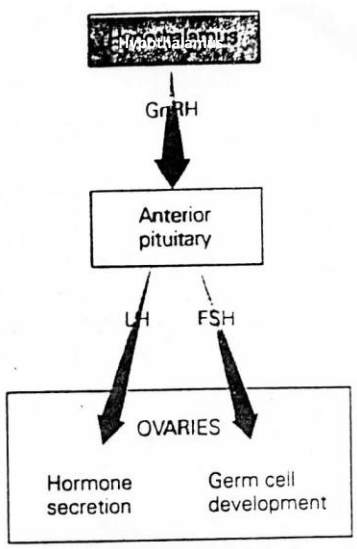
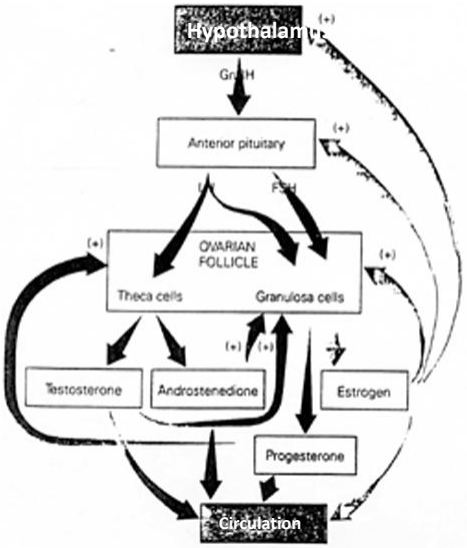
Lecture 20

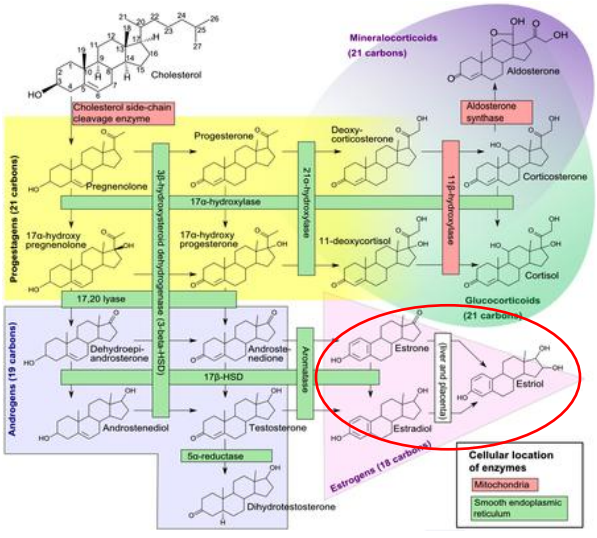
Continuation of Female Reproductive Hormones





Estrogens Pubertal

1) estradiol (17β estradiol)
2) estriol
3) estrone

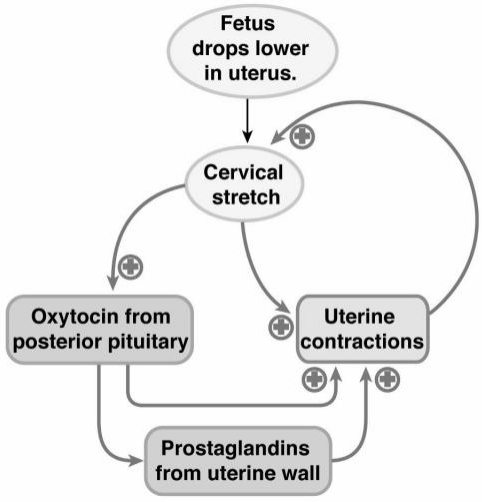


growth & development

- vagina
- uterus
- oviduct
- ovum transport
- zygote maturation
- fertilized ovum implantation

Primary site of action	Physiological action of Estrogens in Mammals
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)

PARTURITION (birth)



PARTURITION (birth)

1) oxytocin (Pitocin)
   a) stimulates contraction of uterine muscles
   b) cervix dilation (cervical stretch) before delivery→ afferent neural input to hypothalamus
   c) hypothalamus → *posterior pituitary* → *oxytocin*
   d) E & relaxin--> ↑# of oxytocin receptors in uterus
      (↑uterine sensitivity to oxytocin at end of pregnancy)

2) prostaglandins (PGF & PGE)
   a) stimulates contraction uterine smooth muscles
   b) oxytocin→ uterus → prostaglandins→ paracrine action→ uterine contractions
   c) administer prostaglandins to induce labor & terminate pregnancy
      (almost any stage of gestation)

3) P
   a) inhibit uterine contractions
   b) ↓ P removes inhibition of uterine contractions
   c) ?? this P ↓not found in all women
   d) placenta secretes P-binding protein before delivery: ↓ P → recent studies

4) relaxin
   a) CL
   b) endometrium
   c) ↑ # oxytocin receptors in uterus
   d) softens the cervix-pliable for facilitation of delivery
   e) relaxation pelvic ligaments →easing fetal passage thru birth canal

DEVELOPMENT OF BREAST DURING PREGNANCY

1) E (ovary/placenta)
   a) stimulates proliferation of glandular tissue & ducts of breast
   b) stimulates PRL release but blocks action of PRL on breast

2) P (ovary/placenta)
   a) stimulates proliferation of glandular tissue & ducts of breast
   b) blocks action of PRL on breast

3) hCG, hCS (placenta)-stimulates mammary growth

4) PRL (anterior pituitary) → stimulates mammary growth

5) oxytocin (posterior pituitary)
   a) no effect on mammary growth
   b) sensitivity of myoepithelial cell to oxytocin ↑during pregnancy

HORMONAL CONTROL OF LACTATION

breast alveolar cells extract from maternal circulation for milk production
   glucose
   amino acids
   fatty acids
   glycerol
1.5 liters of milk/day

1. major differences between human & cow milk
   amount/type of proteins

   A. human protein (**lactalbumin) lower casein-easier to digest**
   B. cow-**casein -forms sizable curds**
      heat
      changes enzymes or pH

2. Contaminants
carrier-mediated diffusion/active transport from maternal during lactation
A. drugs: 2% of maternal dose enters breast milk
1. most pose no risk
2. some harmful: many sedatives:
lithium, reserpine; valium diazepam
symptoms: drowsiness; lethargy

3. anticoagulants-induce bleeding

4. narcotics-heroin painkiller Darvon-lead to addiction
B. caffeine
C. viruses
D. environmental pollutants
E. alcohol

During Pregnancy
1) Fetal alcohol syndrome (FAS)
a) growth retardation & abnormalities of facial development
b) central nervous systems-hyperactivity, tremors,
impairment of intellectual development

2) Smoking, drugs, malnutrition (other factors can contribute)

3) First trimester stop drinking-still risk of congenital abnormalities
a) spontaneous abortion, premature labor, and neonatal death

b) alcohol-impair transport of glucose/amino acids to fetus
-fetal acidosis/hypoxia thru blood constriction to fetus

Conception
1) Heavy drinking → craniofacial deformity & impairment of CNS

Chemical Termination of Early Pregnancy

1) Surgical intervention-risk of infection/postsurgical trauma
2) Chemical → mefipristone (RU486)
   a) synthetic steroid derivative with high affinity for P receptors →
      blocks action of P → antiprogesterone
   b) CL secretes P during ovarian cycle & placenta after 6th week pregnancy
   c) P stimulates
      1. growth & proliferation endometrial lining
      2. strongly inhibits uterine contraction
   d) absence of P stimulation: endometrium undergoes hemorrhagi changes;
      outer layers of endometrium separate from uterus & discharged →
      onset of menstruation
   e) RU486 together with prostaglandin induces uterine contractions
      & onset of menstruation (evacuation of uterine contents) whether or not a fertilized ovum present
      in France authorized for clinical use (U.S.?)

Menopause: cessation of menstruation: 45 - 50 years old

1) several years before onset of menopausemenstruation
   occurs less frequently & variable intervals
2) # of follicles in ovaries decline with age
3) estrogen secretion declines as well
4) follicles disappear: ovary stops E production
5) adrenal glands continue secrete E precursors → E at peripheral tissues
6) remaining follicles less sensitive to LH & FSHcompensate by blood LH/FSH
7) E
   a) loss of vaginal epithelium
   b) decrease in breast mass
   c) vascular flushing ("hot flashes")
   d) rapid shifts in mood & emotion
   e) ↑ coronary vascular disease

f) bone loss = menopausal osteoporosis (total bone mass/bone density)
1. loss of 1-2% bone mass/yr
2. more bone eroded than replaced
3. bones becomes more brittle & easily fractured
4. bone pain: compression vertebrae fractures or long bone fractures
5. spine curvature/x-ray bones appear transparent
6. hormone replacement therapy (HRT): administer E dose
   E associated with certain cancers
7. HRT E accompany with dietary intake of Ca (dairy products)
8. Ca intake limited
   50% absorption by GI tract: rest lost in feces & urine
9. E in men but not prone to osteoporosis
   ?? testosterone may protect from bone loss;
   men with osteoporosis: correlation with cases
   of impairment of gonadal function = **hypogonadism**

T & other androgens

1) secreted by the ovaries in ↓ amounts
2) stimulate sexual drive
3) ↑ titers at ovulation strongest urge in the menstrual cycle
4) ↑ titers - oversecretion of adrenal glands/ovary
   enzymatic defects in adrenal cortisol metabolism →
   oversecretion/production → ovarian tumor

a) **hirsuitism**-excessive growth of hair where hair usually not present
1. 10% of reproductive women
2. incidence higher menopausal women
3. degree (severity) of hirsuitism not correlated with androgen production or titers of serum T
4. unbound T enters membrane → converted to DHT by 5α reductase
5. DHT binds with cytoplasmic receptor: complex enters nucleus → stimulates m-RNA →hair growth
6. skin of hirsute women highly sensitive to available T:
   result of high 5α reductase activity

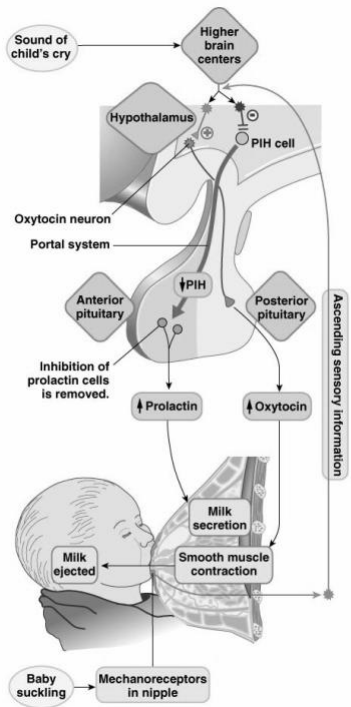
↑

5) extremely high tiers
    a) virilization-masculinization of external genitalia
    b) lead to infertility
        1. T aromatized to estradiol in hypothalamus→ disruption of LH/FSH secretion
        2. interference of follicular growth/maturation
        3. T inhibits ovarian LH/FSH receptor formation
        4. anovulation
            a. oligomenorrhea (few menstrual cycles)
            b. amenorrhea (absence of menstruation)
            c. irregular menstrual cycles

Hyperprolactinemia: oversecretion of pituitary prolactin (PRL)
-excess milk production= **galactorrhea**
-**amenorrhea/anovulation**
-breast engorgement
-normal postpartum lactation fails to discontinue → (Chiari-Frommel syndrome)
-suckling of breast --normal stimulation of PRL
-stimuli afferent impulses in neuroendocrine reflex pathways → PRL secretion
    e.g. tight fitting garments, trauma, surgery, continued breast manipulation
-**amenorrhea** result of PRL? inhibition of hypothalamic GnRH secretion
    → block of FSH/LH
- PRL directly inhibit ovarian E production-resulting amenorrhea
-women PRL &↓ E bone demineralization/bone fractures

1)↑ E & P inhibit milk production prior to parturition by blocking milk-inducing PRL
after birth: placenta expelled: ↓ E & P

2) PRL
a) stimulates milk synthesis/release from breast
b) ↑E during pregnancy stimulate PRL release from maternal pituitary gland
c) ↑PRL at birth & then ↓
d) hypothalamus sensitive to neural signals from breasts
1. suckling by newborn → afferent neurons →spinal cord →hypothalamus →anterior pituitary → (10 fold) ↑PRL for 1 hr then go down to normal
2. single nursing episode → milk production for next nursing
3. no nursing → no PRL release → no milk secretion
4. prolonged nursing → milk production within 7-9 months after birth
5. breast production can still produce significant quantities of milk several yrs



e) inhibits GnRH from hypothalamus: inhibits LH/FSH release from pituitary
1. breast feeding inhibit ovulation & reduce fertility
2. large individual variation during which PRL inhibits GnRH with prolonged nursing →unreliable method of birth control

3) oxytocin
a) stimulates milk release (**milk let down)**
b) stimulates contraction of myoepithelial cells surrounding outer walls of alveoli
c) released episodically during nursing:
1. breast stimulation similar to pathway of PRL
2. auditory stimuli (baby crying) oxytocin release →milk ejection from breast

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 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

*__primary amenorrhea:__ woman >16 yrs no beginning of menstrual period

lack of weight
very athletic