

## 10. Development of genital system. Gonads. Genital ducts. External genitalia.

Gonads, genital ducts and the external genital organs initially pass through an indifferent period of development, which is the same in both male and female embryos. The differentiation of the sexual dimorphism depends on the *SRY* gene (sex-determining region on Y) localized on the short arm of the Y chromosome. The protein product of this gene is the testis-determining factor - a transcription factor that initiates a cascade of gene regulations resulting in formation of testis and male phenotype. Without its presence, female development is formed.

### Indifferent stage of gonads (in both male and female embryos)

- in week 5, the dorsal mesodermal epithelium proliferates, thus forming a pair of longitudinal genital (gonadal) ridges medially to the mesonephric ridge; the splanchnopleuric mesenchyme condenses below these ridges
- the genital ridges are formed from Th6 to S2
- in weeks, primordial germ cells migrate into these genital ridges from the yolk sac entoderm via the dorsal mesentery of the hindgut
- upon arriving into the gonads, the primordial gonocytes induce further differentiation of the gonads
- the epithelium of genital ridge proliferates and epithelial cells penetrate the underlying mesenchyme, thus forming primitive epithelial sex cords connected to the surface

### Indifferent stage of the genital ducts (in both male and female embryos)

- the mesonephric (Wolffian) ducts connect the mesonephros with the cloaca
- laterally to the genital ridge, the coelomic epithelium invaginates on the anterolateral surface of the urogenital ridge, thus forming the paramesonephric (Müllerian) ducts
- the Müllerian duct cranially opens into the abdominal cavity; caudally, it runs lateral to the mesonephric duct, then crosses it ventrally and grows caudomedially
- in the midline, both the left and right Müllerian ducts fuse, and form the uterovaginal canal
- the combined ducts enter the cloaca and after its division, the ducts enter the urogenital sinus, where it causes a small swelling, the sinus tubercle
- the mesonephric ducts open into the urogenital sinus on either side of the sinus tubercle

### Testis

- under the influence of the *SRY* gene coding the testis-determining factor, the testis differentiates from the indifferent gonad
- the primitive sex cords continue to proliferate and penetrate deeper into the medulla; in week 7, the cords separate from the coelom epithelium and become independent as a network of medullary cords, i.e., cells strands
- a dense fibrous connective tissue, the tunica albuginea, separates the testis from the surface epithelium; the testis cords develop into
  - supporting (sustentacular) cells of Sertoli, which surround the primordial germ cells and give rise to the seminiferous tubules
  - the rete testis

- the testis cords remain solid until puberty; during puberty, the gonadotropins of the adenohypophysis stimulate the tubules to differentiate further; the tubules acquire a lumen, thus forming seminiferous tubules
- interstitial cells of Leydig differentiate from the mesenchyme of the gonadal ridge; these lie between the testis cords; by the week 8, the Leydig cells produce androgens (e.g., testosterone)
- the androgens from the testis bind to the testosterone-receptor complex in cell nuclei in target cells, thus becoming the cause of sexual differentiation of the genital ducts and external genitalia

### **Male genital ducts**

- the mesonephric ducts are stimulated by the testosterone from the Leydig cells
- cranial and caudal mesonephric tubules regress and disappear; caudal mesonephric ducts differentiate into the efferent ductules of testis, which connect to the rete testis
- some mesonephric tubules that fail to join the rete testis, may persist as the paradidymis
- the cranial part of the mesonephric duct may persist as the appendix of the epididymidis
- the middle part of the mesonephric duct gives rise to the epididymic duct;
- the caudal part of the mesonephric duct obtains three smooth muscle layers, thus differentiating into the ductus deferens
- seminal vesicles originate as buds from the mesonephric duct; the part of the mesonephric duct caudal to the seminal vesicles forms the ejaculatory duct
- the product of the *SRY* gene results also in to production of steroidogenesis factor 1, that stimulates the production of anti-Müllerian hormone (anti-Müllerian substance) by Sertoli cells; this results in degeneration of the Müllerian duct in male
- the cranial part of the Müllerian duct forms the prostatic utricle (utriculus prostaticus)
- the Müllerian ducts may partially persist in some individuals, thus forming a small projection on the testis, named the appendix testis;

### **Ovary**

- the primitive sex cords dissociate into irregular cell clusters; later on, these clusters disappear, being replaced by vascular stroma of the ovarian medulla
- in week 7, the surface epithelium of the ovary proliferates, giving rise to a second generation of cortical cords; the cortical cords penetrate the mesenchyme
- in month 4, the secondary cords split into isolated clusters, which surround each oogonium with a layer of epithelial follicular cells
- together, each oogonium surrounded by the follicular cells constitute a primordial follicle
- the oogonia proliferate by mitotic cell divisions, thus giving rise to approx.. 4 millions of primordial follicles by prenatal month 6
- at any stage, the follicles degenerate by a process named atresia → at birth, approx. 1-2 millions of primordial follicles are present; further reduction of numbers of follicles results in approx. 200 000 follicles in puberty

### **Female genital ducts. Uterus and vagina**

- in the presence of maternal and placental estrogens and in the absence of the anti-Müllerian hormone, the right and left Müllerian ducts differentiate as follows:
  - the cranial portions give rise to the uterine tubes

- the caudal portions fuse in the midline and give rise to the uterovaginal canal, which further forms the
  - uterine canal (the uterus)
  - cranial portion of the vagina
- the urogenital ridges gradually move to the transverse plane, thus establishing the broad ligament of the uterus; this separates the cavity of the small pelvis into a dorsal rectouterine excavation and a dorsal vesicouterine excavation
- the mesonephros and the mesonephric ducts regress; small parts may persist as epoophoron, paroophoron, and Gartner canal
- the vagina is formed from two parts:
  - the fornix and the cranial third of the vagina and originate from the caudal tip of the mesodermal paramesonephric ducts
  - the caudal two thirds of the vagina originates from the sinovaginal bulbs that originate as evaginations of the entodermal urogenital sinus; the vagina forms as a thin persisting mesenchymal tissue plate lined with epithelium of the sinus and vaginal cells; during the perinatal period, the hymen develops a variable-sized and shaped opening, the ostium vaginae

#### **Indifferent stage of outer genital organs**

- mesenchyme elevates cloacal folds around the cloacal membrane
- cranial to the cloacal membrane, the folds unite into the genital tubercle
- as the urorectal septum divides the cloaca, the cloacal folds are also divided (in week 6) into urethral folds ventrally (these surround the urogenital sinus) and anal folds dorsally (these surround the anus)
- laterally to the urethral folds, outer genital swellings originate
- up to weeks 9-10, the external gross morphology of the outer genital organs looks identical in male and female fetuses; sometimes, the morphological diagnosis of the sex of the fetus monitored by ultrasound is not reliable until approximately week 20-25

#### **External genitalia in male**

- the fetal testes secrete androgens
- the genital tubercle elongates into the phallus
- the urethral folds also grow forwards and they surround an entodermal groove named the urethral groove
- in month 3, the urethral folds fuse, thus closing the urethral groove into the penile urethra (the penile raphe remains on the ventral surface of the penis)
- the distal part of the urethra, the external urethral meatus, originates by ectoderm invaginating from the tip of the penis inward; valves may persist as remnants of incomplete luminization
- the epithelial lamella surrounding the glans penis splits into two layers, thus giving rise to the prepuce (foreskin); this is attached by an elastic band named frenulum
- the outer genital swellings increase in size and become the scrotal swellings
- the scrotal swellings fuse in the midline, thus forming the scrotum; the scrotal raphe and the scrotal septum persist

### External genitalia in female

- the genital tubercle grows a bit, but does not elongate like the male phallus; it remains relatively smaller and forms the clitoris
- the urethral folds persist separately, developing into the labia minora
- the urogenital groove remains open and forms the vestibule
- the outer genital swellings will become the labia majora

### Descent of the testis

- the testes develop retroperitoneally in the lumbar region
- soon, they become intraperitoneal organs, being attached to the posterior abdominal wall with an urogenital mesentery, which develops into the caudal genital ligament
- the mesenchyme condenses into a ligamentous band attaching the caudal pole of the testis to the inguinal region and the outer genital swellings; this ligament is named the gubernaculum
- during weeks 12-28, the testis descends through the inguinal canal toward the scrotal swellings; the testis is followed by the ductus deferens, which originated from the mesonephric (Wolffian) duct
- the descent of the testis is stimulated by androgen hormones and by the Müllerian inhibiting substance
- the blood supply of testis from the aorta is retained (the testicular arteries)
- between weeks 33-38, the testis reaches the scrotum
- from the abdominal wall, following layers are derived and form the wall of scrotum:
  - the subcutaneous abdominal fascia → the tunica dartos
  - the superficial abdominal fascia and the external abdominal oblique muscle → the external spermatic fascia
  - the internal abdominal oblique muscle and the transversus abdominis muscle → the cremasteric fascia and muscle
  - the transversalis fascia forms the internal spermatic fascia
  - the parietal peritoneal layer → the parietal layer of the tunica vaginalis (periorchium)
  - the visceral peritoneal layer → the visceral layer of the tunica vaginalis (epiorchium)

### Descent of the ovaries

- is considerably less than je in the testis
- from the upper lumbar region, the ovaries migrate below the rim of the true pelvis
- the urogenital plica forms the cranial genital ligament, which becomes the suspensory ligament of the ovary (containing also the ovaric artery, ovaric veins, nerve plexuses)
- the upper part of the ovarian gubernaculum differentiates into the ligament of the ovary proper, which connects the ovary with the uterine horn (it contains the ovarian branch of the uterine artery)
- the lower portion of the ovarian gubernaculum → the round ligament of the uterus, extending into the labia

### Developmental defects of the genital system

- lack of fusion of the paramesonephric Müllerian ducts results in persistence of the uterine septum, abnormalities of the uterus and vagina (double uterine cavity or double vagina, uterus arcuatus, uterus bicornis), or partial obliteration of the uterine canal

- vestigial remnants of the mesonephric Wolffian ducts in female result in cysts in the Gartner's duct along the lateral walls of the vagina
- cryptorchidism is the absence of one or both testes from the scrotum when testis or testes fail to descend; the testes may be retained in the abdominal cavity or in the inguinal canal; the undescended testes fail to produce mature spermatozoa
- inborn indirect inguinal hernia: the vaginal process of the parietal peritoneal membrane does not close, but contains herniated intestinal loops that descend toward the scrotum
- disorders of sexual development
  - gonadal dysgenesis: loss of germ cells results in hypoplastic gonads without proper hormonal and reproductive function
  - hypogonadisms: hypoplasia and diminished functional activity of gonads
  - hermaphroditism: both testicular and ovarian tissue is present
  - ambiguous male or female phenotype, such as enlarged clitoris or hypoplastic penis
  - female pseudohermaphroditism (46, XX) or male pseudohermaphroditism (46, XY): the presence of gonads does not correspond with the development of the other genital organs, e.g.
    - congenital adrenal hyperplasia and adrenogenital syndrome: partial masculinization of females due to enzyme abnormalities in the adrenal glands
    - defects in enzymes necessary for synthesis of dihydrotestosterone result in underdeveloped male external genitalia
    - androgen insensitivity syndrome: lack of androgen receptors or the ability to respond to androgens, which results in developing a partially female phenotype or ambiguous genitalia in the presence of testis