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
PARTURITION (birth)

Fetus drops lower in uterus.

Cervical stretch

Oxytocin from posterior pituitary

Uterine contractions

Prostaglandins from uterine wall

Primary site of action | Physiological action of Estrogens in Mammals
---|---
**Cervix** | Increases mucus secretion
**Endometrium** | Increases blood flow
**Increase prostaglandin biosynthesis at term**
**Increase number of oxytocin receptors at term**
**Myometrium** | Synthesizes contractile proteins of smooth muscle cells
**Increase membrane excitability (increases sensitivity to oxytocin)**
**Mammary glands** | Causes ductule and interstitial growth and development, fat accretion
Induces sebaceous gland secretion (thinner hair)
**General body effects** | Stimulates axillary and pubic hair growth (possibly in concert with gonadal and adrenal androgens)
**Increase bone mineral deposition**
**Liver** | Causes hepatic angiotensinogen production
**Blood** | Decreases plasma cholesterol formation
**Progestosterone** | Causes sexual receptivity in estrogen-primed animals (at least in some mammalian species)
Blocks release of preovulatory GnRH and gonadotropin surges during pregnancy
**Oviducts** | Causes growth and development for gamete transport
**Uterus** | Stimulates growth and development in preparation for blastocyst implantation
Decreases estrogen receptor n. b, ather (at least, in the rat)
**Cervix** | Increases mucus consistency
**Myometrium** | Causes antiestrogen effects (mycin, uterine hyperplasia, decreased sensitivity to oxytocin, decreased estrogen receptor number, maintenance of pregnancy)
**Vagina** | Inhibits estrogen-induced vaginal cornification
**Mammary glands** | Necessary for lobular-alveolar development (in some species)
**General body effects** | Causes thermogenic action (rise in basal metabolic rate)
PARTURITION (birth)

1) oxytocin (Pitocin)
   a) stimulates contraction of uterine muscles
   b) cervix dilation (cervical stretch) before delivery \(\rightarrow\) afferent neural input to hypothalamus
   c) hypothalamus \(\rightarrow\) posterior pituitary \(\rightarrow\) oxytocin
   d) E & relaxin\(\rightarrow\) ↑# 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 \(\rightarrow\) uterus \(\rightarrow\) prostaglandins \(\rightarrow\) paracrine action \(\rightarrow\) 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 \(\rightarrow\) 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 \(\rightarrow\) 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 \(\rightarrow\) mefipristone (RU486)
   a) synthetic steroid derivative with high affinity for P receptors \(\rightarrow\) blocks action of P \(\rightarrow\) 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 hemorrhagic changes;
      outer layers of endometrium separate from uterus & discharged \(\rightarrow\) 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 menopause
   menstruation 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 \(\rightarrow\) E at peripheral tissues

6) remaining follicles less sensitive to LH & FSH\(\rightarrow\) E at peripheral tissues

7) E
   a) loss of vaginal epithelium
   b) decrease in breast mass
   c) vascular flushing ("hot flashes")
   d) rapid shifts in mood & emotion
   e) \(\uparrow\) 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