Imaging of Gynecological Disorders in Infants and Children

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Gurdeep S. Mann, Joanne C. Blair, Anne S. Garden

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Embryology of the Female Reproductive Tract

Andrew Healey

Contents

1 Introduction 21

2 Embryology of the Female Genitourinary Tract 22

2.1 Development of the Gonads 22

2.2 Relationship Between the Early Fetal Genital and Urinary Systems 25

2.3 Development of the Fallopian Tubes Uterus, Cervix and Vagina 26

2.4 Development of the Lower Genital Tract 28

2.5 Development of the External Genitalia 28

2.6 Development of the Female Genital Accessory Glands 30

2.7 Embryological Vestigial Structures (Wollfian Vestiges) 30

3 Conclusion 30

References 30

Abstract

The development of the normal female reproductive tract is a complex process. The indifferent gonad differentiates to the ovary. The mesonephros, Wolffian and Müllerian ducts differentiate in an orchestrated manner to form the uterus, vagina and lower urinary tract. Disordered differentiation can result in congenital abnormalities affecting the female reproductive tracts, renal tract and lower intestines. A number of rudimentary structures can persist and be encountered in clinical practice, most commonly these are derived from the Wolffian ducts. This chapter provides an overview of the embryology of the female genital tract relevant to the multidisciplinary team caring for young females presenting with illnesses related to the reproductive system.

Abbreviations

AMH Anti-Müllerian hormone
UGS Urogenital sinus

1 Introduction

The development of the human reproductive tract, urinary system and distal gastrointestinal tract is intertwined sharing a close temporal and spatial relationship. Knowledge of the normal development and anatomy of the gynaecological tract is critical to the understanding of the timing and nature of a variety of paediatric gynaecological conditions. Malformations of the gynaecological tract are associated with

A. Healey (✉)
Department of Paediatric Radiology, Alder Hey NHS Foundation Trust, Liverpool, L12 2AP, UK
e-mail: andrew.healey@alderhey.nhs.uk

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disorders of the renal tract and lower intestines. Rudimentary structures from the immature genitourinary tract may persist and be encountered in clinical practice particularly those from the mesonephric (Wolffian) ducts.

This chapter provides an overview of the embryology of the female genital tract relevant to the multidisciplinary team caring for young females presenting with illnesses related to the reproductive system.

Table 1 Summary of key phases of fetal genital tract development

Phase of genital development	Time (weeks of gestation)
Indifferent gonadal phase	4–6
Gonadal differentiation	7
Ductal differentiation	9–11
External genitalia differentiation	10–12

2 Embryology of the Female Genitourinary Tract

In females the genital organs comprise of gonads, reproductive ducts and external genitalia. Gonadal differentiation occurs before the end of the embryonic period. Both the reproductive ducts and external genitalia differentiate before the end of the first trimester. Development of the female genital tract continues in utero. The gonads descend in utero in girls. The main events critical to the in utero development of the female gynaecological tract are summarised in Table 1. Maturation of the genital tract is continuous during childhood through to puberty. The postnatal development of the reproductive tract is discussed in Normal Pubertal Development and Growth.

2.1 Development of the Gonads

2.1.1 Indifferent Gonadal Phase

The gonads develop from primitive germ cells, the mesothelium of the posterior abdominal wall and adjacent mesenchyme. Gonadal development begins in the fifth fetal week. The mesothelium medial to the mesonephros of the developing kidneys thickens, yielding the paired gonadal (urogenital) ridges (Fig. 1a). Transient epithelial finger-like structures, referred to as the primary sex cords, form and extend into the supporting mesenchyme. The gonadal ridges remain similar in both male and female fetuses until the seventh week. The indifferent (undifferentiated) gonads are located inside the Wolffian body on the medial aspect of the urogenital ridge, either side of the spine.

The primitive or primordial germ cells are the precursors of oocytes or spermatozoa. The primitive germ cells are evident from around the fourth fetal week and migrate from the yolk sac of the embryo along the dorsal mesentery of the hindgut to the mesenchyme of the gonadal ridges by the sixth week and incorporate into the primary sex cords (Fig. 1b). The primary sex cords are not well developed in the female embryo but do extend to the medulla of the future ovary and form the rete ovarii, a transient structure. The primary sex cords regress by the eighth week.

The genotype and chromosomal sex of a fetus is determined at conception. The mammalian fetus begins life with an undifferentiated gonad referred to as the indifferent gonad. The indifferent gonad comprises an inner medulla and outer cortex. The cortex contains the precursors of the ovarian parenchyma and the medulla the ovarian stroma. The presence of primitive germ cells is critical to normal ovarian development. Absence of the primitive germ cells will yield sterile gonads lacking follicles which will contain only stroma.

2.1.2 Gonadal Sexual Differentiation

The fetus has bipotential sexual development for the first 3 months of life. The phenotype depends on the presence of sex chromosomes and the prevailing biochemical and hormonal milieu. The default sex phenotype is female in the presence of two X-chromosomes. Under the influence of two X-chromosomes the cortex of the indifferent gonad is much better developed in the female embryo than the male. The cortex gives rise to the secondary sex cords (cortical cords) which extend from the surface epithelium to the mesenchyme (Fig. 1c). The secondary sex cords sustain and regulate ovarian cortical follicular development. The undifferentiated gonads persist until around the tenth week, at which time the ovaries first become identifiable. A male fetus will

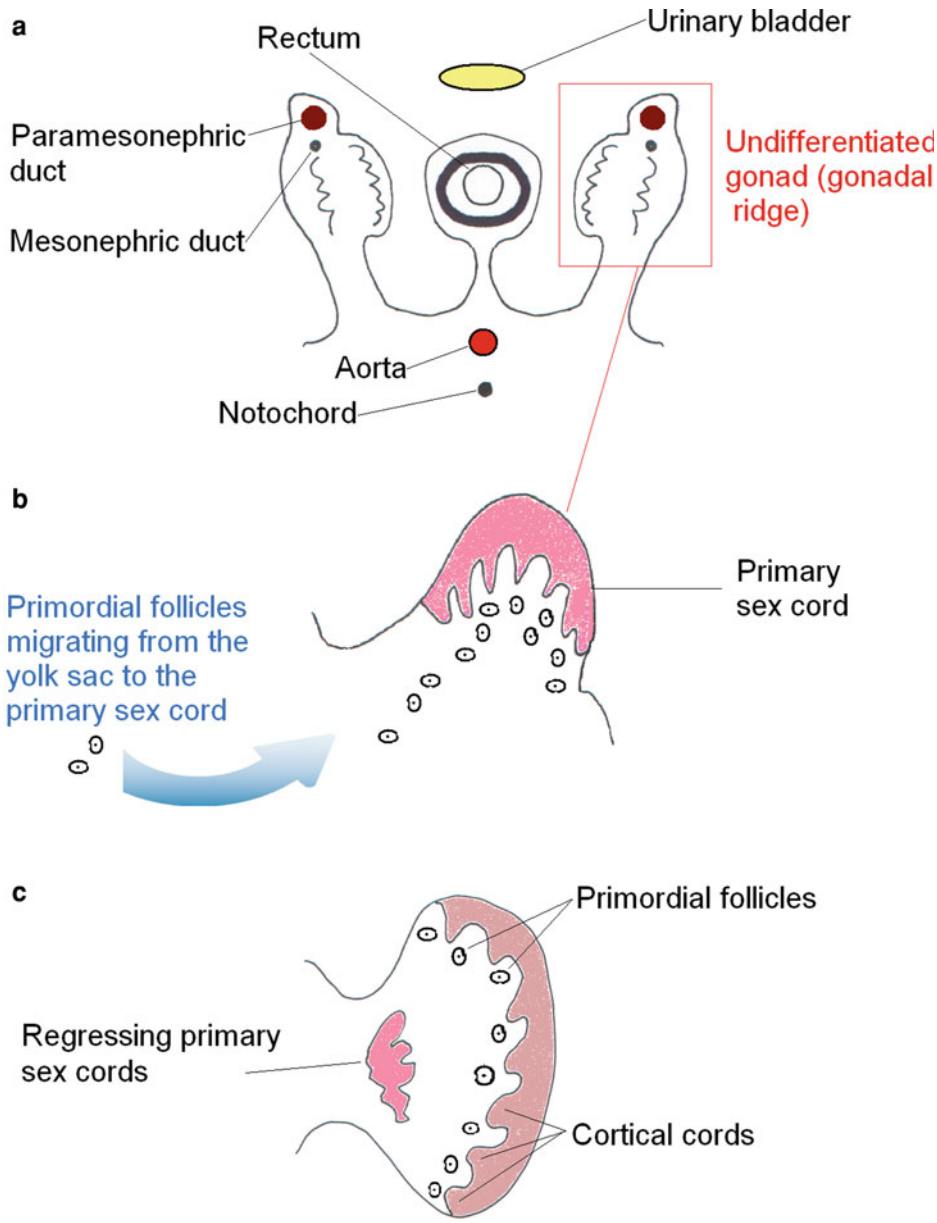


Fig. 1 Development of the ovaries from the undifferentiated (indifferent) gonads: **a** The indifferent gonads appear as primitive longitudinal streaks in the intermediate mesoderm adjacent to the mesonephros. **b** Magnified view of the undifferentiated gonad during 5–6 fetal weeks. The primordial follicles develop in the yolk sac and migrate to the gonadal ridge and are sustained by the primary sex cords. **c** The primary cords are transitory and regress by 8 weeks. The cortical (secondary cords) maintain ovarian follicular development. The ovaries are identifiable by 10 weeks.

develop in the presence of a Y-chromosome which encodes the SRY protein. The SRY protein enables testicular differentiation and the production of androgens including testosterone. The medulla of the indifferent gonad in males differentiates into the testis, the cortex involutes giving rise to vestigial remnants. In addition to the SRY protein and androgens a third factor is required for male development, anti-Müllerian hormone (AMH). AMH prevents female genital ductal differentiation. An immature female will develop in the absence of these three factors. Further maturation of the immature female is contingent upon

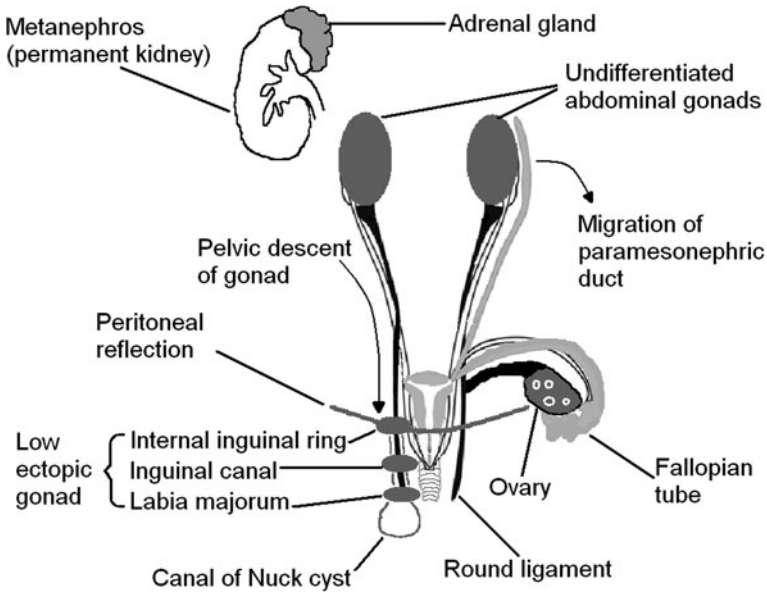


Fig. 2 Pelvic descent of the ovary. The fetal abdominal ovary usually descends into the pelvis as depicted (*left side* of pelvis) lying in close approximation to the fimbrial portion of the lateral aspect of the paramesonephric duct (future fallopian tube). Maldescent of the ovary occurs when the ovary lies above the pelvic brim. Rarely the ovary may be located in the inguinal canal or more inferiorly at the labium majorum (*right hand side* of pelvis). The canal of Nuck is a potential space which results from a patent evagination of the peritoneum to the labium majorum

the influence of oestrogens. Disorders of sexual differentiation are discussed further in Disorders of Sex Development.

2.1.3 Development of the Ovaries (Gonadal Differentiation)

As the cortical cords develop the primitive germ cells are incorporated in the mesenchyme of the ovaries. Gonadal differentiation takes place in the second month of fetal life. The primitive germ cells differentiate under the influence of placental gonadotropins. The germ cells migrating to the genital ridge undergo successive mitotic divisions whilst in contact with the coelomic epithelium differentiating into several million oogonia. By 4–5 fetal months, the primitive follicles organise within the fetal ovarian cortex. By 5–6 months gestation the ovaries contain 6–7 million primordial follicles. At this time, the primordial follicles are enveloped by a layer of epithelial cells, and are referred to as primary oocytes. The fate of an oocyte is determined once meiosis begins and no further mitotic division is possible thereafter. The vast majority of oocytes eventually degenerate over time; the remaining oogonia enter a dormant state referred to as meiotic arrest (first phase of meiosis). First meiosis will not complete until the onset of ovulation. Ovulatory follicles complete meiotic differentiation. At birth, between 2 and 4 million follicles remain. Around 400,000 follicles are present at menarche (Baker 1963). Ovarian follicles undergo varying rates of maturation and involution. The vast majority remain quiescent and eventually involute by apoptosis, but can remain dormant for decades.

2.1.4 Pelvic Descent of the Ovaries

As described previously, the indifferent gonads lie medial to the urogenital ridges at around the seventh fetal week. The ovaries in part undergo descent from the posterior abdominal wall into the pelvis due to the marked growth of the upper abdomen relative to the pelvis. By the third month the maturing ovaries descend into the pelvis guided by the gubernaculum into the ovarian fossae (Fig. 2). The gubernaculum is a peritoneal fold which attaches the caudal aspect of the ovary to the uterus, eventually forming the utero-ovarian (Fig. 3) and round uterine ligaments. Maldescent of the ovaries, although rare, may occur anywhere from the paraspinal posterior abdominal

wall to the pelvic brim. Ovarian maldescent results from a short mesovarium and infundibulopelvic ligament and elongation of the utero-ovarian (ovarian) ligament (Verkauf and Bernhisel 1996). On cross-sectional imaging the position of an ectopic ovary may be traced along the course of its vascular pedicle. The ovaries are classically thought to be located in the adnexae/ovarian fossae. A recent study has shown the typical location of the ovaries in girls from birth to 18 years to be found in the lateral aspect of the pelvis, close to the anterior superior iliac spines, just below the iliac crests and umbilicus, and above the pubic symphysis (Bardo et al. 2009). Supernumerary ovary is an extremely rare entity in which a third ovary complete with follicles arises from a separate primordium.

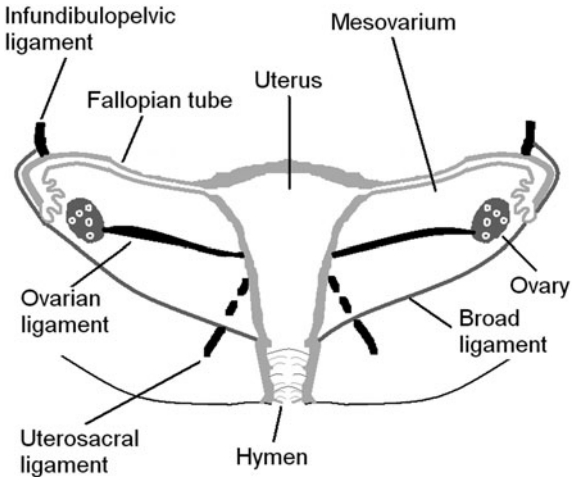


Fig. 3 The pelvic ligaments in the postnatal female

2.2 Relationship Between the Early Fetal Genital and Urinary Systems

A brief description of the embryology of the human kidneys is necessary in order to outline their

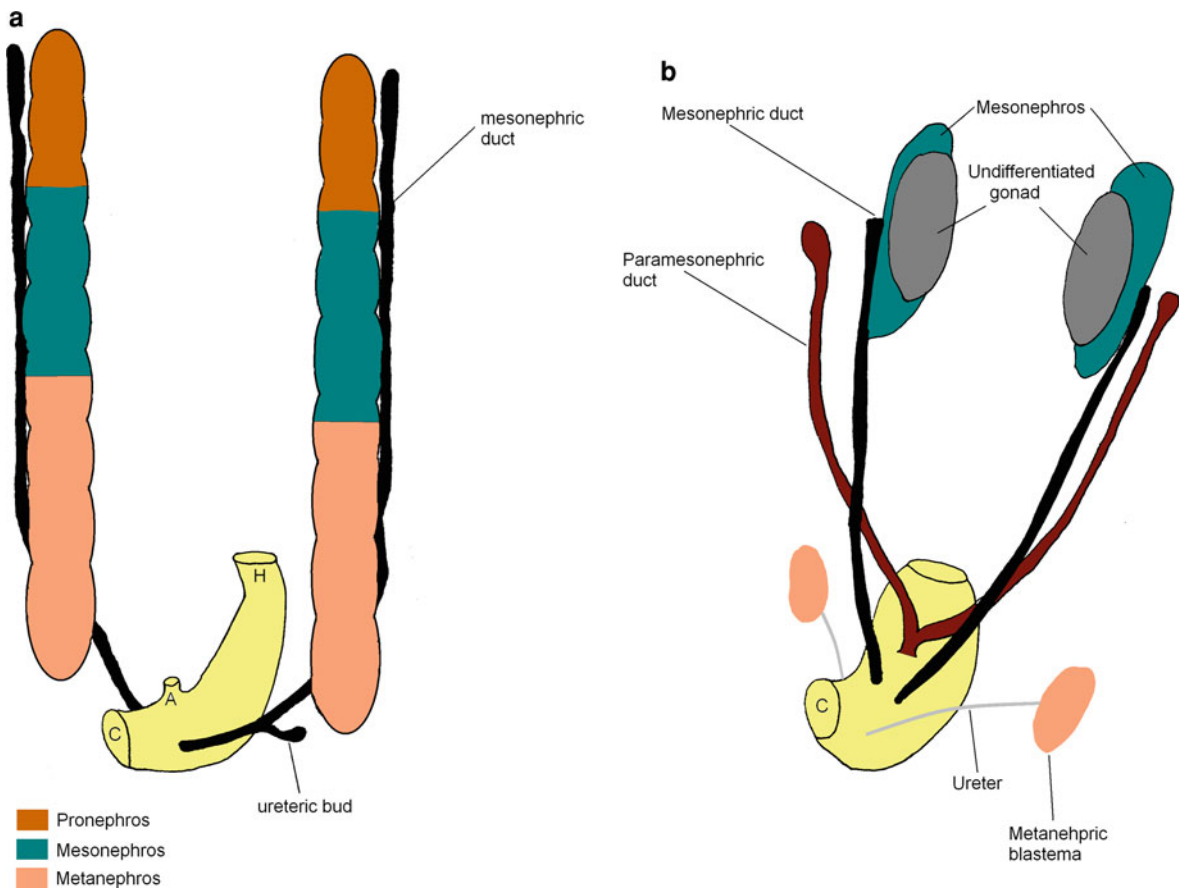


Fig. 4 The embryonic genitourinary tract at **a** 4 weeks and **b** between 6–8 weeks

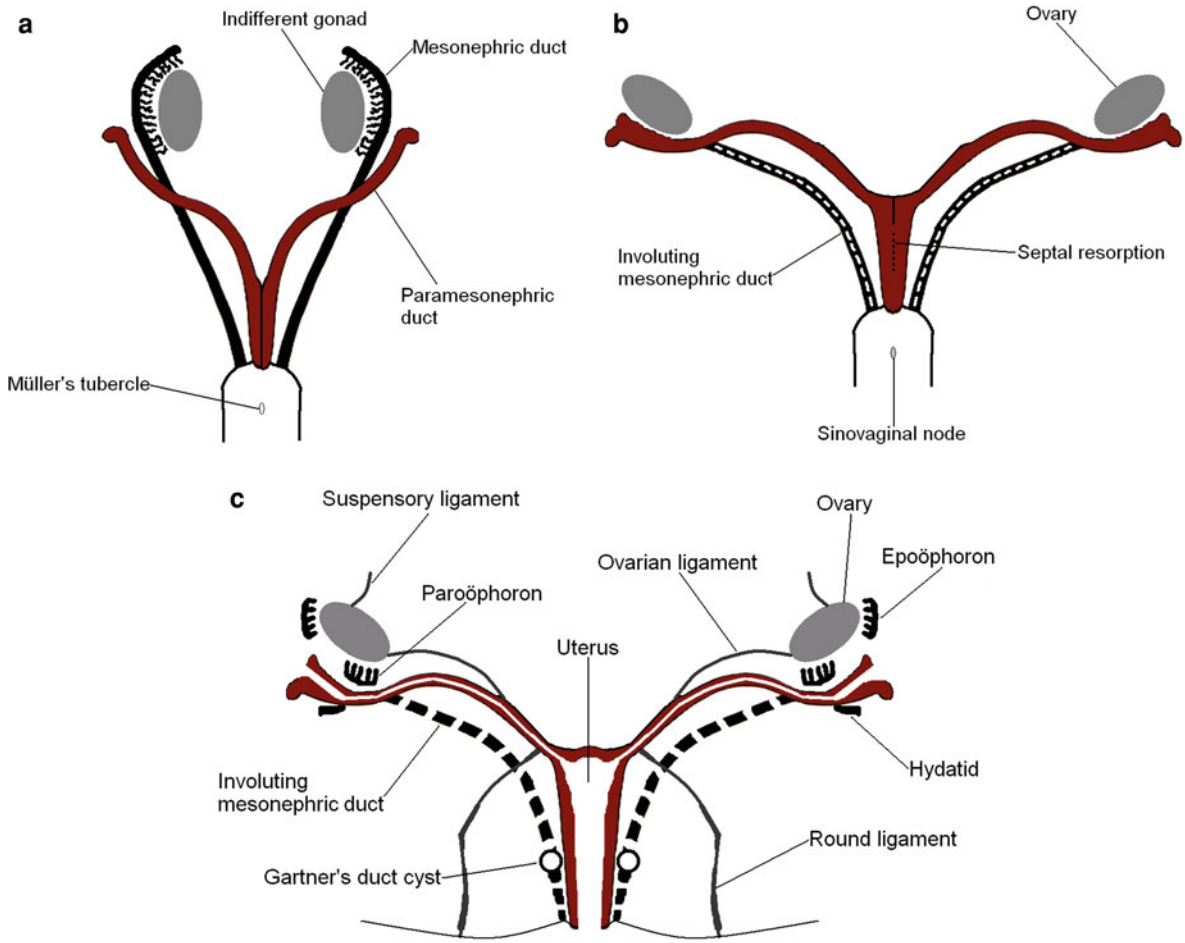


Fig. 5 Differentiation of the paramesonephric (Müllerian) ducts: **a** Indifferent phase with both mesonephric and paramesonephric ducts present. Female internal genital development proceeds in the absence of the male SRY protein. **b** At 7 weeks the paramesonephric ducts differentiate whilst the mesonephric ducts involute. The medial portions of the paramesonephric ducts fuse to form the uterus and upper vagina (lateral fusion 9–11 weeks), the lateral portions give rise to fallopian tubes. Müllerian organogenesis is complete by 5 months with uterine septal resorption. **c** The female internal genitalia at 5 months. Occasionally remnants of the mesonephric duct may persist

relationship to the development of the female reproductive ducts. Three distinct stages of renal development occur (Fig. 4a): the pronephros and mesonephros which are transitory structures but critical to the development of the metanephros (permanent kidney). The paired pronephros develops in the cervical region around the third fetal week and regress by the fifth week. The mesonephros form below the pronephros in the thoracic region in the fourth week and act as the interim kidneys. The paired mesonephric ducts (Wolffian duct) drain the mesonephros into the cloaca ventral to the laterally placed nephrogenic cords (Fig. 4b). In females the mesonephros and mesonephric ducts involute by the third month but vestigial structures such as the Gartner's duct, epoophoron and the paraoophoron may persist and are described later (see Sect. 2.7) (Fig. 5c).

2.3 Development of the Fallopian Tubes Uterus, Cervix and Vagina

In females the paramesonephric (Müllerian) ducts arise from the mesoderm lateral to the mesonephric ducts in the seventh week as focal invaginations of the coelomic epithelium on the upper pole of each

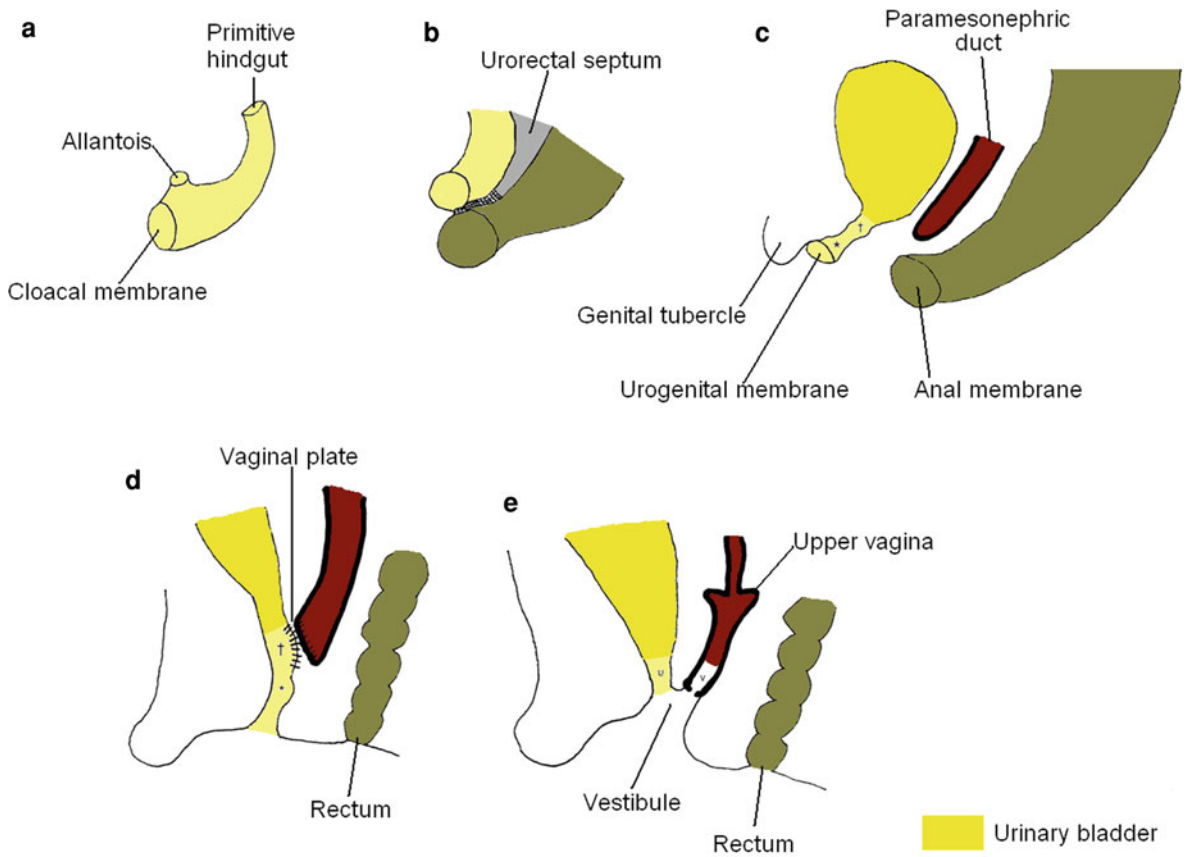


Fig. 6 Division of the cloaca and differentiation of the female lower genitourinary tract. **a** The cloaca. **b** The partition of the cloaca into anorectal and urogenital compartments by the descent of the urorectal septum (4–6 weeks). **c** The formation of the genital tubercle and urogenital sinus (UGS). The phallic (*) and cranial (†) portions of the pelvic UGS form the vaginal vestibule and female urethra, respectively. **d** Canalisation of the vagina at the vaginal plate onto the UGS (vertical fusion). **e** The definitive vaginal vestibule

mesonephros. The paired mesonephric and paramesonephric ducts represent the indifferent stage of the fetal internal genital canal systems. The paramesonephric ducts are the precursors of the uterus, fallopian tubes, cervix and upper vagina.

The paramesonephric ducts grow caudally, coursing lateral to the urogenital ridges. In the eighth week the paired paramesonephric ducts lie medial to the mesonephric ducts. The paramesonephric ducts fuse to form a confluence. This process is referred to as Müllerian organogenesis and represents the initial stage in the development of the upper two-thirds of the vagina, the cervix, uterus and both fallopian tubes (Fig. 5a). The cranial end of the fused ducts yields the future uterus which contains mesoderm that will form the uterine endometrium and myometrium. The unfused cranial ends of the paramesonephric ducts assume a funnel shaped configuration and remain open to the future peritoneal cavity as the fimbrial portions of the fallopian tubes. The caudal end of the fused ducts will form the upper two-thirds of the vagina.

Lateral fusion of the paramesonephric ducts occurs between the seventh and ninth weeks when the lower segments of the paramesonephric ducts fuse. At this stage a midline septum is present in the uterine cavity, this usually regresses at around 20 weeks but can persist (Fig. 5b). Vertical fusion occurs in the eighth week when the lower most fused paramesonephric ducts fuse with the ascending endoderm of the sinovaginal bulb. The lower third of the vagina is formed as the sinovaginal node (bulb) canalises.

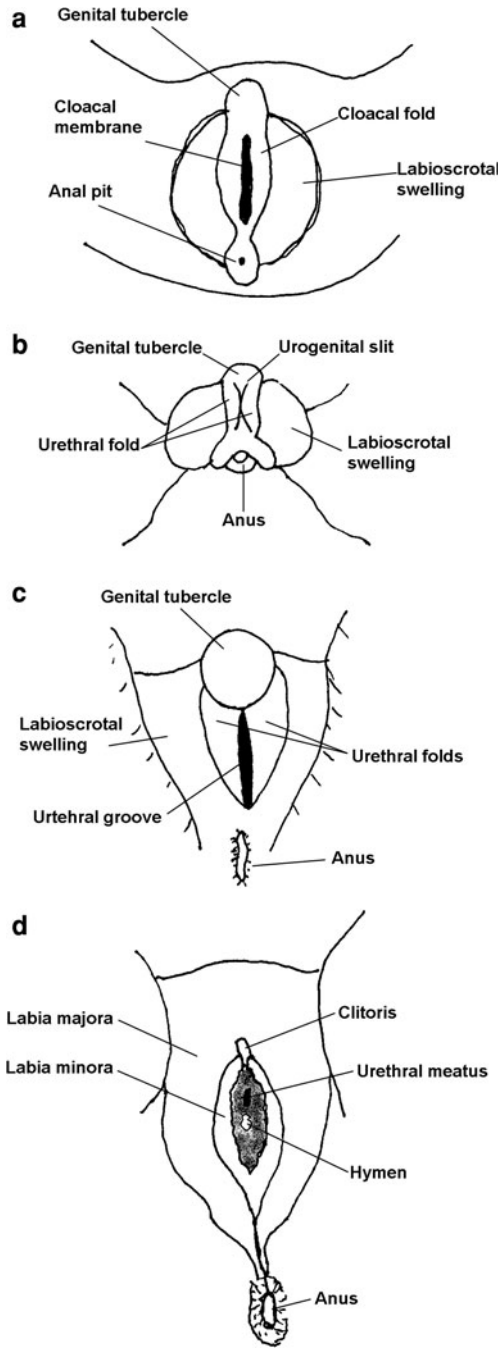


Fig. 7 Differentiation of the female external genitalia. Stages of development at **a** 4 weeks (indifferent stage), **b** 6–7 weeks **c** 9–11 weeks and **d** 12 weeks (full differentiation)

The sinovaginal node inserts into the urogenital sinus at Müller's tubercle. The hymen, a membrane separating the vagina from the urogenital sinus develops and is normally perforated by birth.

2.4 Development of the Lower Genital Tract

2.4.1 The Cloaca

The cloacal membrane is formed in the third fetal week under the umbilical cord (Figs. 4a and 6a). The lower abdominal wall is formed as the cloacal membrane becomes more caudally displaced by adjacent proliferating mesenchyme. By the fifth week the cloacal membrane is delimited laterally by the cloacal folds which fuse anteriorly to give rise to an anlage referred to as the genital tubercle which is formed earlier in the fourth week (see Sect. 2.5.1). The cloacal membrane remains imperforate at this time.

2.4.2 The Urogenital Sinus

During the seventh week the urorectal septum fuses to the inner surface of the cloacal membrane dividing it to form the anterior (ventral) urogenital membrane and the posterior anal membrane dividing the rectum proper from the urogenital tract (Fig. 6b). The urogenital membrane perforates and free communication between the amniotic cavity and the primary urogenital sinus is established. The folds surrounding the urogenital membrane are now referred to as the urethral folds and those around the anus the anal folds.

2.4.3 Differentiation of the Urogenital Sinus

The primary urogenital sinus develops into the definitive urogenital sinus (UGS). The UGS consists of a caudal phallic portion and a pelvic portion (Fig. 6c). The urethral groove and phallic (distal) portion of the UGS enlarge to form the vaginal introitus (vestibule) (Fig. 6d). This is closed off externally by the urogenital membrane which perforates in the seventh week. The narrow pelvic (proximal) segment of the definitive urogenital sinus contributes to the short distal female urethra and lower third of the vagina (Fig. 6e).

2.5 Development of the External Genitalia

The external genitalia remain sexually undifferentiated until around the seventh fetal week. During the tenth week distinct sexual characteristics appear with complete differentiation occurring around the twelfth week.

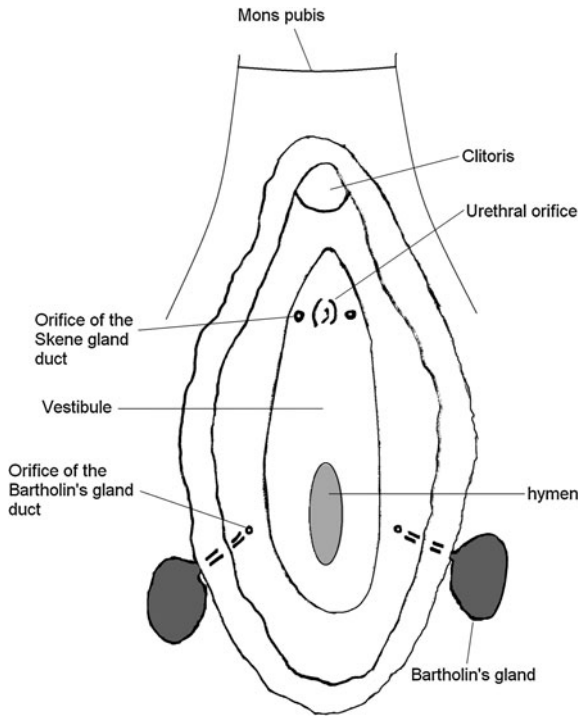


Fig. 8 Anatomy of the vestibular glands and ducts: The position of the greater vestibular glands (Bartholin's) and the lesser vestibular (Skene) or periurethral glands

2.5.1 Indifferent External Genitalia

In the fourth week the genital tubercle results from mesenchymal proliferation and a protophallus ventral to the cloacal membrane begins to develop. During the sixth week, the urethral groove and anal pit form resulting in focal depressions along the cloacal membrane (Fig. 7a). The primary urethral (urogenital) folds surround the primary urethral groove. The genital or labioscrotal swellings form lateral to the urethral folds.

In the seventh week, the cloacal membrane involutes and the primary urethral groove becomes continuous with the definitive urogenital sinus. The secondary urethral groove forms as a result of deepening and widening the primary urethral groove in the eighth week. The external genitalia begin display sexual differentiation during the tenth week (Fig. 7c).

2.5.2 Female External Genitalia

In girls the unfused parts of the labioscrotal (genital) swellings give rise to the labia majora, the folds fuse anteriorly to form the mons pubis and anterior labial commissure, and posteriorly the posterior labial commissure. The urethral folds fuse posteriorly to form the frenulum of the labia minora. The unfused

Table 2 Vestigial remnants and postnatal derivatives of the genitourinary tract

Embryonic structure	Female	Male homologue
Gonad	Ovary	Testis
Cortex	Ovarian follicles	Seminiferous tubules
Medulla	Rete ovarii	Rete testis
Gubernaculum	Ovarian ligament and round ligament of uterus	Gubernaculum
Mesonephric tubules	Epoophoron, paroophoron	Ductuli efferentes
Mesonephric duct	Appendix vesiculosa, duct of epoophoron, duct of Gartner	Appendix of epididymis, duct of epididymis, ductus deferens, ejaculatory duct and seminal vesicles
Paramesonephric duct	Hydatid of Morgagni, uterine tube, uterus	Appendix of testis
Urogenital sinus	Urethra, vagina urethral, paraurethral and greater vestibular glands	Urethra, prostatic utricle, prostate and bulbourethral glands
Sinus tubercle	Hymen	Seminal colliculus
Phallus	Clitoris	Penis
Urogenital folds	Labia minora	Ventral aspect of penis
Labioscrotal swellings	Labia majora	Scrotum

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urethral (urogenital) folds give rise to the labia minora. The unfused genital swellings enable the urogenital sinus to open into the anterior (urethral) part of the vagina and the vaginal vestibule. The genital tubercle becomes the clitoris and is recognisable by the fourteenth week (Fig. 7d).

2.6 Development of the Female Genital Accessory Glands

The accessory urethral glands including the lesser vestibular or paraurethral glands (Skene) and urethral glands arise from the urogenital sinus from endodermal (epithelial) buds growing into the urethral mesenchyme (Fig. 8). The paired greater vestibular glands (Bartholin) form in the 12th week and empty into the vaginal vestibule.

2.7 Embryological Vestigial Structures (Wollfian Vestiges)

In early fetal life the mesonephric Wolffian and paramesonephric ducts co-exist. The mesonephric ducts regress in a female, but remnants of the mesonephric duct typically persist. Their importance relates to the potential for the development of pathology. The mesonephric remnants in a female are reviewed here and summarised in Table 2.

2.7.1 Gartner's Duct

The Gartner's ducts are paired remnants of the mesonephric duct that may give rise to Gartner's duct cysts and are typically located in the broad ligament (Fig. 5c).

2.7.2 Canal of Nuck

The canal of Nuck is a virtual space and is the female analogue of the processus vaginalis in the male, if patent it is abnormal and forms a pouch of peritoneum in the labia majorum (Fig. 2).

2.7.3 Epoophoron

The epoophoron (Fig. 5c) is the most cranial part of the mesonephric duct remnant. It is situated in the lateral portion of the broad ligament and may communicate with the Gartner's ducts more inferiorly in the broad ligament. It is homologous to the epididymis in males.

2.7.4 Paraoophoron

The paraoophoron is also a mesonephric remnant analogous to the paradidymis in males. It is usually positioned medially in each broad ligament (Fig. 5c).

3 Conclusion

Genetic sex is determined at conception. The female fetus does not acquire distinct sexual characteristics until the indifferent gonads differentiate to ovaries and there is differentiation of the external genitalia. The development of the uterus and vagina requires integrated differentiation of the paramesonephric and mesonephric ducts in close relation the development of the excretory system. This interdependence accounts for the association of anomalies of the female genital system, urinary tract and more complex cloacal malformations.

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