Establishing the Ovarian Cycle

- During childhood, until puberty
  - Ovaries grow and secrete small amounts of estrogens
  - Estrogen inhibits release of GnRH
- At puberty
  - Hypothalamus becomes less sensitive to influence of estrogen, due to the action of increased Leptin hormone from adipose tissue (it decreases the estrogen inhibition)
  - GnRH, is released rhythmicly, inducing the release of FSH, and LH
  - In about four years, an adult cyclic pattern is achieved and menarche occurs
The ovarian cycle lasts typically 28 days.

Day 1 until Ovulation is referred to as the follicular phase since the growing follicle determines the hormonal changes of the cycle.

After ovulation until day 28, it is referred to as the luteal phase since the corpus luteum determines the hormonal changes of the cycle.

The follicular phase: Day 1 to Day 14.

On day 1, rising levels of GnRH induce the release of FSH and LH

- FSH targets the follicular cells to grow
- LH targets the theca cells to grow
- Thecal cells produce androgens, which become converted by the granulosa cells into estrogens
- Estrogen levels increase in the blood stream
  - This initial low increase in estrogen inhibits the release of FSH and LH from APG
  - Stimulate synthesis and storage of FSH and LH in APG
  - Enhance further estrogen output by the growing follicle
Granulosa cells start producing Inhibin, which in turn inhibits FSH release.

Estrogen output by the vesicular follicle continues to increase.

While low estrogen levels inhibited FSH, LH release, high estrogen levels have a positive feedback effect on the pituitary at midcycle.

There is a sudden LH surge (and a minor FSH surge) at **day 14**.

The results of this LH surge:

- Completion of meiosis I (secondary oocyte continues on to metaphase II)
- Triggers ovulation
- Transforms ruptured follicle into corpus luteum
Luteal Phase: Day 15-28

- Ovulation damages the dominant estrogen producing follicle; this results in a drop in estrogen levels after day 14.
- The corpus luteum
  - Starts to produce progesterone and estrogen and levels increase in bloodstream
  - These hormones inhibit FSH and LH release, enhanced by additional release of inhibin by the corpus luteum
- Declining LH and FSH ends luteal activity and inhibits new follicles from developing
- Lack of LH causes the corpus luteum to degenerate (day 26-28 of the cycle), resulting in drops in the other hormones as well.
- Low levels of LH, FSH stops the block on GnRH release, and they rise again, starting a new cycle

Hormonal Interactions During a 28-Day Ovarian Cycle
Hormonal Interactions During a 28-Day Ovarian Cycle

The menstrual cycle

The follicular phase and the luteal phase of the menstrual cycle are shown in the diagram. The follicular phase is characterized by the development of follicles under the influence of FSH and LH, leading to the production of estrogen. The luteal phase follows ovulation and is marked by the production of progesterone and estrogen. Hormonal changes during these phases are illustrated with graphs showing the levels of FSH, LH, estrogen, and progesterone over the course of the menstrual cycle.
Hormonal Interactions During a 28-Day Ovarian Cycle

<table>
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<tr>
<th>Phases of the Ovarian Cycle</th>
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<td>Primary follicle</td>
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Fig. 26-13
Uterine (Menstrual) Cycle

• This refers to the cyclic changes in the endometrium in response to ovarian hormones
• Three phases
  1. Days 1–5: menstrual phase
  2. Days 6–14: proliferative (pre-ovulatory) phase
  3. Days 15–28: secretory (postovulatory) phase (constant 14-day length)

Uterine (Menstrual) Cycle

• Menstrual phase (day 1-5)
  • Ovarian hormones are at their lowest levels
  • Gonadotropins are beginning to rise
  • Stratum functionalis is shed and the menstrual flow occurs
  • By day 5, growing follicles start producing more estrogen and levels increase
Uterine (Menstrual) Cycle

- **Proliferative phase (day 5-14)**
  - Rising estrogen levels prompt generation of new functional layer and increased synthesis of *progesterone receptors* in endometrium
  - Glands enlarge and spiral arteries increase in number
  - Estrogen cause cervical plug to become crystalline and thinner, allowing sperm to enter the uterus

Uterine (Menstrual) Cycle

- **Secretory phase**
  - Rising levels of Progesterone result in further development of endometrium; preparation for implantation of embryo
  - Endometrium becomes secretory with many new glands secreting glycogen: initial nutrients for the embryo
  - Formation and thickening of a new cervical mucus plug
Uterine (Menstrual) Cycle

Fluctuating levels of ovarian hormones (estrogens and progesterone) cause the endometrial changes of the uterine cycle.

The three phases of the uterine cycle:
Both the menstrual and proliferative phases occur before ovulation, and together they correspond to the follicular phase of the ovarian cycle. The secretory phase corresponds in time to the luteal phase of the ovarian cycle.
Uterine (Menstrual) Cycle

- If fertilization does not occur
  - Corpus luteum degenerates
  - Progesterone levels fall
  - Spiral arteries kink and spasm
  - Endometrial cells begin to die
  - Spiral arteries constrict again, then relax and open wide
  - Rush of blood fragments weakened capillary beds and the functional layer sloughs

Effects of Estrogens

- Promote oogenesis and follicle growth in the ovary
- Exert anabolic effects on the female reproductive tract
- Support the rapid but short-lived growth spurt at puberty
- Induce secondary sex characteristic such as growth of the breasts, increased deposit of subcutaneous fat (hips and breasts and Widening and lightening of the pelvis
- Metabolic effects of estrogens include
  - Maintain low total blood cholesterol and high HDL levels
  - Facilitates calcium uptake
Effects of Progesterone

- Progesterone works with estrogen to establish and regulate the uterine cycle
- Effects of placental progesterone during pregnancy
  - Inhibits uterine motility
  - Helps prepare the breasts for lactation

Sexually Transmitted Infections (STIs)

- Also called sexually transmitted diseases (STDs) or venereal diseases (VDs)
- The single most important cause of reproductive disorders
Gonorrhea

- Bacterial infection of mucosae of reproductive and urinary tracts
- Spread by contact with genital, anal, and pharyngeal mucosae
- Signs and symptoms
  - Males
    - Urethritis, painful urination, discharge of pus
  - Females
    - 20% display no signs or symptoms
    - Abdominal discomfort, vaginal discharge, or abnormal uterine bleeding
    - Can result in pelvic inflammatory disease and sterility
- Treatment: antibiotics, but resistant strains are becoming prevalent

Syphilis

- Bacterial infection transmitted sexually or contracted congenitally
  - Infected fetuses are stillborn or die shortly after birth
- Infection is asymptomatic for 2–3 weeks
- A painless chancre appears at the site of infection and disappears in a few weeks
- If untreated, secondary signs appear several weeks later for 3–12 weeks, and then disappear: pink skin rash, fever, and joint pain
- The latent period may or may not progress to tertiary syphilis, characterized by gummas (lesions of the CNS, blood vessels, bones, and skin)
- Treatment: penicillin
Chlamydia

- Most common bacterial STI in the United States
- Responsible for 25–50% of all diagnosed cases of pelvic inflammatory disease
- Symptoms: urethritis; penile and vaginal discharges; abdominal, rectal, or testicular pain; painful intercourse; irregular menses
- Can cause arthritis and urinary tract infections in men, and sterility in women
- Treatment: tetracycline

Viral Infections

- Genital warts
  - Caused by human papillomavirus (HPV)
  - Second most common STI in the United States
  - Increase the risk of cancers in infected body regions
- Genital herpes
  - Caused by human herpes virus type 2
  - Characterized by latent periods and flare-ups
  - Congenital herpes can cause malformations of a fetus
  - Treatment: acyclovir and other antiviral drugs
### Developmental Aspects

**Determination of Genetic Sex**

- One of the 23 pairs of chromosomes in body cells are sex chromosomes: X and Y
- Females are XX and each egg has an X chromosome
- Males are XY, so ~50% of sperm contain X, ~50% contain Y
- During fertilization the genetic sex of the embryo is determined:
  - X egg + X sperm → XX (female offspring)
  - X egg + Y sperm → XY (male offspring)

### Genotype versus Phenotype Sex

Genotype of a new individual is determined by the sex chromosomes and cannot be changed.

However, the phenotype of the new individual is under the influence of hormonal control and becomes determined around 2nd month of development.

Before that time, both male and female individual look alike and develop similar structures. Regardless of the genetic sex of the embryo, the embryonic gonadal tissues are bi-potential or in a sexually indifferent stage.
Genotype versus Phenotype Sex

The embryos thus cannot be identified yet as being male or female. In addition, the gonadal tissues have two pairs of accessory ducts: the Wolffian ducts (future male ducts) and the Mullerian ducts (future female ducts). The gonadal tissues (ridge) will become either testes or ovaries depending on the genetic make-up of the embryo.

If the embryo has the XY genetic signature, the TDF binds to the DNA of the bipotential gonadal tissue and activates genes which in turn promote the development of the testes.

The initial Leydig cells start to make testosterone and the Sertoli cells start making the Mullerian-Inhibiting Hormone (MIS) (also called anti-Mullerian Hormone (AMH)).

If MIS and testosterone are present, the reproductive system of the male starts to develop and MIS causes the Mullerian tubes to degenerate, while the Wolffian ducts develop further into vas deferens and rest of male reproductive system.
In the female embryo, the genetic XX signature in the cells does not result in the production of TDF. Thus, no testosterone and no Mullerian Inhibiting Substance (MIS). This results in the degeneration of the Wolffian ducts, and the Mullerian ducts now develop into Fallopian Tubes, while the external genitalia now take on a female characteristic.
Genotype versus Phenotype Sex

Any abnormalities/interference in this hormonal development results in sexual abnormalities. What seems to occur is that the female systems will develop unless testosterone and MIS are present. (the female system is the default programmed system).

For example, if a male embryo fails to develop MIS (AMH), both male and female duct systems develop but external genitelia are male looking (no ovaries are formed).

If a female embryo is exposed to testosterone, the embryo will develop ovaries but also develops male reproductive systems (but no testis are developed).

Lack of testosterone production by the early testis of a male embryo results in a genetic male with female looking genitelia.

True hermaphrodites are rare (both ovaries and testes present)!