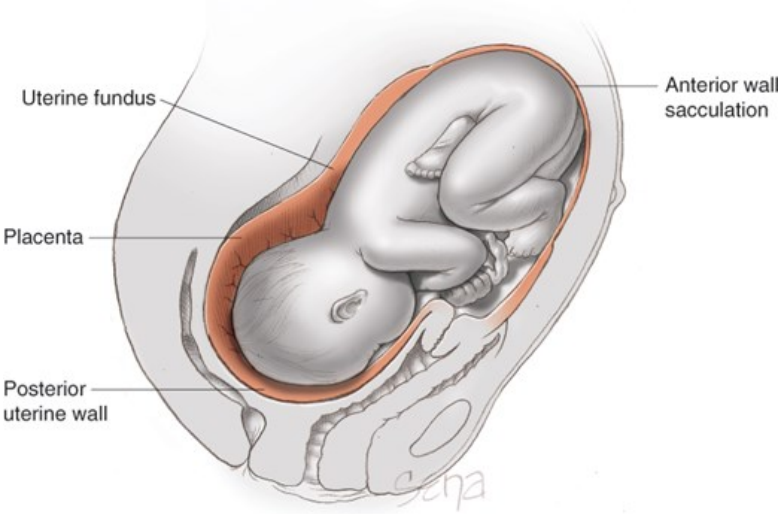
With continued uterine growth, the incarcerated uterus can spontaneously resolve over 1 to 2 weeks. An indwelling urinary catheter or intermittent self-catheterization may be needed in the interim to empty the bladder. Persistent cases require manual repositioning. For this, after bladder catheterization, the uterus can usually be pushed out of the pelvis when the woman is placed in a knee-chest position. Often, this is best accomplished by digital pressure applied through the rectum. Conscious sedation, spinal analgesia, or general anesthesia may be necessary. Following repositioning, the catheter is left in place until bladder tone returns. Insertion of a soft pessary for a few weeks usually prevents recurrent incarceration.

Lettieri and colleagues (1994) described seven cases of uterine incarceration not amenable to these simple procedures. In two women, laparoscopy was used at 14 weeks' gestation to reposition the uterus using the round ligaments for traction. Alternatively, in case series, advancing a colonoscope or colonoscopic insufflation was used to dislodge an incarcerated uterus (Dierickx, 2011; Newell, 2014; Seubert, 1999).

Rarely, *sacculation* may form as extensive lower uterine segment dilatation due to persistent entrapment of the pregnant uterus in the pelvis (Fig. 3-7). In these extreme cases, sonography and MR imaging are typically required to define anatomy (Gottschalk, 2008; Lee, 2008). Cesarean delivery is necessary when sacculation is marked, and Spearing (1978) stressed the importance of clarifying the distorted anatomy. An elongated vagina passing above the level of a fetal head that is deeply placed into the pelvis suggests a sacculation or an abdominal pregnancy. The Foley catheter is frequently palpated above the level of the umbilicus! Spearing (1978) recommended extending the abdominal incision above the umbilicus and delivering the entire uterus from the abdomen before hysterotomy. This will restore correct anatomical relationships and prevent inadvertent incisions into and through the vagina and bladder. Unfortunately, this may not always be possible (Singh, 2007). As a final caveat, a true uterine diverticulum has been mistaken for uterine sacculation (Rajiah, 2009).

FIGURE 3-7

Anterior sacculation of a pregnant uterus. Note the markedly attenuated anterior uterine wall and atypical location of the true uterine fundus.



Source: F. Gary Cunningham, Kenneth J. Leveno, Steven L. Bloom, Catherine Y. Spong, Jodi S. Dashe, Barbara L. Hoffman, Brian M. Casey, Jeanne S. Sheffield: *Williams Obstetrics*, 25th Edition

The uterus commonly rotates to the maternal right during pregnancy. Rarely, uterine rotation exceeds 180 degrees to cause torsion. Most cases of torsion result from uterine leiomyomas, müllerian anomalies, fetal malpresentation, pelvic adhesions, or laxity of the abdominal wall or uterine ligaments. Jensen (1992) reviewed 212 cases and reported that associated symptoms may include obstructed labor, intestinal or urinary complaints, abdominal pain, uterine hypertonus, vaginal bleeding, and hypotension.

Most cases of uterine torsion are found at the time of cesarean delivery. In some women, torsion can be confirmed preoperatively with MR imaging, which shows a twisted vagina that appears X-shaped rather than its normal H-shape (Nicholson, 1995). As with uterine incarceration, during cesarean delivery, a severely displaced uterus should be repositioned anatomically before hysterotomy. In some cases, an inability to reposition or a failure to recognize the torsion may lead to a posterior hysterotomy incision (Albayrak, 2011; Picone, 2006; Rood, 2014).

REFERENCES

Acién P, Acién MI: The history of female genital tract malformation classifications and proposal of an updated system. Hum Reprod Update 17:693, 2011 [PubMed: 21727142]

Aksglaede L, Juul A: Testicular function and fertility in men and Klinefelter syndrome: a review. Eur J Endocrinol 168(4):R67, 2013 [PubMed: 23504510]

Albayrak M, Benian A, Ozdemir I, et al: Deliberate posterior low transverse incision at cesarean section of a gravid uterus in 180 degrees of torsion: a case report. J Reprod Med 56(3–4):181, 2011 [PubMed: 21542541]

Alborzi S, Asefjah H, Amini M, et al: Laparoscopic metroplasty in bicornuate and didelphic uteri: feasibility and outcome. Arch Gynecol Obstet 291(5):1167, 2015 [PubMed: 25373708]

Allen JW, Cardall S, Kittijarukhajorn M, et al: Incidence of ovarian maldescent in women with mullerian duct anomalies: evaluation by MRI. AJR 198(4):W381, 2012 [PubMed: 22451577]

American College of Obstetricians and Gynecologists: Müllerian agenesis: diagnosis, management, and treatment. Committee Opinion No. 562, May 2013, Reaffirmed 2016

American Fertility Society: The American Fertility Society classifications of adnexal adhesions, distal tubal occlusion, tubal occlusion secondary to tubal ligation, tubal pregnancies, Müllerian anomalies and intrauterine adhesions. Fertil Steril 49:944, 1988 [PubMed: 3371491]

Auchus RJ: Management considerations for the adult with congenital adrenal hyperplasia. Mol Cell Endocrinol 408:190, 2015 [PubMed: 25643980]

Bermejo C, Martinez, Ten P, et al: Three-dimensional ultrasound in the diagnosis of müllerian duct anomalies and concordance with magnetic resonance imaging. Ultrasound Obstet Gynecol 35: 593, 2010 [PubMed: 20052665]

Blanton EN, Rouse DJ: Trial of labor in women with transverse vaginal septa. Obstet Gynecol 101:1110, 2003 [PubMed: 12738119]

Bradshaw KD: Anatomical disorders. In Hoffman BL, Schorge JO, Bradshaw KD, et al (eds): Williams Gynecology, 3rd ed. New York, McGraw-Hill Education, 2016

Byrne J, Nussbaum-Blask A, Taylor WS, et al: Prevalence of Müllerian duct anomalies detected at ultrasound. Am J Med Genet 94(1):9, 2000 [PubMed: 10982475]

Calogero AE, Giagulli VA, Mongioì LM, et al: Klinefelter syndrome: cardiovascular abnormalities and metabolic disorders. J Endocrinol Invest 40(7):705, 2017 [PubMed: 28258556]

Chan YY, Jayaprakasan K, Tan A, et al: Reproductive outcomes in women with congenital uterine anomalies: a systematic review. Ultrasound Obstet Gynecol 38(4):371, 2011a

Chan YY, Jayaprakasan K, Zamora J, et al: The prevalence of congenital uterine anomalies in unselected and high-risk populations: a systematic review. Hum Reprod Update 17(6):761, 2011b

Dabirashrafi H, Mohammad K, Moghadami-Tabrizi N: Ovarian malposition in women with uterine anomalies. Obstet Gynecol 83:293, 1994 [PubMed: 8290197]

Deans R, Banks F, Liao LM, et al: Reproductive outcomes in women with classic bladder exstrophy: an observational cross-sectional study. Am J Obstet Gynecol 206(6):496.e1, 2012

DeCherney AH, Cholst I, Naftolin F: Structure and function of the fallopian tubes following exposure to diethylstilbestrol (DES) during gestation. Fertil Steril 36(6):741, 1981 [PubMed: 7308519]

Deutch TD, Abuhamad AZ: The role of 3-dimensional ultrasonography and magnetic resonance imaging in the diagnosis of müllerian duct anomalies: a review of the literature. J Ultrasound Med 27(3):413, 2008 [PubMed: 18314520]

Dierickx I, Van Holsbeke C, Mesens T, et al: Colonoscopy-assisted reposition of the incarcerated uterus in mid-pregnancy: a report of four cases and a literature review. Eur J Obstet Gynecol Reprod Biol 158(2):153, 2011 [PubMed: 21741751]

Di Spiezio Sardo A, Campo R, Gordts S, et al: The comprehensiveness of the ESHRE/ESGE classification of female genital tract congenital anomalies: a systematic review of cases not classified by the AFS system. Hum Reprod 30(5):104, 2015

Donderwinkel PF, Dörr JP, Willemsen WN: The unicornuate uterus: clinical implications. Eur J Obstet Gynecol Reprod Biol 47(2):135, 1992 [PubMed: 1459327]

Dove CK, Harvey SM, Spalluto LB: Sonographic findings of early pregnancy in the rudimentary horn of a unicornuate uterus: a two case report. Clin Imaging 47:25, 2017 [PubMed: 28823603]

Dreisler E, Stampe Sørensen S: Müllerian duct anomalies diagnosed by saline contrast sonohysterography: prevalence in a general population. Fertil Steril 102(2):525, 2014 [PubMed: 24875399]

Dy GW, Willihnganz-Lawson KH, Shnorhavorian M, et al: Successful pregnancy in patients with exstrophy-epispadias complex: a University of Washington experience. J Pediatr Urol 11(4):213.e1, 2015

Edelman AB, Jensen JT, Lee DM, et al: Successful medical abortion of a pregnancy within a noncommunicating rudimentary uterine horn. Am J Obstet Gynecol 189:886, 2003 [PubMed: 14526337]

Eswara JR, Kielb S, Koyle MA, et al: The recommendations of the 2015 American Urological Association Working Group on Genitourinary Congenitalism. Urology 88:1, 2016 [PubMed: 26627372]

Fedele L, Bianchi S, Agnoli B, et al: Urinary tract anomalies associated with unicornuate uterus. J Urol 155:847, 1996 [PubMed: 8583590]

Fedele L, Bianchi S, Zanconato G, et al: Laparoscopic removal of the cavitated noncommunicating rudimentary uterine horn: surgical aspects in 10 cases. Fertil Steril 83(2):432, 2005 [PubMed: 15705386]

Friedler S, Grin L, Liberti G, et al: The reproductive potential of patients with Mayer-Rokitansky-Küster-Hauser syndrome using gestational surrogacy: a systematic review. Reprod Biomed Online 32(1):54, 2016 [PubMed: 26626805]

Gardner CS, Jaffe TA, Hertzberg BS, et al: The incarcerated uterus: a review of MRI and ultrasound imaging appearances. AJR Am J Roentgenol 201(1):223, 2013 [PubMed: 23789679]

Ghi T, De Musso F, Maroni E, et al: The pregnancy outcome in women with incidental diagnosis of septate uterus at first trimester scan. Hum Reprod 27(9):267, 2012

Golan A, Langer R, Neuman M, et al: Obstetric outcome in women with congenital uterine malformations. J Reprod Med 37:233, 1992 [PubMed: 1564709]

Gottschalk EM, Siedentopf JP, Schoenborn I, et al: Prenatal sonographic and MRI findings in a pregnancy complicated by uterine sacculation: case report and review of the literature. Ultrasound Obstet Gynecol 32(4):582, 2008 [PubMed: 18677703]

Graupera B, Pascual MA, Hereter L, et al: Accuracy of three-dimensional ultrasound compared with magnetic resonance imaging in diagnosis of müllerian duct anomalies using ESHRE-ESGE consensus on the classification of congenital anomalies of the female genital tract. Ultrasound Obstet Gynecol 46(5):616, 2015 [PubMed: 25690307]

Greaves R, Hunt RW, Zacharin M: Transient anomalies in genital appearance in some extremely preterm female infants may be the result of foetal programming causing a surge in LH and the over activation of the pituitary-gonadal axis. Clin Endocrinol (Oxf) 69(5):76, 2008

Greenwell TJ, Venn SN, Creighton SM, et al: Pregnancy after lower urinary tract reconstruction for congenital abnormalities. BJU Int 92:773, 2003 [PubMed: 14616465]

Grimbizis GF, Camus M, Tarlatzis BC, et al: Clinical implications of uterine malformations and hysteroscopic treatment results. Hum Reprod Update 7(2):161, 2001 [PubMed: 11284660]

Grimbizis GF, Di Spiezio Sardo A, Saravelos SH, et al: The Thessaloniki ESHRE/ESGE consensus on diagnosis of female genital anomalies. Hum Reprod 31(1):2, 2016 [PubMed: 26537921]

Groom KM, Jones BA, Edmonds DK, et al: Preconception transabdominal cervicoisthmic cerclage. Am J Obstet Gynecol 191(1):230, 2004 [PubMed: 15295371]

Grossenburg NJ, Delaney AA, Berg TG: Treatment of a late second-trimester incarcerated uterus using ultrasound-guided manual reduction. Obstet Gynecol 118(2 Pt 2):436, 2011 [PubMed: 21768846]

Haddad B, Louis-Sylvestre C, Poitout P, et al: Longitudinal vaginal septum: a retrospective study of 202 cases. Eur J Obstet Gynecol Reprod Biol 74(2):197, 1997 [PubMed: 9306118]

Hall-Craggs MA, Kirkham A, Creighton SM: Renal and urological abnormalities occurring with müllerian anomalies. J Pediatr Urol 9(1):27, 2013 [PubMed: 22129802]

Hampton HL, Meeks GR, Bates GW, et al: Pregnancy after successful vaginoplasty and cervical stenting for partial atresia of the cervix. Obstet Gynecol 76:900, 1990 [PubMed: 2216250]

Hatch EE, Troisi R, Wise LA, et al: Age at natural menopause in women exposed to diethylstilbestrol in utero. Am J Epidemiol 164:682, 2006 [PubMed: 16887893]

Helszer Z, Dmochowska A, Szemraj J, et al: A novel mutation (c. 341A>G) in the SRY gene in a 46,XY female patient with gonadal dysgenesis. Gene 526(2):467, 2013 [PubMed: 23624391]

Hoover RN, Hyer M, Pfeiffer RM, et al: Adverse health outcomes in women exposed in utero to diethylstilbestrol. N Engl J Med 365:1304, 2011 [PubMed: 21991952]

Hua M, Odibo AO, Longman RE, et al: Congenital uterine anomalies and adverse pregnancy outcomes. Am J Obstet Gynecol 205(6):558.e1, 2011

Hughes IA, Houk C, Ahmed SF, et al: Consensus statement on management of intersex disorders. J Pediatr Urol 2:148, 2006 [PubMed: 18947601]

Hutson JM, Grover SR, O'Connell M, et al: Malformation syndromes associated with disorders of sex development. Nat Rev Endocrinol 10(8):476, 2014 [PubMed: 24913517]

Jensen JG: Uterine torsion in pregnancy. Acta Obstet Gynecol Scand 71:260, 1992 [PubMed: 1322618]

Jiang JF, Xue W, Deng Y, et al: Gonadal malignancy in 202 female patients with disorders of sex development containing Y-chromosome material. Gynecol Endocrinol 32(4):338, 2016 [PubMed: 26608236]

Johal NS, Bogris S, Mushtaq I: Neonatal imperforate hymen causing obstruction of the urinary tract. Urology 73(4):750, 2009 [PubMed: 19118883]

Johannesson L, Järvholm S: Uterus transplantation: current progress and future prospects. Int J Womens Health 8:43, 2016 [PubMed: 26917976]

Jones ME, Boon WC, McInnes K, et al: Recognizing rare disorders: aromatase deficiency. Nat Clin Pract Endocrinol Metab 3(5):414, 2007 [PubMed: 17452968]

Kaufman RH, Adam E, Hatch EE, et al: Continued follow-up of pregnancy outcomes in diethylstilbestrol-exposed offspring. Obstet Gynecol 96(4):483, 2000 [PubMed: 11004345]

Kaufman RH, Noller K, Adam E, et al: Upper genital tract abnormalities and pregnancy outcome in diethylstilbestrol exposed progeny. Am J Obstet Gynecol 148: 973, 1984 [PubMed: 6711635]

Kenney PJ, Spirt BA, Leeson MD: Genitourinary anomalies: radiologic-anatomic correlations. Radiographics 4(2):233, 1984

Khati NJ, Frazier AA, Brindle KA: The unicornuate uterus and its variants: clinical presentation, imaging findings, and associated complications. J Ultrasound Med 31(2):319, 2012 [PubMed: 22298877]

Kriplani A, Kachhawa G, Awasthi D, et al: Laparoscopic-assisted uterovaginal anastomosis in congenital atresia of uterine cervix: follow-up study. J Minim Invasive Gynecol 19(4):477, 2012 [PubMed: 22748953]

Kumar N, Tayade S: Successful pregnancy outcome in an untreated case of concomitant transverse complete vaginal septum with unicornuate uterus. J Hum Reprod Sci 7(4):27, 2014

Lee SW, Kim MY, Yang JH, et al: Sonographic findings of uterine sacculation during pregnancy. Ultrasound Obstet Gynecol 32(4):595, 2008 [PubMed: 18726934]

Lettieri L, Rodis JF, McLean DA, et al: Incarceration of the gravid uterus. Obstet Gynecol Surv 49:642, 1994 [PubMed: 7991232]

Ludmir J, Jackson GM, Samuels P: Transvaginal cerclage under ultrasound guidance in cases of severe cervical hypoplasia. Obstet Gynecol 78:1067, 1991 [PubMed: 1945209]

Ludwin A, Ludwin I, Pityński K, et al: Differentiating between a double cervix or cervical duplication and a complete septate uterus with longitudinal vaginal septum. Taiwan J Obstet Gynecol 52(2):308, 2013 [PubMed: 23915875]

Matthews D, Bath L, Högler W, et al: Hormone supplementation for pubertal induction in girls. Arch Dis Child 102(10):975, 2017 [PubMed: 28446424]

McCann-Crosby B, Chen MJ, et al: Non-classical congenital adrenal hyperplasia: targets of treatment and transition. Pediatr Endocrinol Rev 12(2):224, 2014 [PubMed: 25581988]

McCann-Crosby B, Sutton VR: Disorders of sexual development. Clin Perinatol 42(2):395, 2015 [PubMed: 26042911]

Miller WL, Auchus RJ: The molecular biology, biochemistry, and physiology of human steroidogenesis and its disorders. Endocr Rev 32(1):81, 2011 [PubMed: 21051590]

Mollo A, De Franciscis P, Colacurci N, et al: Hysteroscopic resection of the septum improves the pregnancy rate of women with unexplained infertility: a prospective controlled trial. Fertil Steril 91(6):2628, 2009 [PubMed: 18571168]

Moore KL, Persaud TV, Torchia MG: The urogenital system. In The Developing Human. Philadelphia, Saunders, 2013, p 272

Mucowski SJ, Herndon CN, Rosen MP: The arcuate uterine anomaly: a critical appraisal of its diagnostic and clinical relevance. Obstet Gynecol Surv 65(7):449, 2010 [PubMed: 20723266]

Murphy C, Allen L, Jamieson MA: Ambiguous genitalia in the newborn: an overview and teaching tool. J Pediatr Adolesc Gynecol 24:236, 2011 [PubMed: 21872773]

Nahum G, Stanislaw H, McMahon C: Preventing ectopic pregnancies: how often does transperitoneal transmigration of sperm occur in effecting human pregnancy? BJOG 111:706, 2004 [PubMed: 15198762]

Nahum GG: Rudimentary uterine horn pregnancy: the 20th-century worldwide experience of 588 cases. J Reprod Med 47:151, 2002 [PubMed: 11883355]

Newell SD, Crofts JF, Grant SR: The incarcerated gravid uterus: complications and lessons learned. Obstet Gynecol 123(2 Pt 2 Suppl (2 Pt 2 Suppl 2)):423, 2014 [PubMed: 24413243]

Nicholson WK, Coulson CC, McCoy MC, et al: Pelvic magnetic resonance imaging in the evaluation of uterine torsion. Obstet Gynecol 85(5 Pt 2):888, 1995 [PubMed: 7724150]

Nielsen J, Wohlert M: Sex chromosome abnormalities found among 34,910 newborn children: results from a 13-year incidence study in Arhus, Denmark. Birth Defects Orig Artic Ser 26:209, 1990 [PubMed: 2090319]

Nistal M, Paniagua R, González-Peramato P, et al: Perspectives in pediatric pathology, chapter 1. normal development of testicular structures: from the bipotential gonad to the fetal testis. Pediatr Dev Pathol 18(2):88, 2015a

Nistal M, Paniagua R, González-Peramato P, et al: Perspectives in pediatric pathology, chapter 5. gonadal dysgenesis. Pediatr Dev Pathol 18(4):259,

2015b

Ocal G: Current concepts in disorders of sexual development. J Clin Res Pediatr Endocrinol 3(3):105, 2011 [PubMed: 21911322]

Oppelt P, Renner SP, Brucker S, et al The VCUAM (Vagina Cervix Uterus Adnex-associated Malformation) Classification: a new classification for genital malformations. Fertil Steril 84:1493, 2005 [PubMed: 16275249]

Pabuçcu R, Gomel V: Reproductive outcome after hysteroscopic metroplasty in women with septate uterus and otherwise unexplained infertility. Fertil Steril 81:1675, 2004 [PubMed: 15193494]

Pados G, Tsolakidis D, Athanatos D, et al: Reproductive and obstetric outcome after laparoscopic excision of functional, non-communicating broadly attached rudimentary horn: a case series. Eur J Obstet Gynecol Reprod Biol 182:33, 2014 [PubMed: 25218549]

Palmer JR, Hatch EE, Rao RS, et al: Infertility among women exposed prenatally to diethylstilbestrol. Am J Epidemiol 154:316, 2001 [PubMed: 11495854]

Pellerito JS, McCarthy SM, Doyle MB, et al: Diagnosis of uterine anomalies: relative accuracy of MR imaging, endovaginal sonography, and hysterosalpingography. Radiology 183:795, 1992 [PubMed: 1584936]

Picone O, Fubini A, Doumerc S, et al: Cesarean delivery by posterior hysterotomy due to torsion of the pregnant uterus. Obstet Gynecol 107(2 Pt 2):533, 2006 [PubMed: 16449177]

Puscheck EE, Cohen L: Congenital malformations of the uterus: the role of ultrasound. Semin Reprod Med 26(3):223, 2008 [PubMed: 18504697]

Rackow BW, Arici A: Reproductive performance of women with müllerian anomalies. Curr Opin Obstet Gynecol 19(3):229, 2007 [PubMed: 17495638]

Rajiah P, Eastwood KL, Gunn ML, et al: Uterine diverticulum. Obstet Gynecol 113(2 Pt 2):525, 2009 [PubMed: 19155944]

Rall K, Eisenbeis S, Henninger V: Typical and atypical associated findings in a group of 346 patients with Mayer-Rokitansky-Kuester-Hauser syndrome. J Pediatr Adolesc Gynecol 28(5):362, 2015 [PubMed: 26148785]

Reichman D, Laufer MR: Congenital uterine anomalies affecting reproduction. Best Pract Res Clin Obstet Gynaecol 24(2):193, 2010 [PubMed: 19897423]

Reichman D, Laufer MR, Robinson BK: Pregnancy outcomes in unicornuate uteri: a review. Fertil Steril 91(5): 1886, 2009 [PubMed: 18439594]

Roberts CP, Rock JA: Surgical methods in the treatment of congenital anomalies of the uterine cervix. Curr Opin Obstet Gynecol 23(4):251, 2011 [PubMed: 21666471]

Rock JA, Roberts CP, Jones HW Jr: Congenital anomalies of the uterine cervix: lessons from 30 cases managed clinically by a common protocol. Fertil Steril 94(5):1858, 2010 [PubMed: 19939371]

Rolen AC, Choquette AJ, Semmens JP: Rudimentary uterine horn: obstetric and gynecologic implications. Obstet Gynecol 27:806, 1966 [PubMed: 5935433]

Rood K, Markham KB: Torsion of a term gravid uterus: a possible cause of intrauterine growth restriction and abnormal umbilical artery Doppler findings. J Ultrasound Med 33(10):1873, 2014 [PubMed: 25253837]

Saravelos SH, Cocksedge KA, Li TC: Prevalence and diagnosis of congenital uterine anomalies in women with reproductive failure: a critical appraisal. Hum Reprod Update 14(5):415, 2008 [PubMed: 18539641]

Seubert DE, Puder KS, Goldmeier P, et al: Colonoscopic release of the incarcerated gravid uterus. Obstet Gynecol 94:792, 1999 [PubMed: 10546731]

Singh MN, Payappagoudar J, Lo J: Incarcerated retroverted uterus in the third trimester complicated by postpartum pulmonary embolism. Obstet Gynecol 109:498, 2007 [PubMed: 17267872]

Spearing GJ: Uterine sacculation. Obstet Gynecol 51:11S, 1978 [PubMed: 618466]

Speiser PW, Azziz R, Baskin LS, et al: Congenital adrenal hyperplasia due to steroid 21-hydroxylase deficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 95(9):4133, 2010 [PubMed: 20823466]

Tong J, Zhu L, Lang J: Clinical characteristics of 70 patients with Herlyn-Werner-Wunderlich syndrome. Int J Gynaecol Obstet 121(2):173, 2013 [PubMed: 23465857]

Troisi R, Hatch EE, Palmer JR, et al: Prenatal diethylstilbestrol exposure and high-grade squamous cell neoplasia of the lower genital tract. Am J Obstet Gynecol 215(3):322.e1, 2016

Valle RF, Ekpo GE: Hysteroscopic metroplasty for the septate uterus: review and meta-analysis. J Minim Invasive Gynecol 20(1):22, 2013 [PubMed: 23312243]

Van Beekhuizen HJ, Bodewes HW, Tepe EM, et al: Role of magnetic resonance imaging in the diagnosis of incarceration of the gravid uterus. Obstet Gynecol 102:1134, 2003 [PubMed: 14607032]

Williams CE, Nakhal RS, Hall-Craggs MA, et al: Transverse vaginal septae: management and long-term outcomes. BJOG 121(13):1653, 2014 [PubMed: 24942132]

Woelfer B, Salim R, Banerjee S, et al: Reproductive outcomes in women with congenital uterine anomalies detected by three-dimensional ultrasound screening. Obstet Gynecol 98:1099, 2001 [PubMed: 11755560]

Worley KC, Hnat MD, Cunningham FG: Advanced extrauterine pregnancy: diagnostic and therapeutic challenges. Am J Obstet Gynecol 198:287.e1, 2008

Wu QY, Li N, Li WW, et al: Clinical, molecular and cytogenetic analysis of 46,XX testicular disorder of sex development with *SRY*-positive. BMC Urol 14:70, 2014 [PubMed: 25169080]