PHYSIOLOGY 301
REPRODUCTIVE PHYSIOLOGY
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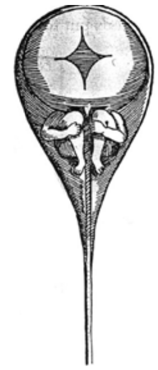

REPRODUCTIVE PHYSIOLOGY: MALE

Following the lectures you should be able to:
- *Describe major components of the male reproductive system*
- *Describe the anatomy of the testis and outline the process of spermatogenesis*
- *Describe the functions of the reproductive tract and accessory glands*
- *Describe the hormonal mechanisms that regulate male reproductive functions*

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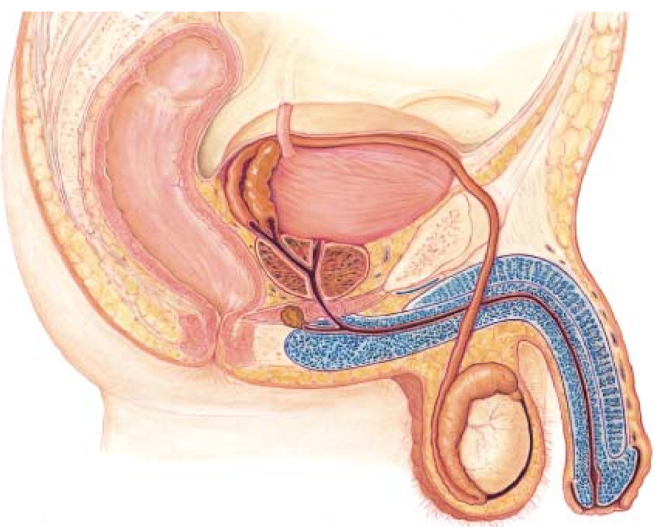
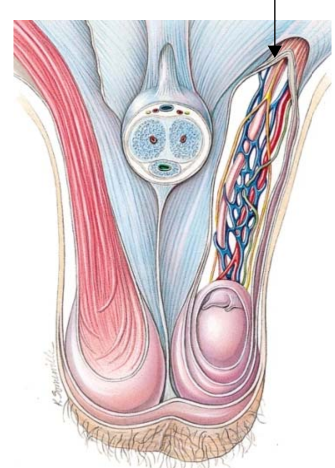
Male reproductive organs include:



- Testes (1) or male gonads producing ***sperm (spermatogenesis)*** and male sex hormone ***testosterone***
- Reproductive tract or a system of ducts specialized to store and/or transport sperm:
  - ***Epididymis*** (2)
  - ***Vas deferens*** (3)
  - ***Urethra*** (4)
- Accessory sex glands that produce supportive secretions:
  - ***Seminal vesicles*** (5)
  - ***Prostate*** (6)
  - ***Bulbourethral (Cowper's) glands*** (7)
- ***Penis*** (8)

inguinal canal



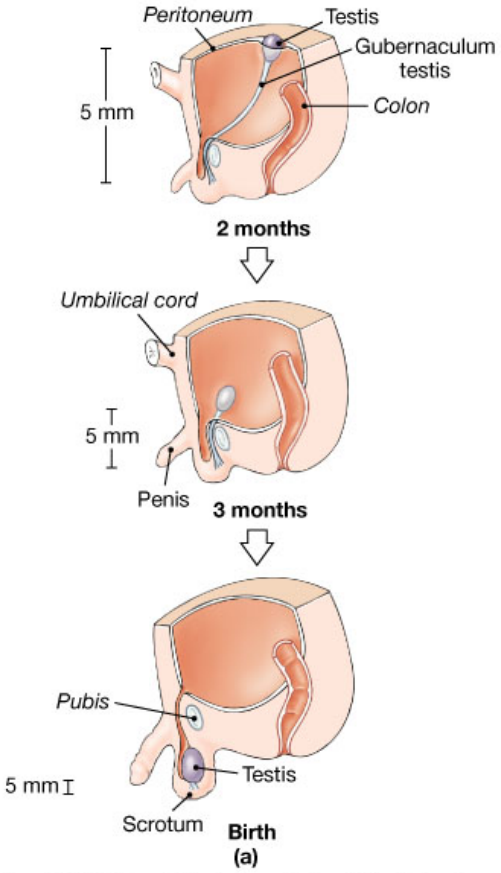
Spermatogenesis cannot occur at normal body temperature
- The optimal temperature for sperm production is 34-36^0 C
- Adaptations to lower temperature include:
  1. superficial location of testes in scrotum
  2. dartos muscle
  3. cremaster muscle – is skeletal
  4. pampiniform plexus

Testes descend to the scrotum during fetal development

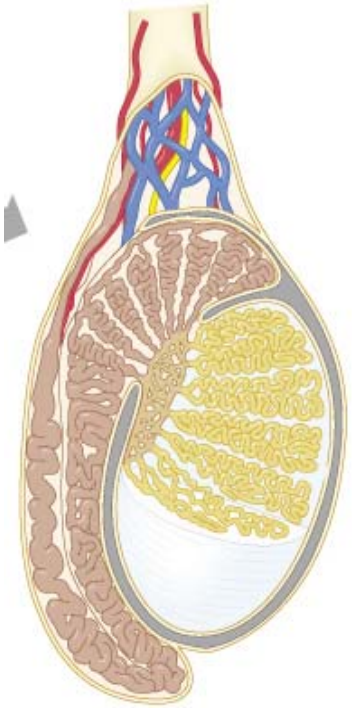
- During embryonic life the testes, their ducts (epididymis and vas deferens), blood vessels and nerves develop in the body cavity near the kidneys; they are connected with the floor of the scrotum via a strong fibrous cord, the gubernaculum.

  increase in cancer risk if testes do not descend

- By the 3rd month the testes descend to the pelvis and by the time of birth they enter the scrotum

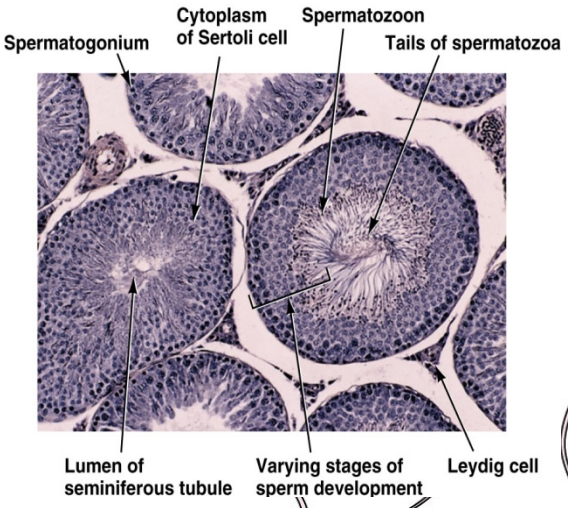


Each testis is a system of ducts

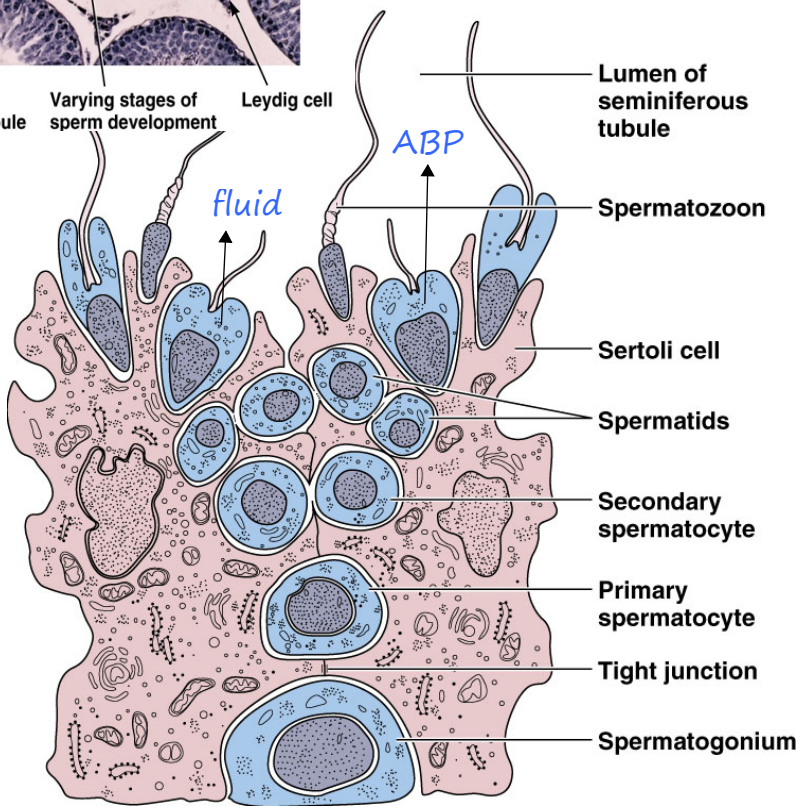


- Each testis is 4x2.5 cm in size and is surrounded by 2 membranes: ***tunica vaginalis*** *(1)* and ***tunica albuginea*** (2) (collagen-rich fibrous capsule).
- ***Septa*** (3) divide testis into 250-300 ***lobules*** *(4)*, each containing 1-4 sperm-producing ***seminiferous tubules*** *(5)*
  - total length of seminiferous tubules is **250 m!!**
  - walls of seminiferous tubules are lined with ***Sertoli*** *cells,* essential for proper sperm development.
  - ***Leydig*** *cells* located between the seminiferous tubules secrete ***testosterone***, the male sex hormone.
- Within each septum, the seminiferous tubules extend into 15-20 ***efferent ducts*** (6) → combine to form the ***epididymis*** (7).

Spermatogenesis takes place within the seminiferous tubules



Sperm cells develop in close relationship to the Sertoli cells



Stages	# of chromosomes in each cell

Sertoli cells perform critical functions in spermatogenesis

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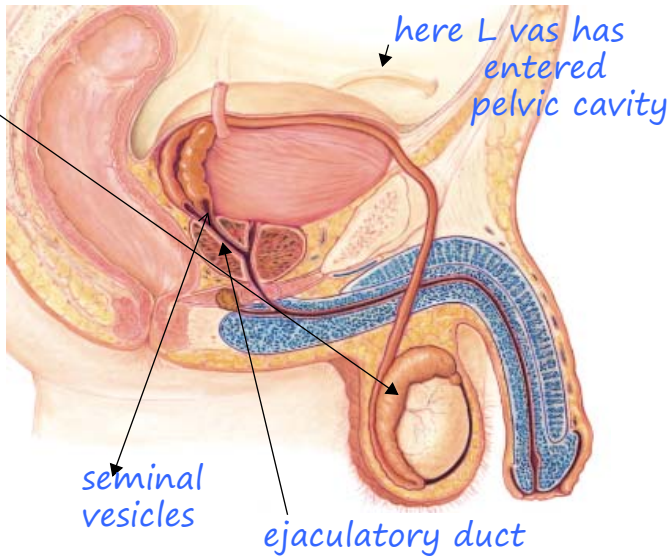
missing previous

1. Form the ***blood-testis barrier*** formed by tight junctions do not want to expose sperm to molecules that can interfere with spermatogenesis
2. Provide ***nourishment*** for the developing sperm cells
3. ***Secrete fluid*** into the lumen of seminiferous tubules to force the spermatozoa into the epididymis due to pressure of the fluid - need the correct pressure to move them at correct speed
4. Secrete ***androgen-binding protein (ABP)*** which binds ***testosterone*** (T): this maintains high concentration of T required for proper spermatogenesis
5. Secrete hormone ***inhibin*** involved in regulation of FSH secretion secreted into the blood circulation to reach anterior pituitary

Following spermatogenesis, the sperm enter the epididymis and then vas deference

maturation storage

- **Epididymis**
  - 6 m long, highly coiled tubule
  - The sperm spend 14-20 days there to gain the ability to move and to undergo **functional maturation** before entering the *vas deferens*.
- **Vas deferens**
  - A 45 cm long extension of the epididymis
  - It enters the pelvic cavity through the *inguinal canal;* on the posterior wall of the urinary bladder it joins the duct of ***seminal vesicle*** to form short ***ejaculatory duct*** within the ***prostate gland*** to finally unite with the ***urethra***.



The accessory glands contribute the bulk of the semen

- **Seminal Vesicles**
  - 5 cm long, located on the posterior wall of the bladder
  - The alkaline secretions form 60% of the semen volume and include *fructose*, used by spermatozoa to produce ATP (allowing for their motility!), *vesiculase*, a coagulating enzyme, and prostaglandins which induce contractions of the vagina and uterus to facilitate fertilization.
- **Prostate**
  - Walnut-size single gland made up of secretory tissue embedded in a mass of smooth muscle.
  - Its secretions account for about 30% of the semen volume, are milky, slightly acidic, contain nutrient *citrate*, several enzymes, antibiotic *seminalplasmin*, and *prostate-specific antigen* (PSA); all play important role in sperm activation.

    Prostatitis*: benign enlargement (inflammation) of the prostate; is of medical importance as it is very common in men after the age of 50, leads to difficulties associated with normal urination.*

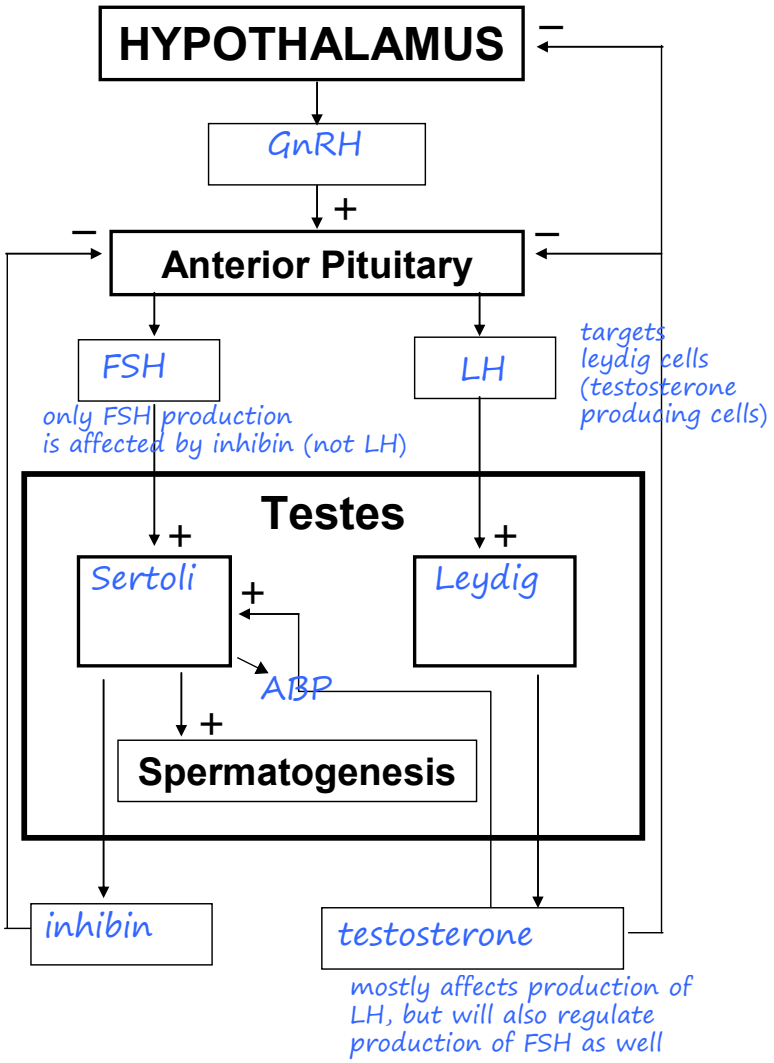
    Prostatic cancer*: most prevalent cancer and second leading cause of cancer deaths in men; screening involves assay of prostate-specific antigen (PSA) (tumor marker, increases with progression of disease) levels in the blood*
- **Bulbourethral (Cowper's) glands**
  - Pea-size, located just inferior to the prostate
  - Produce thick alkaline mucus, which drains into the penile urethra where it neutralizes traces of acidic urine.

sperm stats
- production ~6.5 million/gram/day
- testis weight: 10-15g
- semen volume: 2-6ml
- sperm density: > 20 million sperm/ml. Less than 5 mill/ml = sterile

Endocrine activity of testes is regulated by the hypothalamus – pituitary – testicular axis

LH and FSH control testosterone secretion and spermatogenesis respectively

High [T] is required for proper spermatogenesis
Binding of T to ABP produced by the Sertoli cells maintains very high concentrations of T within testes



REPRODUCTIVE PHYSIOLOGY: FEMALE

Following the lectures you should be able to:

- *Describe major components of the female reproductive system*
- *Describe and distinguish the processes of oogenesis and folliculogenesis*
- *Identify the phases and describe the events of the ovarian and uterine cycles*
- *Describe the hormonal mechanisms that regulate female reproductive functions*

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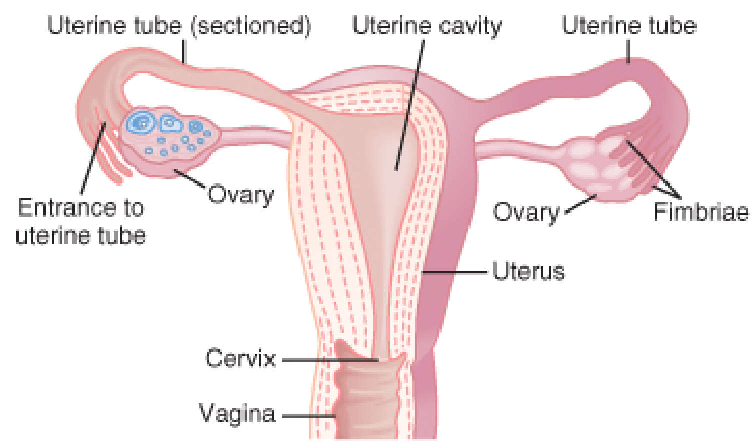
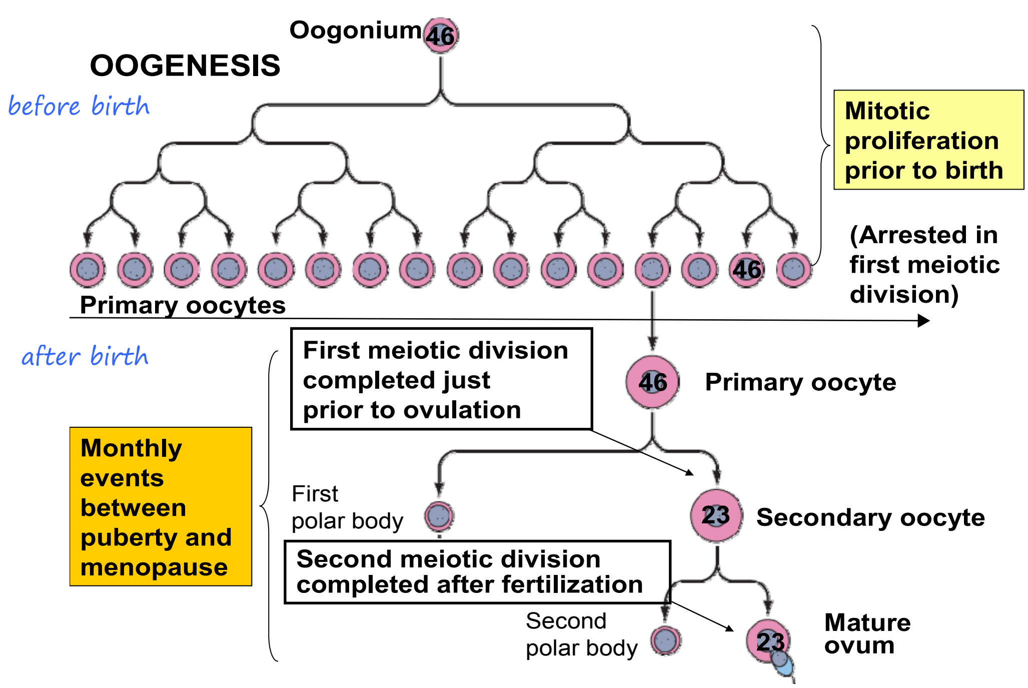
Female reproductive organs include:

- ***Ovaries*** or female gonads: produce gametes (***ova***) in a process called ***oogenesis*** as well as female sex steroids ***estrogen*** and ***progesterone***
- ***Reproductive tract*** that consists of:
  - ***Oviducts (Fallopian tubes)***: receive ovulated ova, are the site of fertilization
  - ***Uterus***: the site of menstrual bleeding as well as embryonic and fetal development
  - ***Vagina***: connects the uterus to the external environment, site of sperm deposition



Production of ova by the ovary

- Oogenesis in females is very different than spermatogenesis in males:
  - ❖ The total supply of eggs is determined at birth
  - ❖ The eggs are released in monthly cycles from puberty until menopause (at the age of ~51 in Canada).



- ***Oogonia*** (similar to spermatogonia) appear during early prenatal development, divide by mitosis and are diploid.
- Before birth, about 400,000 of the oogonia enlarge in each ovary to form ***primary oocytes***; these enter meiosis but become arrested at the prophase I of the first meiotic division.

- At birth each primary oocyte is surrounded by a single layer of flat follicular cells to form a ***primordial follicle***
- The number of primordial follicles in ovaries at the time of birth is referred to as the ***ovary reserve***
- No new oocytes are produced after birth and all primordial follicles remain dormant until puberty
- After puberty, the ovaries enter monthly **ovarian cycles** to produce a single "dominant" follicle that releases its oocyte during ovulation.
  - Only about 400 follicles ovulate during the reproductive life of a woman
  - The remaining 99.9% undergo *atresia* (degeneration) due to *apoptosis* or programmed cell death.

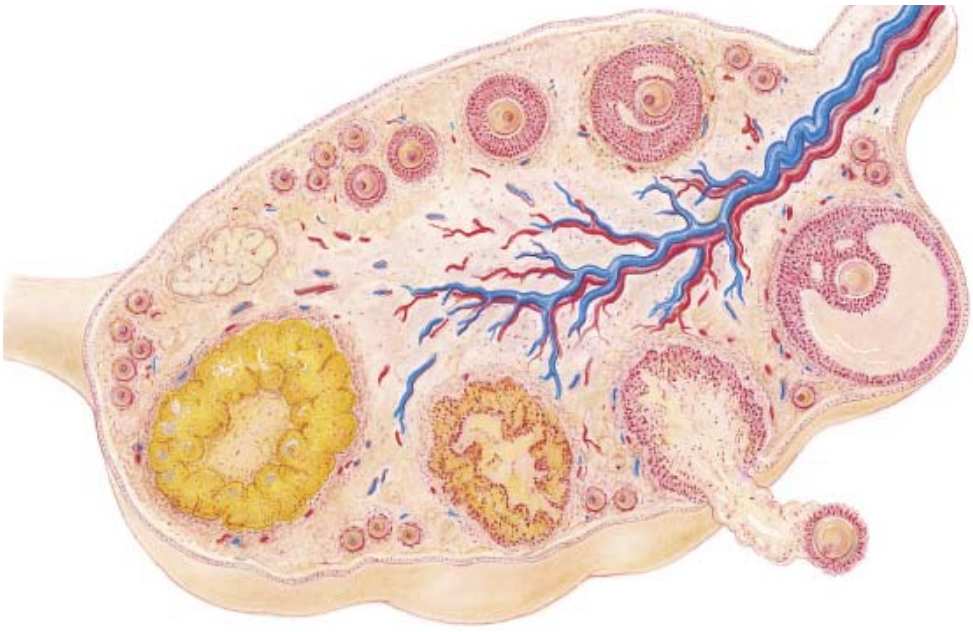
primary oocyte + follicular cells = primordial follicle

Recruited primordial follicles become primary follicles

- Pools of primordial follicles are recruited throughout the reproductive life of a woman to form primary follicles surrounded by a single layer of cube-shaped **granulosa cells** (GCs)
- Recruitment continues until the pool of primordial follicles is exhausted at menopause

In the pool of recruited primary follicles, most will undergo atresia, some will become secondary follicles and a few will develop into tertiary (Graafian) follicles from which a single dominant (ovulating) follicle will emerge.

- Primary follicles become **secondary follicles** as they begin to accumulate multiple layers of GCs and acquire an additional external layer of the *theca cells*
- Secondary follicles develop into **tertiary (Graafian) follicles** as a result of formation of fluid-filled *antrum* and rapid growth (as much as 100X)
- During each cycle, one of tertiary follicles becomes **dominant** and *ovulates*, the remaining follicles undergo atresia



- Just prior to ovulation, the oocyte completes the first meiotic division and a large **secondary oocyte** (*ovum*) and a *first polar body* are formed; the secondary oocyte becomes arrested at the metaphase II of the 2nd meiotic division.
- Following ovulation, the ovum enters and passes down the oviduct and, if sperm are present, may be fertilized there.
- The 2nd meiotic division is completed only after a haploid sperm has penetrated the ovum's cell membrane to produce a haploid mature ovum and a second polar body.

It takes several months for a follicle to grow form the primordial to tertiary or Graafian stage

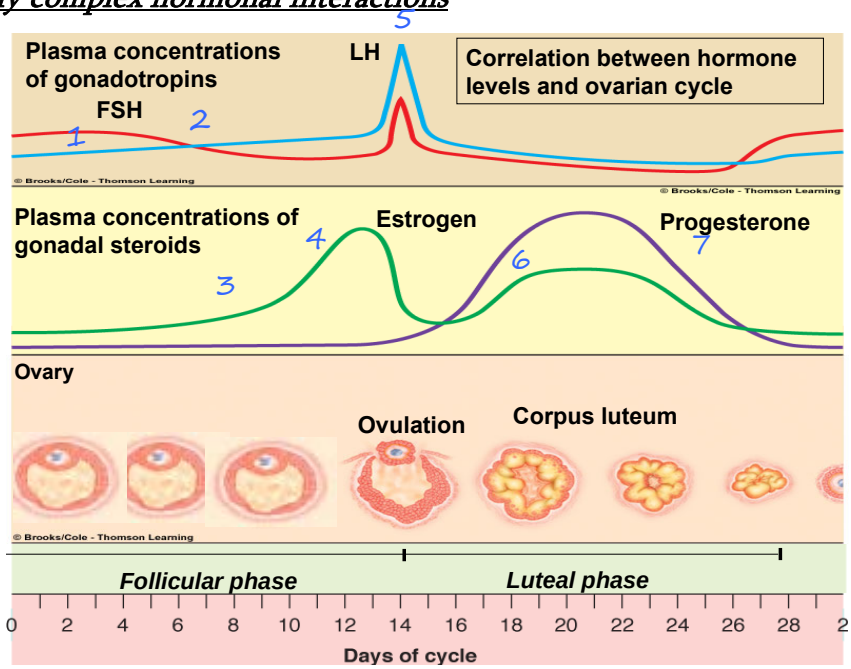
- Follicle growth (***folliculogenesis***) consists of 2 phases:
  1. ***Preantral*** or ***gonadotropin-independent phase***, characterized by the growth and differentiation of follicles; is controlled by locally produced growth factors through autocrine/paracrine mechanisms and
  2. ***Antral or gonadotropin-dependent phase***, controlled by FSH, LH, estrogen and growth factors; characterized by additional growth and selection of a single *dominant follicle*, which ultimately releases its oocyte as a result of *ovulation*.
- After ovulation, the dominant follicle transforms into ***corpus luteum*** (CL).

The ovarian cycle

- Encompasses the events of selection and development of the dominant follicle, ovulation and formation of the CL .
- The average length = 28 days
- Days 1-14: **follicular phase**, characterized by the presence of maturing follicles; it culminates in *ovulation*
- Days 15-28: **luteal phase**, characterized by the presence of the CL; it culminates in **menstruation,** UNLESS THE OVULATED EGG HAS BEEN FERTILIZED.

The ovarian cycle is controlled by extremely complex hormonal interactions

- **Estrogen (E) regulated changes in the hypothalamic GnRH pulse frequency and amplitude control the release of FSH and LH from the anterior pituitary.**



1. Early in the follicular phase, *relatively* low E levels produced by the maturing tertiary follicles maintain low frequency of GnRH pulses: <u>this favors the release of FSH over LH</u>
2. As follicles continue to develop, FSH release declines due to the negative feedback effects of follicular *inhibin*.
3. E production by what is now a single **dominant follicle** increases sharply; this slowly increases GnRH pulse frequency which gradually increases secretion of LH.
4. At roughly day 10 of the cycle, E levels are high enough to reach threshold; now very high concentration of E induces a very high GnRH pulse frequency which, in turn, stimulates the release of large quantities of LH from the anterior pituitary.
5. These changes result in the <u>LH peak</u> at about day 14 of the cycle, triggering the following: (1) completion of meiosis I by the oocyte (inducing the transition of primary oocyte → **secondary** oocyte.), (2) rupture of the follicular wall, (3) ovulation and (4) formation of CL.
6. The CL begins to secrete high levels of progesterone (P) and moderate amounts of E which results in a very sharp ↓ of GnRH pulse frequency → inhibition of LH and FSH.
7. P levels remain high for about a week but unless pregnancy occurs, the CL begins to deteriorate → rapid ↓ in levels of P and E → a small ↑ in the frequency of GnRH pulses that stimulates FSH secretion to initiate next ovarian cycle.
8. Such hormonal changes affect the activity and function of other reproductive structures such as the uterus.

Administration of appropriate quantities of estrogen, progesterone or both during the early stages of the follicular phase will inhibit the pre-ovulatory LH peak. Can you think of a practical application of this phenomenon?

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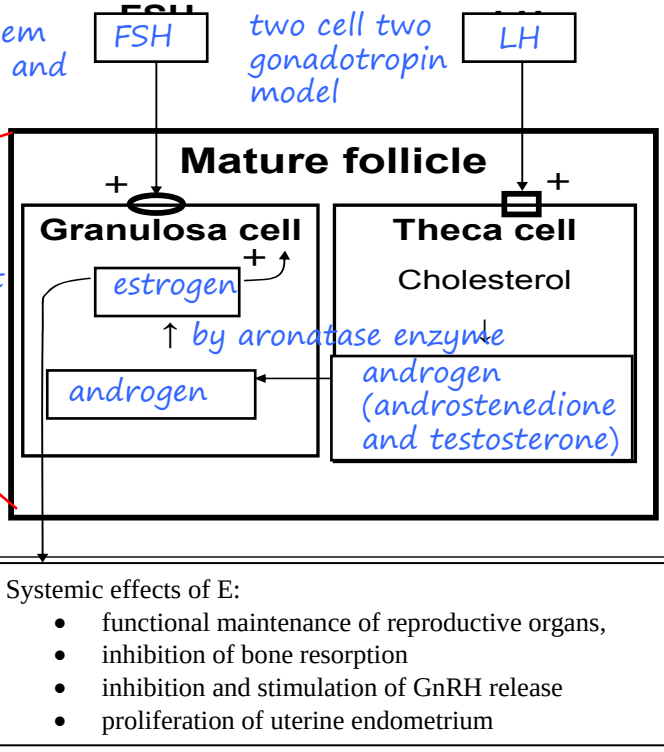
key points:
changes in GnRH pulse frequencies control the release of LH and FSH
  low freq GnRH pulses = FSH
  high fre GnRH pulses = LH
GnRH release is controlled by follicular estrogen

low E = low freq GnRH pulses = FSH (1)
gradual increase in estrogen = gradual increase in GnRH pulses = gradual increase in LH
very very high estrogen = very very high frequency GnRH = very very high LH (4 and 5) - right before ovulation

Estrogen production by follicles is regulated by LH and FSH and requires close interactions between the theca and granulosa cells

LH binds to receptors on theca - stimulates them to use cholesterol to synthesize androgen (test, and androstenedione



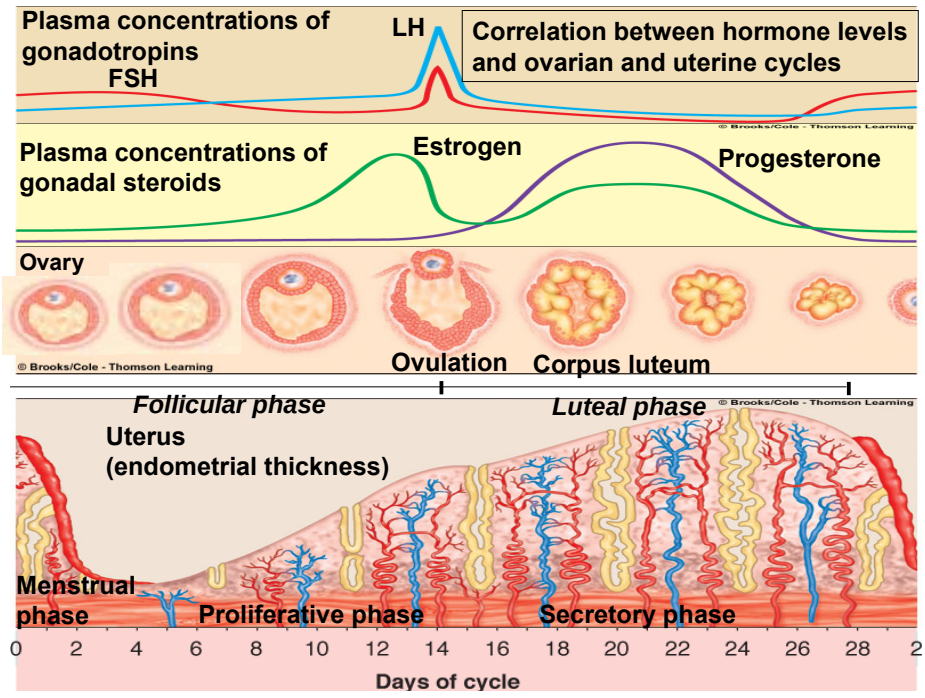
Systemic effects of E:
- functional maintenance of reproductive organs,
- inhibition of bone resorption
- inhibition and stimulation of GnRH release
- proliferation of uterine endometrium

Hormonal changes associated with the ovarian cycle have significant effects on the uterus

- The ***uterine (menstrual) cycle*** consists of repeating changes in the structure of uterine lining or ***endometrium*** and is divided into 3 phases: (1) ***proliferative***, (2) ***secretory*** and (3) ***menstrual***.
  1. The ***proliferative*** phase is stimulated and sustained by increasing levels of E produced by the rapidly developing follicles and involves development of the endometrial glands and vascularization of the lining.
     - As a result, by the time of ovulation the so called 'functional zone' of endometrium is several mm thick, the glands secrete mucus rich in glycogen and numerous spiral arteries are present.

changes in the uterus

two weeks before menstration



2. The ***secretory*** phase begins at ovulation, as endometrial glands enlarge and produce large amounts of secretions under the combined stimulatory effects of P and E from the CL.

synchronized with luteal

- Secretory activities peak at about day 12 after ovulation and then decline as the CL begins to degenerate.

estrogen still needed to maintain lining

- As a result of ↓ P and E levels, the spiral arteries constrict reducing blood flow to the endometrium and causing rapid degeneration of its functional zone.

3. As weakened arterial walls rupture, blood and degenerating lining enter the uterine lumen and are discharged from the vagina, giving rise to the ***menstrual*** phase. The sloughing off of endometrial tissue continues for several days until rising E levels produced by the next batch of developing follicles stimulate the repair and regeneration of the lining.

prog needed to activate glands

no fertilization - corpus luteum begins to degenerate = decrease in estrogen and progesterone = changes in lining (decrease in blood supply due to decrease in progesterone - the spiral arteries degenerate) and tissue is sloughed off during menstration, the next batch of follicles is ready. Estrogen is low enough to stimulate FSH

REPRODUCTIVE SYSTEM: PREGNANCY

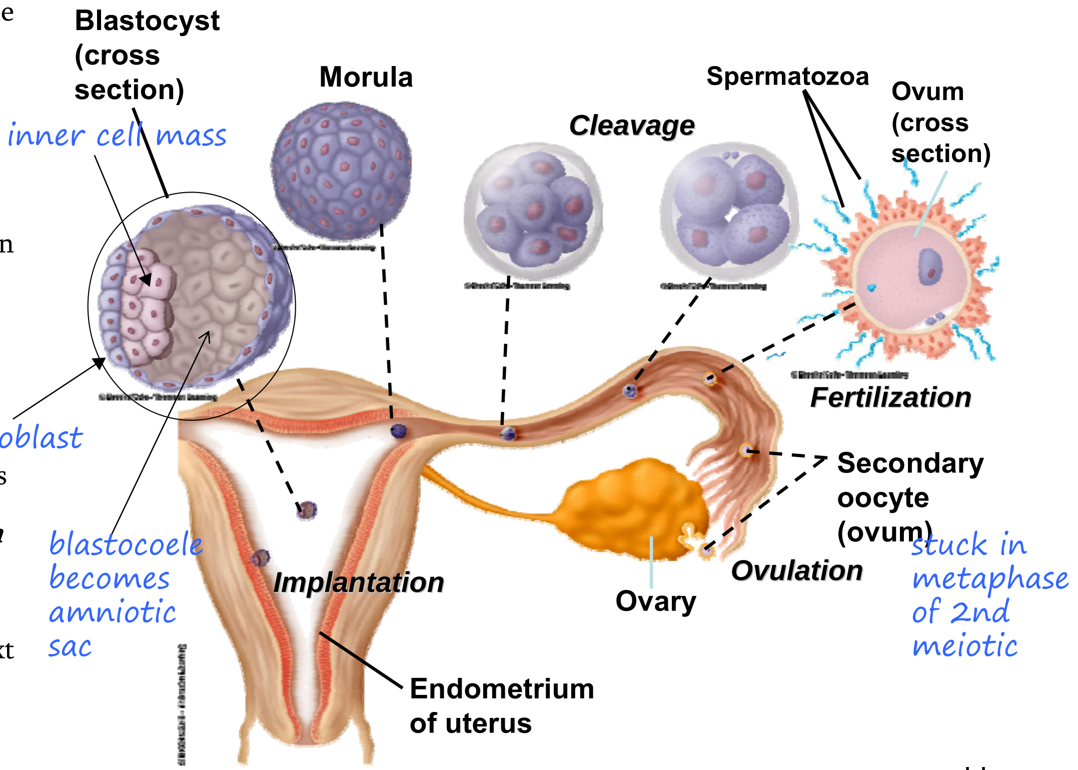
Following the lectures you should be able to:

- *Describe the events occurring between fertilization and implantation*
- *Describe the role of the placenta in exchanges between the maternal and fetal blood*
- *Describe and distinguish between the hormonal control of pregnancy provided by the corpus luteum and the placenta*

♂♀

The oviduct is the site of fertilization

- Fertilization usually occurs in the upper third of the oviduct, typically within 24 hours after ovulation (sperm cells can actually survive up to five days in the female reproductive tract).
- The fertilized ovum = ***zygote***
- The zygote undergoes rapid mitotic divisions and after 3 days a solid ball of cells or the ***morula*** is formed; morula reaches the uterus on day 4 and over the next



two days develops into the ***blastocyst***, a hollow ball with an inner cavity known as the ***blastocoele*** ,that is ready to be implanted in the uterine wall.

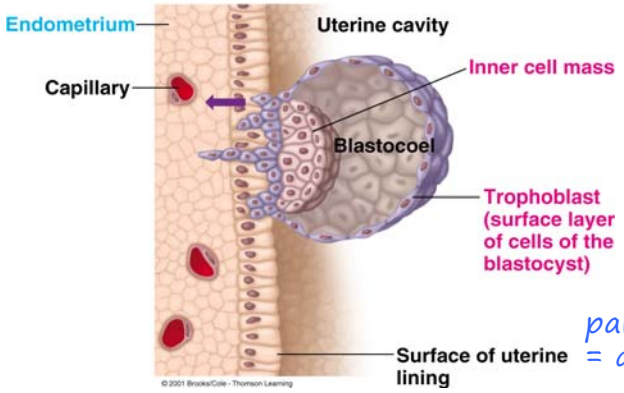
involved in implantation and contributes to fetal port of placenta

- The outer layer of the blastocyst cells called the ***trophoblast*** is responsible for providing nutrients to the developing embryo; a cluster of cells at one end of the blastocyst is called the ***inner cell mass*** and will form the embryo itself.

develops into fetus

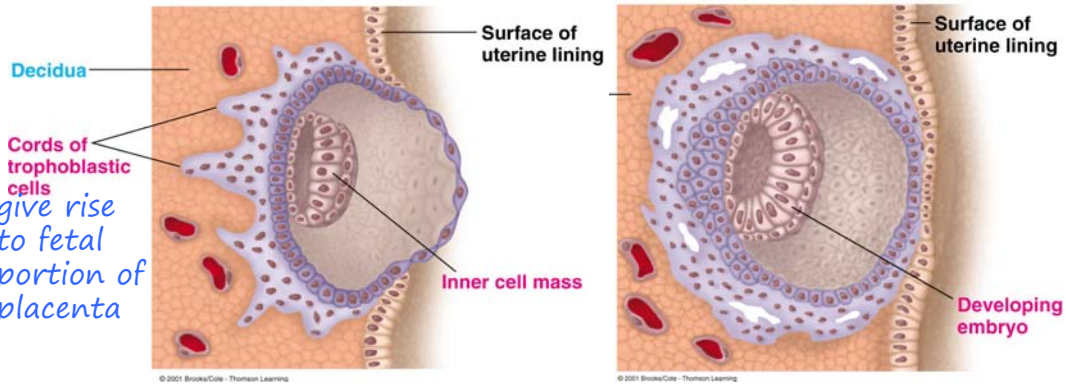
<u>The trophoblast secretes enzymes involved in implantation and a hormone hCG that maintains the CL</u>

- The trophoblast performs two critically important functions:
  1. It secretes enzymes that digest proteins on the uterine lining: this carves a hole in the endometrium for ***implantation***.
  2. It secretes a hormone ***human chorionic gonadotropin (hCG) that is <u>absolutely essential</u>*** for the success of pregnancy as it maintains a functional CL in the ovary until the placenta takes over steroid hormone production at the end of the first trimester.



Implantation of the blastocyst

part of endometrium near blasto = decidua



give rise to fetal portion of placenta

functional CL = produces estrogen and progest

most cause of spontaneous abortion = low hCG

estrogen maintains functional uterus.

progest prevents spontaneous uterine muscle contractions (myometrial contractions)

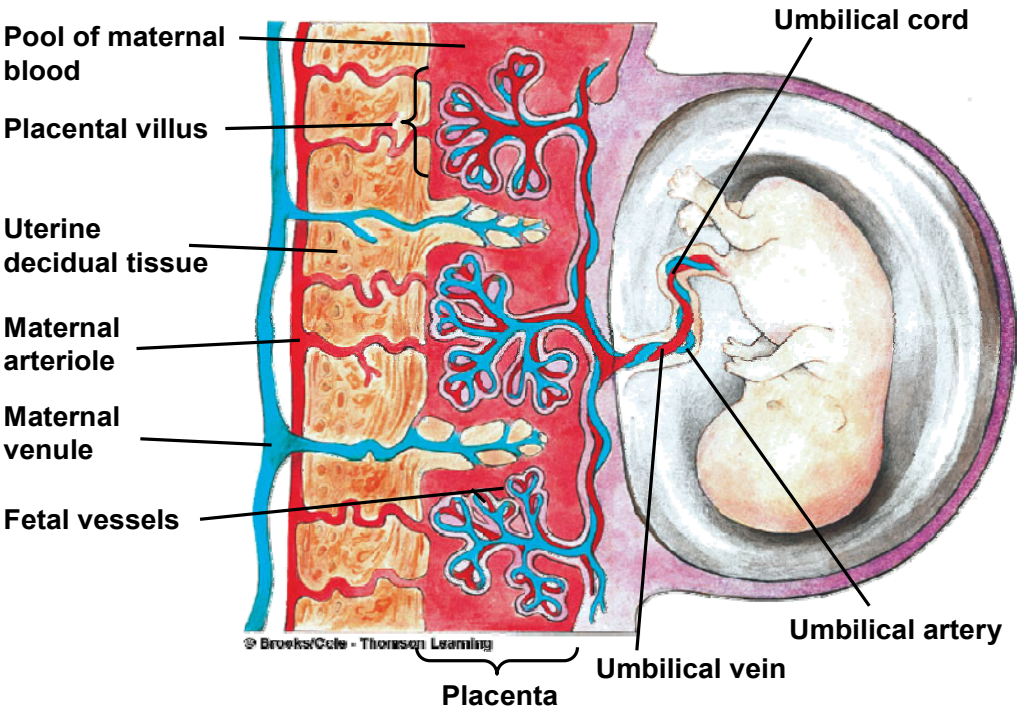
- ➢ *Progesterone from the CL is continuously required to prevent myometrial (uterine muscle) contractions that would expel the newly implanted blastocyst.*
  - *This is the basis for RU486 (the "morning after" pill), a progesterone antagonist that maintains uterine contractility and thus prevents implantation.*
- ➢ *Commercially available pregnancy tests detect presence of hCG in urine*

only produced upon fertilization

- The trophoblast also contributes to the formation of ***placenta***

Placenta allows for the exchange of nutrients and metabolic wastes between maternal and fetal blood

- Formed by interlocking maternal and fetal structures.
- Fetal structures include the placental villi, fingerlike projections that protrude into pools of maternal blood within intervillus spaces that are supplied by maternal arterioles.
- Fetal blood continuously flows between the placental villi and the fetal circulation by means of the umbilical artery and vein found within the umbilical cord.
- As the maternal blood percolates through the intervillus spaces, it exchanges oxygen, nutrients and fetal metabolic wastes with fetal blood in the villi and then exits through the uterine vein.



maternal arterioles empty into spaces and the veins take blood away

knots of capillaries (placental villi) are fetal blood vessels that are linked to umbilical – the vein is red because the blood is being delivered to the heart of the fetus (oxygenated blood from placenta)

exchange of wastes and nutrients

Hormones secreted by the placenta play a critical role in the maintenance of pregnancy

- ***hCG*** maintains the CL of pregnancy until the end of first trimester.
- ***E*** stimulates growth of the myometrium, strengthening it for parturition.
- ***P*** suppresses uterine contractions.
- Human placental lactogen (***hPL***) affects maternal metabolism to make more glucose and fatty acids available for the fetus.
- ***E***, ***P*** and ***hPL*** are involved in the maturation of mammary glands.
- ***Relaxin*** softens the cervix and loosens the pubic symphysis between pelvic bones in preparation for parturition.