

Chapter 2

Development of the Male Reproductive System

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Abstract Male and female reproductive systems develop in close relation to the urinary tract. Until approximately 7 weeks gestation, the human embryo remains sexually bipotential. Subsequently, in males, testis-inducing factors cause differentiation from the default female phenotype. As the testis forms, testosterone and other androgens drive the formation of the external genitalia and internal male reproductive structures, while other testicular factors cause regression of female reproductive organ precursors. Androgens also play a role in the descent of the testicles from their origin in the upper abdomen. Germ cells enter an arrested phase of maturation in the first trimester. A surge of testosterone in the neonatal period plays a role in testicular development, but it is not until the largest androgen surge of puberty that gonadarche occurs with the onset of spermatogenesis. In this chapter, we review the formation and maturation of the reproductive system, with an emphasis on hormonal factors and aspects relevant to clinical care of male reproductive patients.

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20 Abbreviations

21	AGD	Anogenital distance
22	AMH	Anti-Müllerian hormone
23	CDGP	Constitutional delay of growth and puberty
24	CF	Cystic fibrosis
25	CFTR	Cystic fibrosis transmembrane conductance regulator
26	CGRP	Calcitonin gene-related peptide
27	CSL	Cranial suspensory ligament or cranial mesonephric ligament
28	DHT	Dihydrotestosterone
29	FSH	Follicle-stimulating hormone
30	GnRH	Gonadotropin-releasing hormone
31	INSL3	Insulin-like factor 3
32	LH	Luteinizing hormone
33	MIS	Müllerian-inhibiting substance
34	PGC	Primordial germ cell
35	SRY	Sex-determining region of the Y chromosome
36	TDS	Testicular dysgenesis syndrome

37 Developmental Stages Before Sex Divergence (< ~7 Weeks)

38 The formation and development of reproductive and urinary structures are closely
 39 related. Each system begins as bilateral craniocaudal elongations of intermediate
 40 mesoderm forming nephrogenic cords. Each of these cords ultimately forms a uro-
 41 genital ridge – the site of early genital and renal structure formation. Figure 2.1
 42 outlines the parallel development of the renal, internal ductal, and gonadal systems,
 43 as well as the external genitalia.

44 During week three of gestation, a nonfunctional kidney precursor called the pro-
 45 nephros develops in a location of the urogenital ridge corresponding to the future
 46 thorax. More caudally, the pronephros is continuous with the nephric duct, also called
 47 the mesonephric duct or Wolffian duct. By week five of gestation, the pronephros
 48 degenerates along with the most cranial part of the nephric duct. The middle and cau-
 49 dal aspects of the nephric duct can be seen by approximately 3½ weeks gestation. At
 50 approximately 4 weeks gestation, the caudal end reaches and fuses with the cloaca,
 51 forming a lumen that then canalizes the nephric duct back toward its cranial end.

52 After week four of gestation, masses of mesonephric tubules form, resembling
 53 nephrons with excretory function into the nephric duct. This transiently functioning
 54 renal precursor is called the mesonephros. Soon after forming from the cranial end
 55 toward the caudal end of the nephric duct, the mesonephric tubules regress in the
 56 same direction. A small number of the most cranial tubules of the mesonephros
 57 persist and later become the 12–20 efferent ductules of the testis. As the lumened
 58 mesonephric duct later becomes the epididymis and vas deferens, these efferent
 59 ductules ultimately connect the rete testis to the remainder of the ejaculatory tract.

Week	Renal	Internal ducts	Gonadal	External genitalia
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2	Nephrogenic cord formation			
3	Pronephros formation and degeneration		PGC's in posterior yolk sac	
4	Mesonephros formation, function, and degeneration	Future vas deferens canalized as mesonephric duct		Cloacal formation and division, forming urogenital sinus
5	Ureteric bud meets metanephric mesenchyme Nephrogenesis begins	Future efferent ductules persist	PGC's migrate, genital ridge forms	Ureter joins forming bladder
6		Formation of Müllerian ducts		Cloacal folds/labioscrotal fold formation
7	Pelvis/calyceal formation (6–10 weeks)		SRY production (Pre-sertoli) testis cord formation	
8	Renal ascent	Müllerian duct regression	MIS expression (Pre-sertoli) gonad becomes ovoid	Cloacal membrane rupture
9			Leydig cell formation Testosterone production INSL3 production	DHT
10		Seminal vesicle and prostate formation		Anogenital distance increases
11				Closure of urethra, male genitalia formation complete
12		Vasa deferentia and epididymides formation complete		
13			Completion of transabdominal descent (12–14 weeks)	
14				
15				
2nd trimester			Transinguinal descent	
3rd trimester	Collecting duct maturation Nephrogenesis completion		Scrotal descent completion	Growth of genitalia

Fig. 2.1 Parallel development and interactions of the kidneys, internal ducts, gonads, and external genitalia

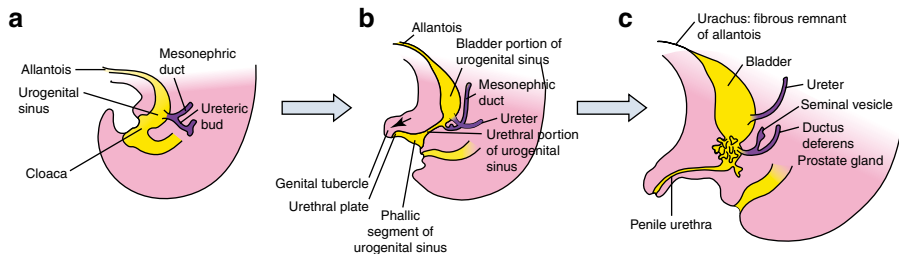


Fig. 2.2 Development of the cloaca, urogenital sinus, and accessory glands. (a) At 35 days, the common excretory duct and ureter are being absorbed into part of the cloaca, the primitive bladder. Also seen is the lumened allantois, which later forms the urachus. (b) By 53 days, the urorectal septum has divided the cloaca into the urogenital sinus and the anorectal canal. (c) By 10 weeks gestation, the penile urethra, prostate, and seminal vesicles have begun formation [15]

60 At approximately week four of gestation, the ureteric bud branches from the
 61 nephric duct toward the metanephric mesenchyme. Interactions between mesenchyme
 62 and the ureteric bud tissue lead to the formation of the metanephros, which later per-
 63 sists as the definitive kidney. The ureteric bud sequentially branches to become the
 64 ureter, renal pelvis, calyces, and collecting ducts. The remaining nephron segments
 65 and renal parenchyma develop from the metanephric mesenchyme. The portion of the
 66 nephric duct distal to the ureteric bud is termed the common excretory duct.

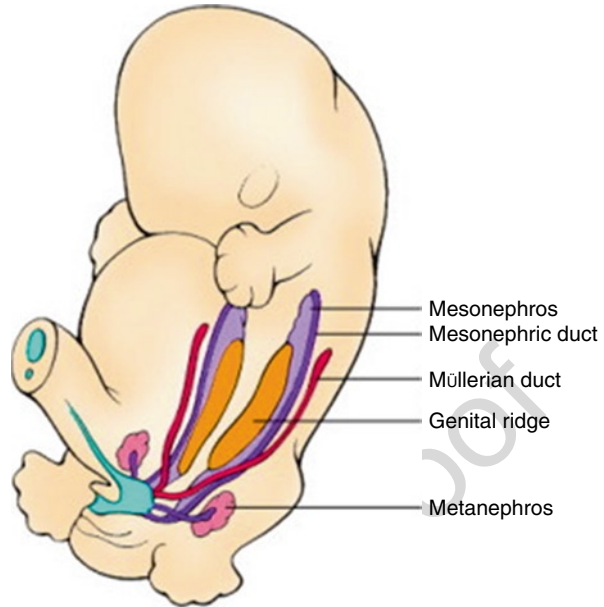
67 During this same time period, folding of the forming body creates the primitive
 68 gut. At the caudal region of the embryo, this endodermal tube transitions to an
 69 endoderm-lined sinus called the cloaca, and the opening of the sinus is covered by
 70 the cloacal membrane. The allantois forms from the primitive gut and connects the
 71 placenta and the future bladder, and this tube later closes off to become the solid
 72 cord-like urachus (Fig. 2.2).

73 When the nephric ducts meet the cloaca, the cloacal regions anterior to this fusion
 74 point form the vesicourethral canal that will eventually form the structures of the blad-
 75 der and pelvic urethra in males and females. The posterior portion of the cloaca is fur-
 76 ther separated into the urogenital sinus (anteriorly) and the anorectal canal (posteriorly)
 77 by the urorectal septum, as it descends in the coronal plane. As this separation occurs,
 78 the cloacal membrane ruptures to open the anus and urogenital sinus cavities, and the
 79 urorectal septum forms the perineum between the genitalia and anus (Fig. 2.2b). The
 80 urogenital sinus becomes the phallic urethra in males and the distal vagina in females.

81 As the developing bladder grows, the distal nephric duct (viz., the common
 82 excretory duct) is absorbed into the cloaca and undergoes apoptosis. This brings its
 83 two branches, the nephric duct and the ureteric bud, to the forming urogenital sinus.
 84 After 5 weeks gestation, the ureter opens into the primitive bladder and moves cra-
 85 nially and laterally to the bladder trigone, while the nephric ducts, or forming vasa
 86 deferentia, travel caudally and rotate posteriorly.

87 In the third week of gestation, primordial germ cells (precursors to male and
 88 female gametes) are located near the endoderm of the posterior yolk sac. The germ
 89 cells soon start to migrate to the lower thoracic regions just medially to the

Fig. 2.3 Internal ductal system at 6 weeks gestation, prior to sexual differentiation. The urinary and genital/gonadal ridges (mesonephros and mesonephric duct) make up the urogenital ridge. The paramesonephric (Müllerian) ducts are just lateral to the urogenital ridge. The metanephros, Müllerian ducts, and mesonephric ducts all join to the bipotential urogenital sinus [15]



mesonephros. Likely guided by chemotactic molecules from the gonadal tissue, they reach and penetrate the region of the medial urogenital ridges at approximately 5 weeks gestation. Signaled by the arrival of primordial germ cells, the genital ridge develops from coelomic epithelium and some cells from the mesonephros. Soon after its development, the indifferent gonad becomes suspended from the mesonephros or future vas deferens in males. Until this point, all internal and external genital and reproductive structures have bipotential sexual differentiation and appear identical in males and females (Fig. 2.3).

Sex Determination and Gonadal Differentiation (>7 Weeks)

The sex-determining region of the genome is located on the short arm of the Y chromosome and is called the SRY gene. In males, SRY gene expression by somatic mesenchymal cells of the forming gonad generates SRY protein also known as the testis-determining factor. During the seventh and eighth weeks of gestation, the SRY protein initiates a cascade of events leading to male differentiation. Without these events, the embryo follows the default development pathway, forming female reproductive structures and external genitalia. The mesenchymal cells producing SRY differentiate into Sertoli cells, also known as nurse cells or sustentacular cells for their role in supporting spermatogenesis. Table 2.1 lists some of the key molecular factors along with their origins and functions in male reproductive development.

t1.1 **Table 2.1** Principal molecular factors, their origins, and their roles in male reproductive develop-
 t1.2 ment [9, 20]

t1.3	Molecule/hormone	Origin	Role/function
t1.4	SF1	–	Gonadal ridge formation (bipotential)
t1.5			Adrenal development
t1.6	SRY	Pre-Sertoli cells	Male differentiation
t1.7			Testis formation
t1.8			Stimulates SOX-9 production
t1.9	SOX-9	Pre-Sertoli cells	Testis formation
t1.10			Promotes MIS production
t1.11	WT1	–	Tumor suppressor gene
t1.12			Germ cell/gonadal development
t1.13	DAX1, WNT4	–	Can antagonize SF1 and SRY
t1.14			Can promote female differentiation
t1.15	MIS	Pre-Sertoli cells	Regression of Müllerian ducts
t1.16	hCG	Placenta	Early stimulation of testosterone production
t1.17			
t1.18	LH	Anterior pituitary	Later stimulation of testosterone production
t1.19			
t1.20	Testosterone	Leydig cells	Wolffian differentiation
t1.21			Testicular descent
t1.22			Inguinoscrotal > transabdominal
t1.23			Converted to DHT
t1.24	INSL3	Leydig cells	Testicular descent (transabdominal)
t1.25	CGRP	Genitofemoral nerve	Gubernacular growth/contraction for inguinoscrotal descent
t1.26			
t1.27	DHT	Target organ conversion from testosterone by 5 α -reductase	External genitalia differentiation, prostate development
t1.28			
t1.29	Kisspeptin	Brain	Activates GnRH neurons and triggers GnRH release
t1.30			

110 The cells of the male genital ridge form the genital blastema, a mix of primitive
 111 Sertoli cells, interstitial cells, and primordial germ cells. During the seventh week of
 112 gestation, the Sertoli precursor cells begin to surround the primordial germ cells to
 113 form primitive sex cords or testis cords. Once enveloped by Sertoli cells, the primor-
 114 dial germ cells interact with the surrounding cells and differentiate into gonocytes or
 115 prespermatogonia precursor cells. Shortly after SRY expression commences, pro-
 116 duction of Müllerian-inhibiting substance (MIS), also termed anti-Müllerian hor-
 117 mone (AMH), ensues by the same Sertoli cell precursors at 7–8 weeks gestation.

118 During the seventh week of gestation, the sex cords begin to shorten and assume
 119 the ovoid shape of the testicle, and the area in contact with the mesonephros
 120 decreases. The sex cords then enlarge and become the immature seminiferous
 121 tubules, which later function for spermatogenesis. The gonocytes then enter mitotic
 122 arrest and largely stay dormant until puberty.

123 Meanwhile, the sex cords that are located in the region between the mesonephros
 124 and germ cells form the tubular structures of the rete testis, which links the semini-
 125 ferous tubules to the mesonephric tubules and nephric duct or the efferent ductules

and vas deferens, respectively. A thick layer of connective tissue then condenses around the gonad, forming the tunica albuginea that separates the gonadal contents from surrounding tissues.

Concomitantly, paracrine factors from Sertoli cells are thought to guide the development and structure of the other cell types within the testis. Under the influence of SRY, gonadal cells in the interstitium outside the seminiferous tubules differentiate into Leydig cells after 8–9 weeks gestation. These interstitial cells are located outside the seminiferous tubules, within the gonad. SRY is also thought to cause proliferation of Sertoli precursor cells in mice [1].

Leydig cells begin producing testosterone soon after their formation. Until 12 weeks gestation, testosterone secretion is mainly stimulated by chorionic gonadotropin from the placenta. Early in the second trimester, there is a peak in placental chorionic gonadotropin that stimulates gonadal testosterone production. Luteinizing hormone (LH) receptors are expressed in Leydig cells at approximately 12 weeks, and by 16 weeks, the control of testosterone production becomes dependent on pituitary gonadotropin (LH) production. In a similar fashion, Sertoli cells express receptors for follicle-stimulating hormone (FSH) and are eventually regulated by pituitary FSH production.

Testosterone and other androgens then cause the development of male internal structures and external genitalia, and the testes continue to mature and begin their descent to the scrotum.

Clinical Correlate

Approximately 5–10 % of germ cell tumors arise from a site outside of the testes and are termed extragonadal germ cell tumors. The germ cells forming these tumors likely failed to properly migrate to the genital ridges during testis development and then failed to degenerate when they did not reach their destination. These tumors usually develop near the midline in the retroperitoneum and mediastinum, though they have been found in suspected primary sites throughout the body [2].

Testicular Descent

The testicle initially forms high in the abdominal cavity near the lower thoracic vertebral level. At approximately 5 weeks gestation, during formation of the genital ridge, the caudal mesonephros and the future gubernaculum are connected near the internal inguinal ring. Upon testis formation, a dorsally located cranial suspensory ligament (CSL), or cranial mesonephric ligament, connects the upper mesonephros to the diaphragm. Together, the cranial and caudal ligaments loosely stabilize the position of the testis. As the fetus elongates and the abdominal cavity grows differentially, the CSL elongates, and its cranial aspect, mesonephros, regresses, and the testis is held near the inguinal ring. As a result, the relative position of the testis

157 becomes more caudal, following a path toward the junction of the mesonephros and
158 gubernaculum. Ultimately, the transabdominal descent of the testis is usually com-
159 plete by approximately 10–15 weeks gestation, with the testis reaching the inguinal
160 region.

161 Early in the second trimester, there is a surge in testosterone and insulin-like fac-
162 tor 3 (INSL3) production by fetal Leydig cells. This generally occurs after transab-
163 dominal descent and is accompanied by a shortening and swelling or outgrowth of
164 the gubernaculum that is thought to draw the testis closer to the internal ring and
165 create space in the inguinal canal for the testis to pass.

166 Transinguinal descent of the testis usually occurs between weeks 22 and 27 of
167 gestation. During the inguinoscrotal phase of testis migration, intra-abdominal pres-
168 sure is thought to provide the main driving force for descent. However, evidence in
169 rodents suggests the genitofemoral nerve (GFN) produces calcitonin gene-related
170 peptide (CGRP), which stimulates contractions in the muscle fibers in and around
171 the gubernaculum, further propagating this stage of testicular descent [3].

172 During the inguinoscrotal phase, the processus vaginalis extends caudally as an
173 outpouching of the parietal peritoneum, increasing in length as the testis descends to
174 its final location. Upon completion of inguinoscrotal descent, the processus vaginalis
175 closes off from the peritoneum, forming the tunica vaginalis of the testis. During the
176 remainder of the pregnancy, much of the gubernacular tissue involutes as the testis
177 settles in the dependent part of the scrotum between 32 weeks gestation and birth.

178 There is contradictory evidence, and there are questions regarding gonadal
179 descent and the applicability of animal models to human testicular development. It
180 is unclear by what exact mechanisms androgens affect intra-abdominal descent in
181 humans. INSL3 likely primarily promotes transabdominal descent by early effects
182 on the gubernacular development, while androgens contribute to CSL regression.
183 During inguinoscrotal descent, testosterone is thought to be the dominant factor
184 resulting in masculinization of the GFN with subsequent gubernacular growth and
185 contractions. While MIS was once thought to be the most important factor in trans-
186 abdominal descent of the testis, now, there is conflicting evidence as to the impor-
187 tance of MIS' role in testicular descent [4]. Table 2.1 details a summary of key
188 molecular factors driving male sexual differentiation and testicular descent.

Clinical Correlation

Testicular Dysgenesis Syndrome. Multiple studies have shown an increased incidence of testicular germ cell tumors in men with cryptorchidism and/or infertility [5, 6]. In 2001, Skakkebaek et al. proposed a unifying entity that includes undescended testes, male infertility, testicular cancer, and hypospadias. In this condition, called testicular dysgenesis syndrome (TDS), genetic defects and various environmental endocrine disruptors lead to poor testis tissue development. Subsequently, impaired germ cell differentiation leads to problems with fertility and an increased risk of testicular cancer, while poor andro-

gen production by the testes leads to hypospadias and cryptorchidism [7]. More recently, Kraft et al. found that in patients with suspected unilateral neonatal testicular torsion, the contralateral descended testes had more normal histological findings when compared to those in patients with unilateral undescended testis [8]. Their findings support the theory of a systemic/genetic cause for testis maldevelopment impairing bilateral testis development in TDS. Furthermore, the findings point to an important distinction for clinicians to consider when evaluating fertility in patients with a history of cryptorchidism: Patients with cryptorchidism due to torsion are likely to have much better function of the contralateral testis than those with cryptorchidism due to maldescent.

Müllerian Formation/Regression/Remnants

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At approximately 6 weeks gestation, while the undifferentiated gonad is forming, an additional ridge of folded and thickened coelomic epithelium forms lateral to the gonad and mesonephric ducts, called the paramesonephric ducts or Müllerian ducts. The left and right paramesonephric ducts fuse inferiorly at the midline as they join the urogenital sinus. As one of the earliest phenotypically recognized signs of male and female development divergence, MIS production at gestational weeks 7–8 then initiates the degeneration of the paramesonephric ducts through weeks 8 and 9 of gestation. Shortly thereafter, the Müllerian ducts become insensitive to MIS [9], and two small remnants are left behind in males.

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The first paramesonephric remnant, the appendix testis, is typically located at the upper pole of the testis near the groove of the epididymis. Distally, the prostatic utricle remains as a small diverticulum of the urethra at the verumontanum of the prostatic urethra. Usually, it is of diminutive size, but rarely, it can form larger cysts or collections of urine, leading to ejaculatory duct obstruction, sexual or urinary dysfunction, hematospermia, or urinary tract infections [10].

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In females, Sertoli cells do not form, MIS is not produced, and androgen levels remain low. Thus, the paramesonephric ducts persist, male internal and external structures do not develop, and the mesonephric ducts regress. The caudal, fused portions of the paramesonephric ducts form the proximal vagina and the uterus; the more cranial portions form the fallopian tubes, with the conical ends forming the openings to the peritoneum. In females, remnants of the mesonephric ducts form the nonfunctional epoophoron and paroophoron in the mesosalpinx.

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Vas Deferens, Epididymis, Prostate, and Seminal Vesicle Development

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Under the influence of testosterone, the mesonephric duct becomes the vas deferens by approximately 12 weeks gestation, with the epididymis forming from its testicu-

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215 lar end. At the epididymis' superior end, 12–20 efferent ductules persisting from the
216 mesonephros extend toward the testes to meet the rete testis. The degenerated cran-
217 ial end of the mesonephric duct often leaves a small remnant called the appendix
218 epididymis.

219 At 10–13 weeks gestation, testosterone induces the formation of the seminal
220 vesicles from the caudal ends of the mesonephric ducts. The seminal vesicles and
221 vasa deferentia then empty into the prostatic urethra through the ejaculatory ducts at
222 the verumontanum.

223 Unlike the mesodermal seminal vesicles, at approximately 10 weeks, the pros-
224 tate and bulbourethral glands develop from the urogenital sinus as a branching out-
225 growth of endodermal glandular epithelium into the surrounding mesenchyme
226 (Fig. 2.2c). In prostate tissue, testosterone is converted by 5α -reductase to dihy-
227 drotestosterone (DHT), which binds to the mesenchymal androgen receptors with
228 an exceptionally high affinity and is the principal androgen driving gland develop-
229 ment. Bidirectional interactions between mesenchyme and epithelium then allow
230 development of the smooth muscle and glandular tissue of the prostate.

Clinical Correlate

Essentially all men with cystic fibrosis (CF) have congenital bilateral absence of the vas deferens (CBAVD), leading to obstructive azoospermia. This is linked to mutations of the cystic fibrosis transmembrane conductance regulator (CFTR) gene that is responsible for clinical CF and is thought to occur due to in utero obstruction due to thickened secretions with subsequent vasal dissolution. Low-volume ejaculates (commonly defined as under 1.5 mL) occur in most of these men and result from concomitant defects of the seminal vesicles, which normally produce the largest contribution to ejaculate volume. Phenotypically normal men presenting for infertility or azoospermia may be found to have CBAVD or unilateral absence of the vas deferens. In these men, the findings are usually linked to a clinically milder group of CFTR mutations or developmental abnormalities of the mesonephric duct or future vas deferens [11]. As the ureteric bud forms as a branch of the mesonephric duct, a subset of these men are at increased risk for renal agenesis, and they should be counseled and screened appropriately.

231 *External Genitalia/Penis*

232 The cloacal membrane initially extends from the umbilicus to the future caudal end
233 of the fetus. Mesodermal cells infiltrate the cranial end of the cloaca to form the
234 abdominal musculature and part of the bladder, and the caudal end covers the open-
235 ing of the cloacal sinus. In the fifth week of gestation, mesenchymal cells collect at
236 the lateral edges of the cloacal membrane to form cloacal folds around the sinus

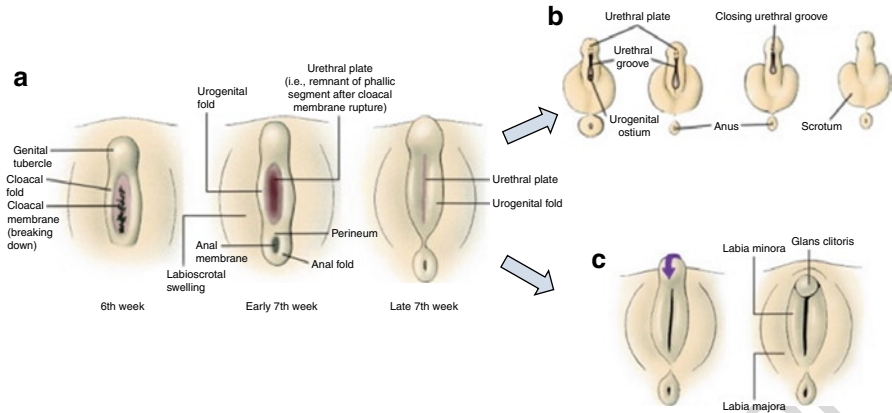


Fig. 2.4 Formation of the male and female external genitalia. Development of the external genitalia (a) during the bipotential stages through 7 weeks gestation and upon differentiation to (b) male and (c) female phenotypes [15]

opening. Anteriorly, the folds meet in the midline and form the genital tubercle. As the urorectal septum divides the urogenital sinus to form the perineum, it also divides the cloacal folds, resulting in the delineation of the anteriorly located urogenital folds, from the more posterior anal folds. Additional swellings called the labioscrotal folds, or genital swellings, form on either side of the urogenital folds. At approximately 8 weeks gestation, the cloacal membrane ruptures to open the genital sinus and anus to the outside, and the forming genitalia still appear identical in males and females (Fig. 2.4a).

At approximately 9 weeks gestation, the male differentiation of the external genitalia proceeds under the influence of androgens. Like prostate development, genital differentiation is mainly driven by DHT, which is converted from testosterone by 5α -reductase in the cells of the forming external genitalia. The genital tubercle lengthens to form the phallus and develops a urethral groove on its ventral side. The distal urethra develops in the forming glans penis from canalization of a solid epithelial urethral plate. More proximally, the urethral groove is lined by endodermal tissue forming the urethral plate, and it is flanked by urethral folds that are contiguous with the urogenital folds (Fig. 2.4b). After the distal urethra is formed, ventral fusion of the endoderm-lined urethral folds forms the remainder of the penile urethra in a proximal to distal direction.

The anogenital distance (AGD) elongates at approximately 9–10 weeks gestation, and the labioscrotal folds migrate caudally and fuse below the phallus to form the scrotum. By 12–14 weeks gestation, the male genitalia are fully formed, though the phallus is of equivalent size to the female clitoris [9]. Subsequent growth of the external genitalia occurs mostly during the third trimester, and the testes usually reach their scrotal destination during the same time period.

In females, the genital tubercle folds inward to become the clitoris, while the urethral folds form the labia minora, and the labioscrotal folds develop into the labia majora (Fig. 2.4c).

Clinical Correlate

Abnormalities of the external genitalia can be indicators of developmental abnormalities that can affect fertility. Hypospadias and cryptorchidism may be signs of in utero androgen deficiency and global testicular dysfunction [7]. Similarly, micropenis is associated with Kallmann syndrome (idiopathic hypogonadotropic hypogonadism with anosmia) and Prader-Willi syndrome, as well as nonsyndromic congenital hypogonadotropic hypogonadism [12]. Shorter AGD is a marker for exposure to endocrine disruptors in animal studies, and shorter AGD's in humans has been correlated to decreased fatherhood and lower sperm concentrations [13].

264 Postnatal Development

265 After birth, maternal and placental estrogens no longer suppress the hypogonadal
266 production of gonadotropin-releasing hormone (GnRH) and pituitary gonadotropin
267 production. This results in the second major surge of testicular testosterone produc-
268 tion in male development. During infancy, this surge in testosterone is accompanied
269 by a relatively rapid increase in seminiferous tubule volume and testicular size, fol-
270 lowed by relatively little growth until 5 years of age [14]. Germ cells undergo some
271 differentiation during this time as well, although most stages of spermatogenesis are
272 delayed until puberty [15, 16].

273 Before puberty, adrenal androgens drive adrenarche or the development of the
274 first signs of approaching puberty. At this time, boys often develop increased body
275 and pubic hair, acne, and development of adult body odor.

276 Male puberty occurs around age 12, although normal variants of onset range
277 from age 9 to 14 years of age [17]. At the onset of puberty, increased GnRH pulsati-
278 lity drives a surge in LH levels and increases LH pulsatility, with a resultant increase
279 in Leydig cell testosterone production. This is soon thereafter followed by increased
280 FSH secretion, canalization and functionalization of seminiferous tubules, and
281 Sertoli cell maturation with increased production of inhibin B, which serves as the
282 principal factor in negative feedback regulation of FSH levels. Sperm production is
283 driven by both FSH and testosterone, and the induction of the first cycle of sper-
284 matogenesis is called gonadarche. This event results in the growth of testes, which
285 is the first physical sign of male puberty. The increased testosterone then causes the
286 appearance of male secondary sexual characteristics [18].

287 In addition to the maturation of gamete production, changes in the reproductive
288 system seen at puberty include stimulation of libido, increase in penile length and
289 girth, increased scrotal size, rugae and pigmentation of the scrotum, enlargement
290 and increased fluid production by the prostate and accessory sex glands, and body
291 hair changes including pubic hair growth and frontal scalp recession.

292 The pubertal rise in testosterone marks the third and final surge in testicular
293 androgen production, and levels continue to rise to peak adult levels, which are

reached around the third decade [18]. Throughout adulthood, testosterone maintains many of the changes that were induced during puberty. Beginning in the third decade of life, testosterone levels begin a gradual decline through the rest of life. Sex hormone-binding globulin levels rise with age, and the percentage of men with low fractions of free testosterone rises quickly after the fifth decade [19]. These events are accompanied by a decline in some aspects of reproductive and sexual function such as sperm production, rigidity of erections, and libido.

Clinical Correlate

Delayed puberty in males is usually defined as the absence of testicular enlargement by age 14. Most commonly, this is due to constitutional delay of growth and puberty (CDGP), which is a transient and largely benign condition associated with low basal levels of LH and FSH. However, CDGP is a diagnosis of exclusion, and more serious conditions should be ruled out. Primary testicular failure (Klinefelter's syndrome, gonadal dysgenesis) can be distinguished by elevated gonadotropin levels, and clinical signs can help detect pathologic causes of hypogonadotropic hypogonadism (systemic illnesses or infiltrating tumors of the pituitary). Thus far, no test can reliably distinguish CDGP from isolated hypogonadotropic hypogonadism [17].

Summary

Male and female reproductive systems develop in close relation to the urinary tract. Until approximately 7 weeks gestation, the human embryo remains sexually bipotential. Subsequently, in males, testis-inducing factors cause differentiation from the default female phenotype. As the testis forms, testosterone and other androgens drive the formation of external genitalia and internal male reproductive structures, while other testicular factors cause regression of female reproductive organ precursors. Androgens play a role in the descent of the testicles from their origin in the upper abdomen down to their position in the scrotum. In the first trimester, germ cells enter an arrested phase of maturation. A surge of testosterone in the neonatal period plays a role in testicular development, but it is not until the largest androgen surge of puberty that gonadarche occurs with the onset of spermatogenesis.

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