Reproductive Endocrine System

A. Hypothalamus-pituitary
1. Ontogeny/embryology
   a. General
   b. Hormonal
2. Gonadotropin synthesis/biochemistry
3. Gonadotropin secretion
4. Gonadotropin action

B. Gonadal function and disorders
1. Development and differentiation of the reproductive system
   a. General
      1. Know the events associated with development of an embryo, including the contribution of the three germ layers

The primordial germ cells are the common origins of spermatozoa and oocytes and thus represent the ancestors of the germline. Primordial germ cells develop from the primary ectoderm in the second week.

The Urogenital ridges, the common precursors of the urinary and genital systems, develop at approximately 4 weeks post-fertilization in the human embryo as a thickening of the mesodermic mesonephros covered by coelomic epithelium.

Each urogenital ridge divides into a urinary and an adreno-gonadal ridge. The adreno-gonadal ridge is the common precursor of the gonads and adrenal glands. The gonadal ridge is bipotential and can develop into an ovary or a testis.

Gonadal ridge gets colonized by primordial germ cells.

The gonadal ridge also gives rise to two unipotential duct systems in both XX and XY embryos. Wolffian ducts are the primordia of the epididymides, vasa deferentia and seminal vesicles in the male fetus, whereas Müllerian ducts give rise to the Fallopian tubes, uterus and upper vagina in the female.

Fig 6 cross section of the human embryo during the undifferentiated phase of sexual development.
(Susan Standring, 2008)
2. Understand the mechanism and genetic regulation of the differentiation and growth of external genitalia in the fetus including the tissues of origin

The cloaca, the terminal portion of the hindgut limited by the cloacal membrane, is later divided into the urogenital sinus and the rectoanal sinus.

The urogenital sinus gives origin to the bladder in both sexes, the prostate and the prostatic & membranous portions of the urethra in the male, and the whole urethra & the lower portion of the vagina in the female.

Two mesodermal swellings developing under the ectoderm of the genital membrane, the urethral folds and the labioscrotal swellings are the precursors of the external genitalia, which remain undifferentiated until the 9th week.

The urethral folds form the labia minora in the female and the penile urethra in the male, and the labioscrotal swellings give rise to the labia majora in the female and the scrotum in the male.

3. Understand the relative functions and time of action of LH and hCG in fetal sexual differentiation

Leydig cells appear between weeks 7 and 8 in the human fetus, and proliferate until the 18th week of gestation. Receptors for human chorionic gonadotropin (hCG) are present on fetal Leydig cells by at least 12 weeks of gestation and help to insure continued testosterone secretion.
During the second half of pregnancy, LH becomes the principal regulator of testosterone secretion, and LH secretion is regulated in part by testosterone through negative feedback at the level of the hypothalamus.

4. Know that the yolk sac endoderm is the source of primordial germ cells

5. Know the role(s) of key genes on the X and Y chromosomes for gonadal differentiation

Expression of SF1 and WT1 in the undifferentiated gonad begin about simultaneously. WT1 activates the SF1 as well as SRY. Other potential targets during gonad formation include WNT-4, DAX1 and anti Mullerian hormone gene (AMH), all of which seem to be activated by WT1 variants.

Early studies revealed that SRY is first expressed around 10.5 days post coitus (DPC), shortly after the emergence of the genital ridges, reaches peak levels of expression at 11.5 DPC, and is extinguished.
shortly after 12.5 DPC in mouse. SRY clearly throws a molecular switch to engage a male specific cascade of molecular events, but continued expression of SRY is not required for these events to unfold.

The expression pattern of SF-1 is consistent with its central role in regulating adrenal development, gonad determination and differentiation and in the hypothalamic-pituitary control of reproduction and metabolism.

WNT4 is produced in ovarian somatic cells (pre-granulosa cells). Wnt4 up-regulates DAX1 which is known to antagonize SF1, and there by inhibits steroidogenic enzymes.

RSPO1 is the first gene described that, if mutated, leads to male development in XX subjects in absence of SRY together with other manifestations.

6. Know the gene maps of the X and Y chromosomes and relationships between genes on the respective chromosome

7. Understand X chromosome inactivation

Early in embryonic development in females, one of the two X chromosomes is randomly and permanently inactivated in cells other than gonadal cells. This phenomenon is called X-inactivation or Lyonization. X-inactivation ensures that females, like males, have one functional copy of the X chromosome in each body cell. Because X-inactivation is random, in normal females the X chromosome inherited from the mother is active in some cells, and the X chromosome inherited from the father is active in other cells.
8. Understand that germ cells migrate to the urogenital ridge to form the undifferentiated gonad

b. Gonads

1. Gonads - General
   a. Know the common derivation of the cell types of the testes and ovaries

2. Ovaries
   a. Know the relationship of egg meiotic phases to ovulation and the developmental stages at which the phases are reached

   By the fifth week of gestation, the premeiotic germ cells are referred to as oogonia arrive at the genital ridge (the “indifferent stage”)
   Between weeks 8 and 13 of fetal life, some of the oogonia depart from the mitotic cycle to enter the prophase of the first meiotic division
   Once formed, the primary oocyte persists in prophase of the first meiotic division until the time of ovulation, when meiosis is resumed and the first polar body is formed and extruded.

   ![Diagram of meiosis](image)

   b. Know that two X-chromosomes are necessary for maintenance of primordial follicle
      Primordial follicles are not found in the ovaries of 45,X fetuses
      Implies that 2 X chromosomes are necessary for development (or maybe maintenance of) primordial follicles, but no information on why this is true is available

   c. Know the changes in the number, size, and composition of ovarian follicles with age
      Class 1 follicle is a secondary follicle with theca cells and is presumed to become responsive to gonadotropins. Although the tonic (early) stage of follicle development (class 1 to 4) is likely to be gonadotropin-dependent (albeit to a lesser extent), the final stages of follicular development (class
5 to 8) are the ones heavily dependent on gonadotropins. According to this view, late luteal phase, class 5 follicles constitute the cohort from which the follicle destined to ovulate in the following cycle is recruited. The exponential gonadotropin-dependent growth phase (class 5 to 8) takes place during the follicular phase of the cycle following the third menses from initiation of the growth phase. During this time, follicular selection and dominance are accomplished.

Mean number (±S.E.M.) per ovary of growing ovarian follicles in humans in relation to women’s age

<table>
<thead>
<tr>
<th>Follicle class</th>
<th>Age groups (years)</th>
<th>19–30</th>
<th>31–35</th>
<th>36–40</th>
<th>41–45</th>
<th>≥46</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (Preamtra 0.15–0.2 mm)</td>
<td></td>
<td>26.8±2.5</td>
<td>14.9±3.5</td>
<td>23.0±4.4</td>
<td>10.1±1.2a</td>
<td>6.9±1.0c</td>
</tr>
<tr>
<td>2 (Early antra 0.2–0.4 mm)</td>
<td></td>
<td>31.4±8.9</td>
<td>16.2±4.1</td>
<td>19.8±3.8</td>
<td>7.4±1.2a</td>
<td>5.9±0.8</td>
</tr>
<tr>
<td>3 (Small antra 0.5–0.9 mm)</td>
<td></td>
<td>16.6±2.0</td>
<td>10.1±1.9</td>
<td>9.8±2.2</td>
<td>4.3±0.7a</td>
<td>2.5±0.3b</td>
</tr>
<tr>
<td>4 (Small antra 1–2 mm)</td>
<td></td>
<td>13.4±2.6</td>
<td>5.0±1.0a</td>
<td>5.6±1.3</td>
<td>2.5±0.5b</td>
<td>1.0±0.2b</td>
</tr>
<tr>
<td>5 (Selectable 2–5 mm)</td>
<td></td>
<td>10.6±1.7</td>
<td>4.5±0.7b</td>
<td>6.0±1.4</td>
<td>1.7±0.3a</td>
<td>1.1±0.2</td>
</tr>
</tbody>
</table>
d. Know the hormonal determinants of antral follicle formation and follicular growth

Antral follicles contain a fully grown oocyte, a large number of granulosa cells, a fluid-filled cavity, and a well-developed theca external to the basement membrane.

Class 5-8 follicles are antral follicles

Granulosa cells respond to FSH, whereas theca cells respond to LH and hCG, leading to formation of ovarian C19 steroids.

e. Know the cells types in the ovary and the hormones they secrete

In the primary ovarian follicle, and later in follicle development (folliculogenesis), granulosa cells advance to form a multilayered cumulus oophorus surrounding the oocyte in the preovulatory or antral (or Graafian) follicle.

The major functions of granulosa cells include the production of sex steroids, as well as myriad growth factors thought to interact with the oocyte during its development. The sex steroid production consists of follicle-stimulating hormone (FSH) stimulating granulosa cells to convert androgens (coming from the thecal cells) to estradiol by aromatase during the follicular phase of the menstrual cycle. However, after ovulation the granulosa cells turn into granulosa lutein cells that produce progesterone.

Theca cells function in a diverse range of necessary roles during folliculogenesis; to synthesize androgens, provide crosstalk with granulosa cells and oocytes during development, and provide structural support of the growing follicle as it progresses through the developmental stages to produce a mature and fertilizable oocyte. Androgen production from thecal cells in the gonadotropin-dependent stage is largely under the control of LH from the pituitary.

Androgens are then transported to the granulosa cells where P450 aromatase converts these androgens to estrone and 17β-estradiol.

f. Know the hormonal determinants of ovulation

- There is a dramatic rise in circulating estradiol level as midcycle approaches
- This increase in estradiol is followed by a striking LH and to a lesser extent an FSH surge
- This triggers the dominant follicle to ovulate
- Either LH or its surrogate hCG is essential to stimulate the rupture of the mature follicle
- Ovulation consists of rapid follicular enlargement followed by protrusion of the follicle from the surface of the ovarian cortex
- This is followed by the rupture of the follicle and extrusion of an egg-cumulus complex into the peritoneal cavity
- Follicular rupture or ovulation occurs predictably 34 to 36 hours from the start of the LH surge
- The gonadotropin-dependent production of proteases acting locally on protein substrates in the basal lamina may play an important role in stigma formation and follicular rupture
- Plasminogen activator–mediated conversion of plasminogen to plasmin may contribute to the proteolytic digestion of the follicular wall, which is a prerequisite for follicular rupture

3. Testes

a. Know the determinants of spermatogenesis and the developmental stages at which various phases are reached
• Migration of the germ cells to the genital ridge is completed during the second month of gestation (see diagram below for timing later in life)
• FSH acts directly on the spermatogenic tubule, whereas LH enhances spermatogenesis indirectly by increasing testosterone formation in Leydig cells
• FSH stimulates mitosis of Sertoli cells, increasing their number during puberty, and promotes maturation and development of tight junctions between Sertoli cells
• FSH actions in Sertoli cells include increased production of androgen-binding protein, transferrin, inhibin, aromatase, and plasminogen activators and enhanced uptake of glucose and enhanced conversion of glucose to lactate

b. Know the cell types in the testes and the hormones they secrete

• Leydig cells respond to LH/hCG and produce androstendione \(\rightarrow\) testosterone \(\rightarrow\) DHT
• Sertoli cells respond to FSH and multiple functions:
  o **Secrete:**
    ▪ AMH - secreted during the early stages of fetal life (see below for more)
    ▪ Inhibin and activins - secreted after puberty, and work together to regulate FSH secretion (see below for more)
    ▪ Androgen binding protein (also called testosterone binding globulin) - increases testosterone concentration in the seminiferous tubules to stimulate spermatogenesis
    ▪ Estradiol - aromatase from Sertoli cells convert testosterone to 17 beta estradiol to direct spermatogenesis
  o **Function:**
    ▪ Tight junctions of Sertoli cells form the blood-testis barrier
    ▪ Control the entry and exit of nutrients, hormones and other chemicals into the tubules of the testis as well as make the adluminal compartment an immune-privileged site.
    ▪ Ensures the renewal of stem cells and the differentiation of spermatogonia into mature germ cells that progress stepwise process of spermatogenesis \(\rightarrow\) ends in the release of spermatozoa
c. Know the hormonal regulation of Leydig cell steroidogenesis and the rate limiting steps

- See figure below.
- Limiting step is entry of cholesterol into cell by sTAR proteins

![Diagram of cholesterol metabolism]

**FIRST SIDE CHAIN CLEAVAGE**

- **PLASMA CHOLESTEROL**
- **CYP11A1**
- **3β-HSDII**
- **CYP17**
- **17α-HSD3**
- **17β-HSD3**

**SECOND SIDE CHAIN CLEAVAGE**

- **ACETATE**
- **CHOLESTEROL**
- **CHOLESTEROL ESTERS**
- **REDUCTION OF 17-KETO GROUP**

**A RING OXIDATION**

**d. Know the steps of testicular differentiation and the developmental ages at which they are reached**

- **SRY** expression directs proliferating somatic cells derived from the coelomic epithelium to differentiate into Sertoli cells at about 3-4 weeks
- The differentiation of Sertoli cells drives development of the testis
- An early endocrine function of the fetal testis is the secretion by the Sertoli cells of AMH
- Leydig cells are first found in 32- to 35-mm fetuses (about 60 days' gestation)
- After differentiation of the primitive testicular cords, leydig cells rapidly proliferate during the third month and the first half of the fourth month
- The onset of testosterone biosynthesis occurs at about 9 weeks
- HCG/LH receptors are present on fetal leydig cells by 10 to 12 weeks of gestation, which suggests that the initial T secretion is independent of these factors
- T secretion increases until about 20 weeks, then begins to decrease to prepubertal levels (see below)
4. Cryptorchidism

- Definition: congenital condition in which one or both testicles are not appropriately positioned in the scrotum at birth and cannot be moved into the proper position manually

a. Know the incidence of cryptorchidism at different ages and related conditions

- Relatively common condition – increases with prematurity
  - 4-5% in full term infants
  - 9-30% in premature infants
- Usually UNILATERAL (90%) and often right sided
  - Undescended testis can be located in abdomen (8%), inguinal canal (72%) and just distal to the inguinal ring (20%). Can also be ectopic → migrates along an abnormal pathway and can end up in perineum, femoral canal, contralateral scrotum, superficial inguinal pouch
- Factors that predispose to cryptorchidism include prematurity, low birth weight, small size for gestational age, twinning, and maternal exposure to estrogen during the first trimester
- Associated conditions include:
  - Abdominal wall defects (eg. gastroschisis, PBS)
  - Other urogenital defects (eg hypospadias, testicular CA, abnormal spermatogenesis)
  - Disorders of sexual development (eg, mixed gonadal dysgenesis, ovotesticular disorders of sex development, persistent Müllerian duct syndrome)
  - Genetic disorders causing diminished testosterone secretion (eg, Kallmann syndrome, Klinefelter syndrome, Prader-Willi syndrome) or action (androgen insensitivity syndrome)
  - Genetic disorders associated with primary hypogonadism and increased gonadotropin levels (eg, Noonan syndrome)
Genetic disorders that do not affect gonadotropins or testosterone (eg, trisomy 18, trisomy 13, 22q11.2 deletion syndrome, 1p36 deletion syndrome, Beckwith-Wiedemann syndrome, Smith-Lemli-Opitz syndrome, Cornelia de Lange syndrome)

b. Know the various etiologic factors in cryptorchidism

- Results from disruption in testicular descent – multifactorial → hormonal and mechanical
- Normal testicular development begins at conception → SRY gene is the testis-determining factor → presence of this gene and an intact downstream pathway generally result in testicular formation.
  - At 3-5 weeks' gestation, the gonadal ridge or indifferent gonad develops, and, at 6 weeks' gestation, primordial germ cell migration occurs.  
    - Soon after, Sertoli cells develop and secrete müllerian-inhibiting substance (MIS), the level of which remains high throughout gestation and causes regression of müllerian ducts.
  - At 9 weeks' gestation, Leydig cells develop and secrete testosterone. Prenatal ultrasonography shows no testicular descent before 28 weeks' gestation, other than transabdominal movement to the internal inguinal ring.
  - Furthermore, testosterone and its conversion to DHT are also necessary for continued migration, especially during the inguinoscrotal phase at 28-40wks gestation

Therefore disruption may be a result from:
  - Androgen Related
    - HPG Axis abnormalities – pituitary aplasia, Kallmann
    - Decreased androgen production
      - HPG axis abnormalities – pituitary aplasia, Kallmann, etc.
      - Androgen synthesis defects
    - Androgen Sensitivity
  - Mechanical anomalies
    - Urogenital obstruction – Prune Belly Syndrome, PUV, abdominal wall defects
  - Chromosomal Abnormalities
    - Genetic etiology suggested by the occurrence of undescended testes in 1.5-4% of fathers and 6.2% of brothers of patients with cryptorchidism

c. Know the pros and cons of chorionic gonadotropin or gonadotropin analog treatment of cryptorchidism and the age at which it may be indicated

- Testicular descent depends upon local concentrations of testosterone considerably greater than can be achieved through systemic administration
  - Administration of gonadotropins → HCG or GnRH analogs can stimulate the testes to increase production of testosterone achieve the necessary local concentration
• **PROS:** Noninvasive, but **CON:** How effective is it?
  o A 2012 systematic review of seven heterogeneous studies (including 995 boys, 1215 testes) of hormonal treatment of cryptorchidism found that:
    • Initial location of the testis may influence the likelihood of success → greater rates of descent usually are achieved with more distally located testes
      • However, it is possible that some of the distally located testes may have been retractile rather than truly undescended
    o GnRH analogs and hCG appeared to be similarly effective in achieving testicular descent (range 6 to 35 percent)
      • Only hCG is available in U.S.
  • Adverse effects are mild and transient, typically resolving within six months of treatment → most common adverse effects were virilization (eg, hair growth, increase in penis size, erections) and aggressive behavior.
  • **Bottom Line:** *Hormonal treatment is controversial*
    o Divergent results have been reported likely due to suboptimal study design, differences in patient age and treatment schedules, possible inclusion of retractile testes and variable follow-up.
      • Several meta-analyses of published literature suggest that the effectiveness of primary hormonal therapy in cryptorchidism is less than 20%

**d. Know the pros and cons of surgical treatment of cryptorchidism and the age at which it is indicated**

• **PROS:** goal of management is to place and fix viable undescended testes in a normal scrotal position or to remove nonviable testicular remnants.
  o Scrotal positioning reduces the risk of torsion and blunt traumatic injury (for intracanalicular testes) and permits easier examination of the testis.
  o If performed sufficiently early, surgical correction also may reduce the risk of infertility and testicular cancer.

• **CONS:** It’s SURGERY → complications include testicular atrophy (related to ischemic injury secondary to the dissection of the testicular vessels and/or postoperative swelling and inflammation), reascent of the testis (requiring repeat procedure), recurrence of inguinal hernia, infection, and bleeding, anesthesia
• Surgical treatment of undescended testes is recommended as soon as possible after six months of age for congenitally undescended testes and definitely should be completed before the child is two years old
  o In children with testicular ascent later in childhood, surgery generally should be performed within six months of identification.

e. Know the roles of testosterone and INSL3 in the process of testicular descent

• Descent is divided into 1) transabdominal and 2) transinguinal descent

• Androgens play a role in both these processes, particularly with respect to enabling the testis to traverse the inguinal canal in the final phase of descent.
  o Sertoli cells produce anti-Mullerian hormone (AMH) during a critical short window in early development to cause regression of Mullerian structures.
  o Contemporaneously, Leydig cells produce testosterone in large concentrations to act in a paracrine manner to stabilize the Wolffian ducts and systemically to masculinize the external genitalia.
    ▪ Later, high intratesticular concentrations are required for spermatogenesis
  o All these androgen effects are mediated by the ligand binding to the intracellular nuclear androgen receptor (AR) and activating androgen-responsive genes
    ▪ Experiments in animals suggest that androgens mediate this effect via the release of calcitonin gene-related peptide by the genitofemoral nerve, but direct evidence for such a mechanism is lacking in humans.

• The transabdominal phase of descent is under the control of insulin-like 3 (INSL3)
  o The Leydig cell also produces insulin-like 3 (INSL3) that is at least part controlled by HCG and LH → this peptide, by binding to its receptor leucine-rich repeat-containing G protein-coupled receptor 8 (LGR8), is also a factor in the control of testis descent.
  o Definitive evidence of its role in rodent testis descent is illustrated by the phenotype of bilateral cryptorchidism in Ins3−/− null mice.
  o Circulating levels of INSL3 are higher in boys at puberty, are undetectable in girls and are lower in boys with undescended testes.
    ▪ A minority also have a mutation either in the INSL3 gene or affecting its receptor gene, relaxin/insulin-like family peptide receptor 2 (LGRF8).
Component of fetal testis cells and their respective function. AR = androgen receptor

f. Know the role of measuring testicular products in the diagnosis of cryptorchidism versus anorchia

- With bilateral nonpalpable testes and is less than three months of age, serum luteinizing hormone, follicle-stimulating hormone, mullerian inhibiting substance, and testosterone will help determine whether testes are present.
  - **Testosterone:**
    - In infants with bilateral nonpalpable testes, the postnatal testosterone surge will be absent if anorchia is present.
    - After three months age, human chorionic gonadotropin stimulation will result in a measurable serum testosterone if testes are present.
      - A failure to respond to human chorionic gonadotropin stimulation in combination with elevated luteinizing hormone/ follicle-stimulating hormone levels is consistent with anorchia
  - **AMH:**
    - Marker of the prepubertal Sertoli cell.
      - In postnatal life, AMH testicular production is stimulated by FSH and potently inhibited by androgens.
      - Serum AMH is high from fetal life until puberty.
    - In anorchid patients, AMH is undetectable
    - In prepubertal males with fetal- or childhood-onset primary or central hypogonadism affecting the whole gonad, serum AMH is low
    - When hypogonadism only affects Leydig cells (i.e., LH/human chorionic gonadotrophin receptor or steroidogenic enzyme defects), serum AMH is normal/high
    - CAIS/PAIS - AMH is also normal/high
    - Pubertal age with central hypogonadism - AMH is low for Tanner stage – reflecting lack of FSH stimulus, – but high for age – reflecting lack of testosterone inhibitory effect
Inhibin B:
- Produced predominantly by the Sertoli cells in the prepubertal testis (adult site controversial)
- Controls FSH secretion via a negative feedback mechanism
- The regulation of inhibin B production changes during life.
  - Peak in serum shortly after birth → partly correlated with an increase in serum FSH, probably reflecting the proliferating activity of the Sertoli cells during this phase of life.
  - Afterwards, inhibin B levels decrease and remain low until puberty, when they rise again, first as a consequence of FSH stimulation and then as a result of the combined regulation by FSH and the ongoing spermatogenesis.
- In the adult, serum inhibin B shows a clear diurnal variation closely related to that of testosterone.
  - Serum inhibin B levels are strongly positively correlated with testicular volume and sperm counts.

g. Know that the contralateral testis in a patient with an undescended testis might itself be abnormal
- Higher rates of:
  - Testicular cancer – Approx 15% of tumors arise in the contralateral descended testis
  - Structural defects → patent processus vaginalis, horizontal lie, and ectopic testis → may increase risk for torsion
  - Other abnormalities were abnormal epididymal-testicular fusion, hydrocele

h. Recognize how compensatory hypertrophy in a testis relates to the function of the other testis
- Undescended testis often has reduced number of Leydig/interstitial cells in undescended as compared to contralateral descended testis and with increasing age at orchidopexy
  - Disruption of morphology, failure of maturation at puberty and evidence for reduced number of Sertoli cells after 4 months of age in the cryptorchid testis → results in atrophy of affected (undescended) testis and therefore hypertrophy of contralateral (descended testis)

i. Know that fertility may be affected in unilateral cryptorchidism
- In patients who have undergone orchiopexy at an early age, abnormal semen quality is common, with reduced sperm counts reported in 75-100% (bilaterally) and 18-43% (unilaterally) cryptorchid men
  - However, 90% of boys with unilateral cryptorchidism and 65% with bilateral cryptorchidism will achieve paternity
  - Patients who are interested in their risk for infertility may have a semen analysis performed at age 18
• Elevated follicle stimulating hormone (FSH) concentration and decreased serum inhibin B concentration are endocrinologic markers of Sertoli cell/seminiferous tubule dysfunction
• In most studies of men with a history of cryptorchidism, Sertoli cell/seminiferous tubule function (spermatogenesis) is impaired, but Leydig cell function (virilization) is not

j. Know that cryptorchidism may lead to testicular carcinoma, the relative incidence of such carcinoma, and recommend monitoring

• Strong positive correlation between cryptorchidism and testicular cancer → seminoma, germ cell carcinomas
  o An estimated ten percent of all testicular tumors develop from an undescended testicle
  o A commonly used estimate for cancer risk is that relative risk of incidence of a testicular tumor is about 2 to 8 times greater in men with cryptorchidism when compared to the general population.
    ▪ Prepubertal orchiopexy may decrease the risk of testicular cancer and that early surgical intervention is indicated in children with cryptorchidism
• Monitoring:
  o After successful orchiopexy, patients are examined at 6 to 12 months to check on testicular size and position
  o All patients should be taught proper monthly testicular self-exam at the time of puberty
  o Some patients with cryptorchidism are at a higher risk of cancer (prune belly syndrome, ambiguous genitalia, karyotypic abnormalities, or the postpubertal boy)

c. Genital tract: differentiation and development

1. Müllerian ducts
a. Embryonic differentiation

1. Know that anti-Müllerian hormone is a member of the TGF-beta superfamily and that it is secreted by sertoli cells

AMH is secreted from Sertoli cells and promotes regression of the Mullerian ducts in 46,XY fetuses from weeks 8-10 of gestation. It does this by inducing apoptosis and loss of basement membrane integrity of the epithelial and mesenchymal cells. The vestigial remnants of the mullerian duct become the prostatic utricle.

TGFβ (transforming growth factor) family – Includes AMH, inhibin, activins and others.

2. Know that the Müllerian duct differentiates to the uterus, fallopian tubes, and upper vagina