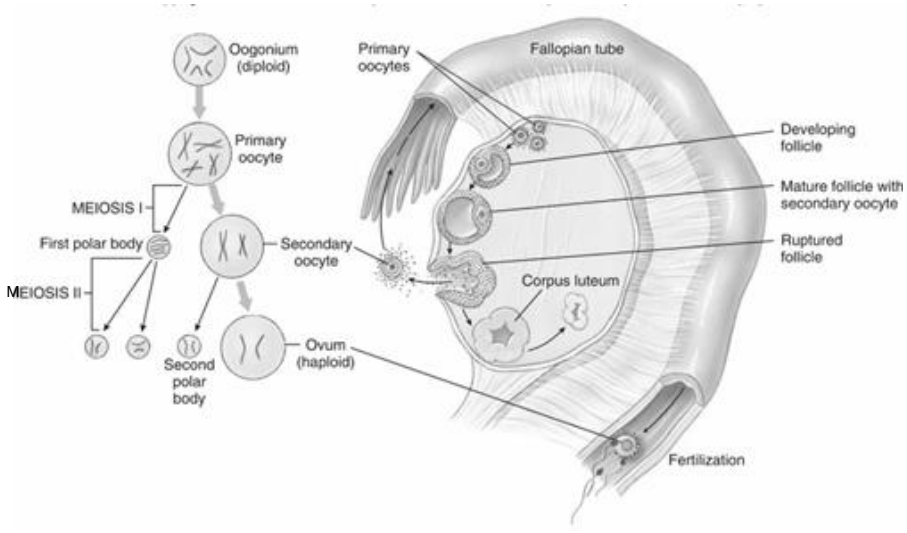
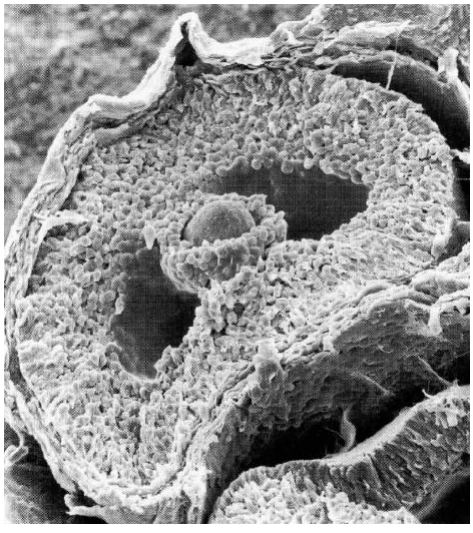
Chapter 18: Hormones Involved in Female Reproduction (Lecture 18)

I. NEUROENDOCRINE CONTROL OF FOLLICULAR (PREOVULATORY) PHASE



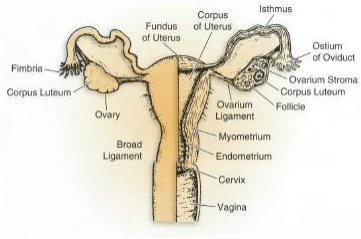


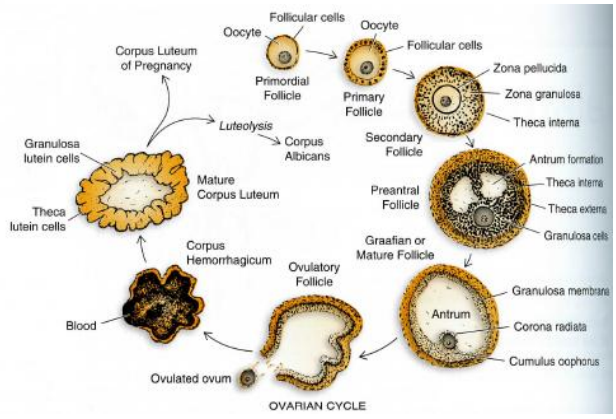
After menstruation: pituitary hormone (FSH) stimulate follicular growth

1. granulosa cells
   a. hypertrophy (↑ size)
   b. hyperplasia (↑ #s)
   c. synthesize estrogen (E) from androgen precursors
   d. secretion E
   e. ↑ E stimulates
      1) further GnRH secretion from hypothalamus
      2) ↑ LH & ↑ FSH secretion from pituitary
      3) ↑ # receptors in follicle for both E & FSH
      4) ↑ E retained in follicle
      5) ↑ FSH augments growth of granulosa cells
      6) growth follicle → ↑ E

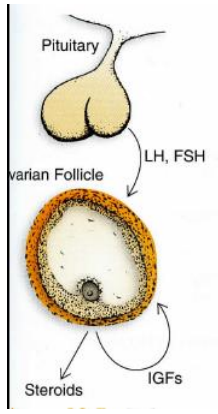
autocine: granolusa cells act themselves

2. Interaction between ovary & pituitary (↑ E)
   a. further GnRH secretion from hypothalamus
   b. ↑ LH & FSH secretion from pituitary
   c. ↑ # receptors in follicle for both E & FSH
   d. ↑ E retained in follicle
   e. ↑ FSH augments growth of granulosa cells
   f. growth follicle → ↑ E
   g. ↑ FSH pituitary & ↑ E follicle
      ↑ # LH receptors on granulosa cells → corpus luteum

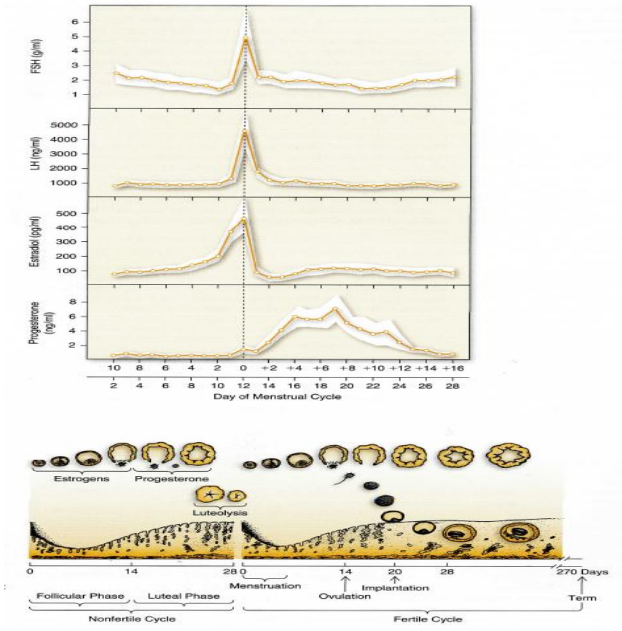




Two cell, two gonadotropin hypothesis of estrogen synthesis

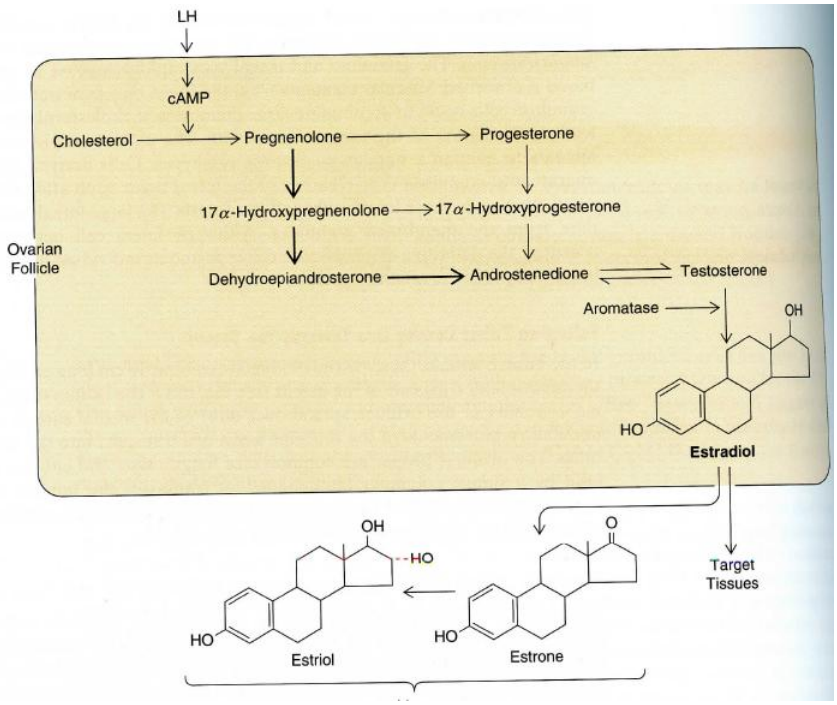


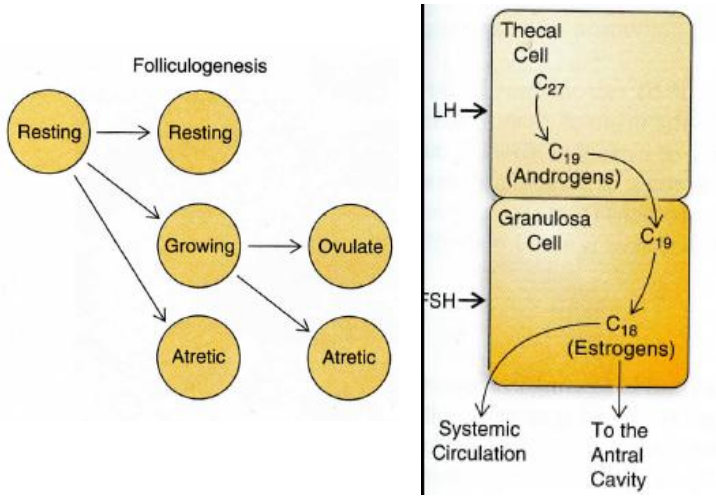
Cycle of uterine endometrial growth & development
During nonfertile & fertile cycles in the human female

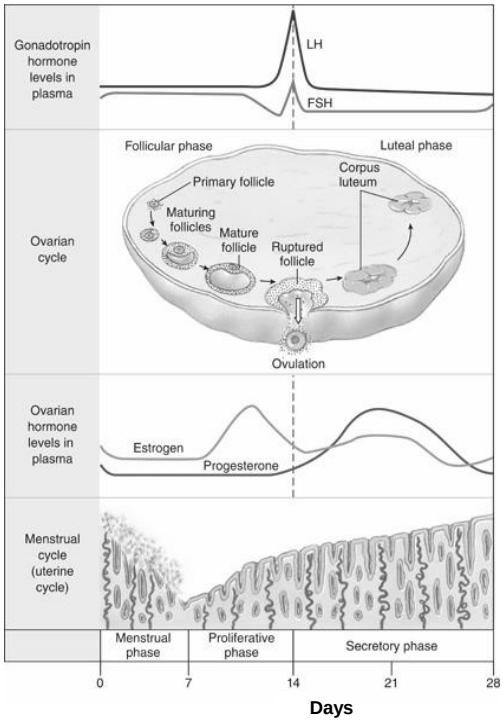


Species	Length of cycle (days)	Duration of estrus	Ovulation	
			Type	Time
Cow (*Bos taurus*)	21	13–14 hours	Spontaneous	12–16 hours after end of estrus
Goat (*Capra hircus*)	20–21	1–3 days	Spontaneous	30–36 hours after onset of estrus
Sheep (*Ovis aries*)	16	20–48 hours	Spontaneous	12–24 hours before end of estrus
Pig (*Sus scrofa*)	21	2–3 days	Spontaneous	35 hours after onset of estrus
Horse (*Equus caballus*)	19–23	4–7 days	Spontaneous	1–2 days before end of estrus
Dog (*Canis familiaris*)	60	7–9 days	Spontaneous	1–3 days after start of estrus
Cat (*Felis catus*)	–	4 days with male; 9–10 days without male	Induced	20–30 hours after mating
Ferret (*Mustela furo*)	–	Continuous	Induced	30 hours after mating
Mink (*Mustela vison*)	8–9	2 days	Induced	40–50 hours after mating
Fox (*Vulpes vulpes*)	90	1–5 days	Spontaneous	1–2 days after onset of estrus
Ground squirrel (*Citellus tridecemlineatus*)	16	6–11 hours	Induced	8–12 hours after mating
Guinea pig (*Cavia porcellus*)	16	20 hours	Spontaneous	10 hours after start of estrus
Golden hamster (*Mesocricetus auratus*)	4	10 hours	Spontaneous	8–12 hours after start of estrus
Mouse (*Mus musculus*)	4	10 hours	Spontaneous	2–3 hours after start of estrus
Rat (*Rattus norvegicus*)	4–5	13–15 hours	Spontaneous	8–10 hours after start of estrus
Rabbit (*Orcytolagus cuniculus*)	No cycle	Continuous	Induced	10 hours after mating
Rhesus monkey (*Macaca mulatta*)	28[b]	None	Spontaneous	14 days prior to onset of menstrual bleeding
Human (*Homo sapiens*)	28[b]	None	Spontaneous	14 days prior to onset of menstrual bleeding

[a]From van Tienhoven [59], with permission.
[b]Menstrual cycle.


LH
cAMP
Cholesterol
Pregnenolone
Progesterone
17α-Hydroxypregnenolone
17α-Hydroxyprogesterone
Ovarian Follicle
Dehydroepiandrosterone
Androstenedione
Testosterone
Aromatase
OH
HO
Estradiol
Target Tissues
OH
HO
HO
Estriol
O
HO
Estrone


Folliculogenesis
Resting
Resting
Growing
Ovulate
Atretic
Atretic
Thecal Cell
LH
C_{27}
C_{19}
(Androgens)
Granulosa Cell
C_{19}
FSH
C_{18}
(Estrogens)
Systemic Circulation
To the Antral Cavity



III. NEUROENDOCRINE CONTROL OF LUTEAL (POSTOVULATORY) PHASE

After day 14 (ovulation) remaining follicular granulosa cells increase size & # undergo chemical changes to form corpus luteum (**luteinization)**

1) LH stimulates growth/differentiation of corpus luteum (CL)

2) ? role of FSH unknown

3) ? ovary substance to inhibit formation of CL in the mature follicle prior to ovulation as well as follicles that do not ovulate

4. CL secretes ↑P & ↓E: ↑P & E blood titers
   a) CL E structurally identical to follicular E *stimulates GnRH, LH, FSH*
   b) CL E with P during luteal phase ***inhibit*** *GnRH (hypothalamus)* & pituitary LH/FSH
      1) due to change in hypothalamic sensitivity to E/P during follicular & luteal phases
      2) birth control pill (bcp) -blocks ovulation
         a. different types varying synthetic E &/or P inhibit LH/FSH release which during midpoint of ovarian cycle stimulates maturation of ovarian follicle resulting in its release
         b. continuous use inhibit follicular maturation, ovulation & onset of menstruation
         c. discontinuous for week/month: ↓ E & P blood titers stimulates onset of menstruation: discontinuous not affect bcp
         d. P in bcp: ↑viscosity of cervical mucus
            1. blocks sperm entry into uterus
            2. interferes with ovum implantation in uterus inhibiting E → induced proliferation of endometrial lining of uterus needed for implantation

         e. side effects
            1. nausea
            2. constipation
            3. elevated blood pressure
            4. skin rashes
            5. salt retention with weight gain
            6. inc. risk cardiovascular disease (>35 years) → bcp/tobacco
      3. morning-after pill
         a. ↑ E
         b. alters endometrial lining of uterus: prevents implantation of fertilized ovum
         c. side effects severe nausea/vomiting

5. blood LH/FSH decrease during luteal phase
   a. no new follicles grow
   b. 7-8 days post ovulation: ↑ CL size then degenerates days 23-24
      1) degeneration causes ?
      2) decreases LH a signal but not sufficient ?
      3) CL secrete hormones prostaglandins ??

6. degeneration of CL: ↓ blood P & E
   a. ↑ blood GnRH, LH, FSH increase
      due to removal of P & E
   b. GnRH, LH, FSH stimulate growth of another set of follicles

Primary site of action	Physiological action
Estradiol	
CNS	Maintains libido and sexual behavior
	Facilitates maternal behavior
	Has negative and positive feedback effects on GnRH release
	Stabilizes thermoregulatory systems
	Provides neuroprotection
Pituitary	Has negative and positive feedback effects on gonadotropin secretion
	Increases pituitary GnRH receptor number
	Increases oxytocin production
	Increases prolactin production
Ovary	Is required for ovum maturation (is luteolytic in some mammalian species)
Vagina	Causes proliferation and cornification of the mucosa
Oviducts	Causes growth and development in preparation for gamete transport
Uterus	
Cervix	Increases mucus secretion
Endometrium	Increases blood flow
	Increases prostaglandin biosynthesis at term
	Increases number of oxytocin receptors at term
	Causes decidualization response (increases the number of estrogen receptors in the decidua)
Myometrium	Synthesizes contractile proteins of smooth muscle cells
	Increases membrane excitability (increases sensitivity to oxytocin)
Mammary glands	Causes ductule and stromal growth and development, fat accretion
Skin	Induces sebaceous gland secretion (thinner fluid)
	Stimulates axillary and pubic hair growth (possibly in concert with gonadal and adrenal androgens)
General body effects	Causes H_2O and Na^+ retention, weight gain (anabolic action), and female type of fat distribution
	Maintains bone mineral deposition
Liver	Causes hepatic angiotensinogen production
	Causes hepatic production of thyroid-binding globulin
Blood	Decreases plasma cholesterol formation
Progesterone	
CNS	Increases sexual receptivity in estrogen-primed animals (at least in some mammalian species)
	Inhibits basal GnRH and gonadotropin secretion during the ovarian luteal phase
	Blocks release of preovulatory GnRH and gonadotropin surges during pregnancy
Oviducts	Causes growth and development for gamete transport
Uterus	
Endometrium	Stimulates growth and development in preparation for blastocyst implantation
	Decreases estrogen receptor number (at least, in the rat)
Cervix	Increases mucus consistency
Myometrium	Causes antiestrogen effects (myometrial hyperpolarization, decreased sensitivity to oxytocin, decreased estrogen receptor number, maintenance of pregnancy)
Vagina	Inhibits estrogen-induced vaginal cornification
Mammary glands	Is necessary for lobular-alveolar development (in some species)
	Inhibits prepartum prolactin-induced lactogenesis by decreasing PRL receptor number
General body effects	Causes thermogenic action (rise in basal metabolic rate)

PATHOPHYSIOLOGY

1 Amenorrhea (absence of menstruation)

A. Primary Amenorrhea

1) females who have never menstruated
2) rare
3) developmental abnormalities of ovaries or reproductive tract
4) scar tissue on reproductive structures in response to physical injury
5) infections before first menstrual cycle

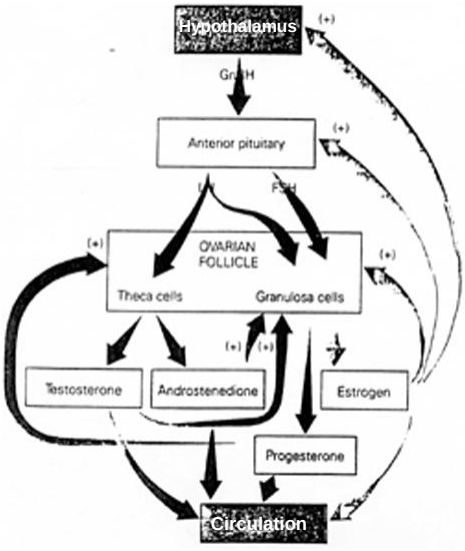
B. Secondary Amenorrhea

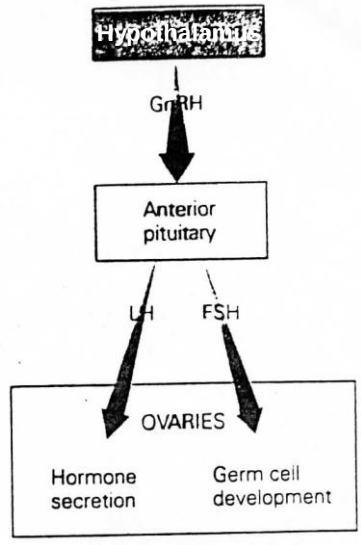
1) cessation of menstruation in females who previously menstruated
2) common
3) diagnose in absence of menstruation for an interval
   > 3X individual's normal cycle
4) malfunction of ovary, uterus, pituitary, hypothalamus
   adulthood-autoimmune diseases, radiotherapy, chemotherapy, surgery, infections, scar tissues, tumors result in ovarian failure & reduction in #s of viable follicles

2 Altered Gonadotropin Secretion in Female Athletes (secondary amenorrhea)

A. strenuous exercise in female athletes
B. menstrual alterations/disturbances

1) weight loss
2) decreased bpdu fat-to-lean ratios
3) discrete brain-pituitary-ovarian axis ??
4) long distance runners –
   secondary amenorrhea -severe oligomenorrhea
   (irregular menstrual cycles) →↓ spontaneous LH pulse frequencies


Hypothalamus
(+)
GnRH
Anterior pituitary
(+)
LH
FSH
(+)
OVARIAN FOLLICLE
(+)
Theca cells
Granulosa cells
(+)
(+)
Testosterone
Androstenedione
Estrogen
Progesterone
Circulation


Hypothalamus
GnRH
Anterior pituitary
LH
FSH
OVARIES
Hormone secretion
Germ cell development