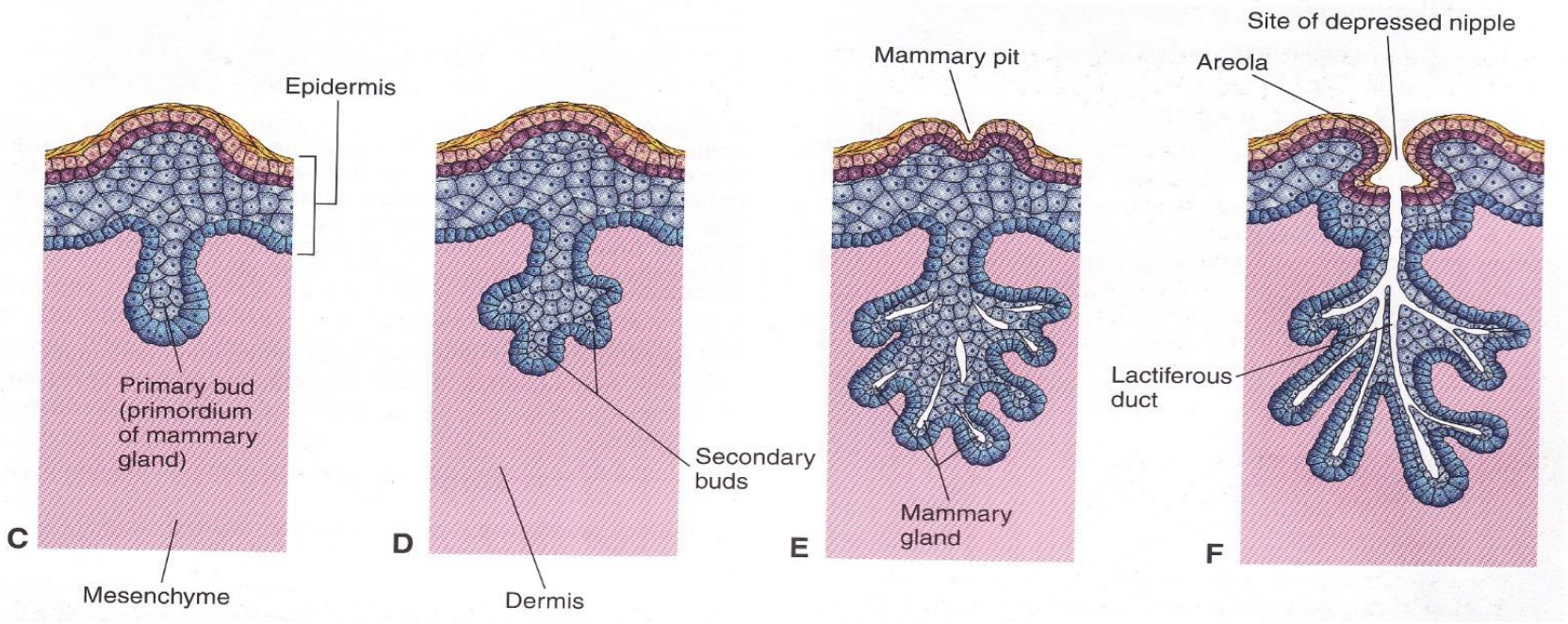
2017년 제 19차 대한산부인과내분비학회 학술대회 및 연수강좌
일반의와 간호사를 위한 강좌

생식기와 유방의발달 그리고 연관질환: 호르몬의 역할

아주대학교 의과대학 산부인과 김미란

출생 전 유방의 발달

- 태령 10일째, Wolfian ridge 배부 융선의 형성, palcode 형성
- 태령 16일부터 mammary bud로부터 상피세포로 구성된 일차유방
- 출생 전후까지 10~15 개 유관 형성
- 출생 후 사춘기까지 유관조직 성장



Mammary gland

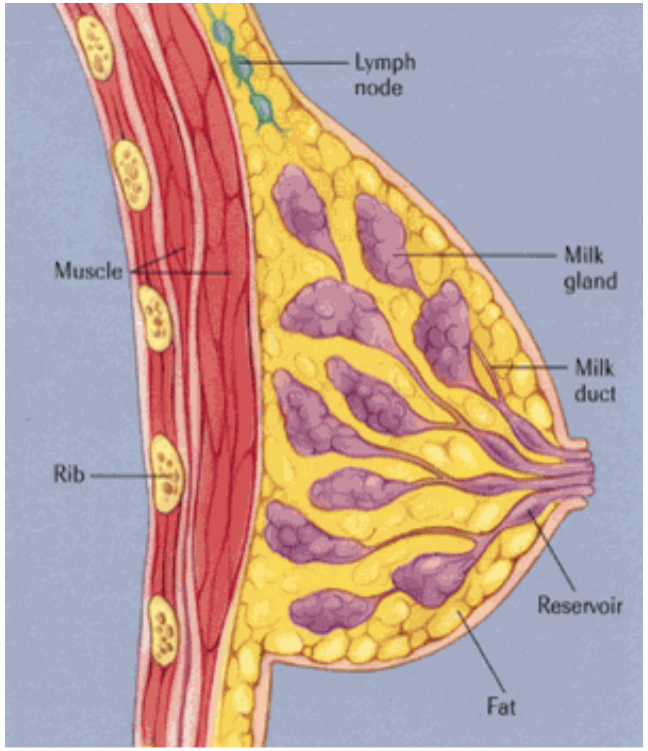
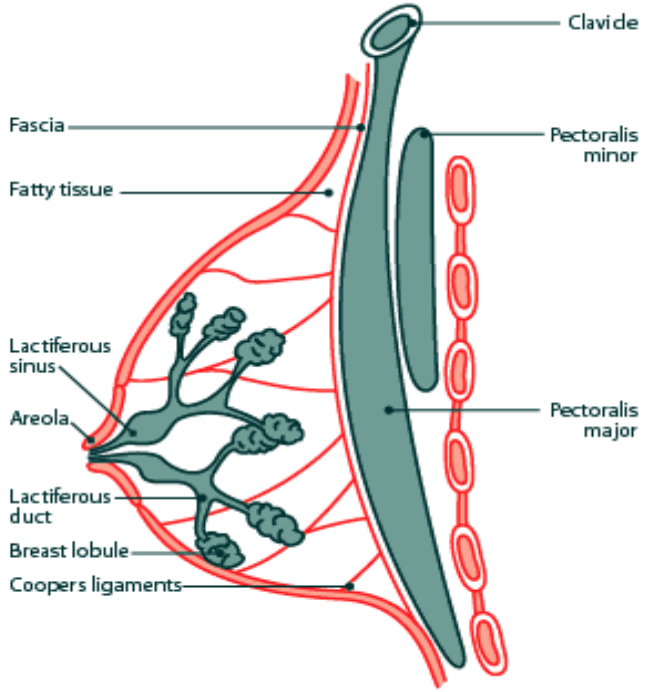
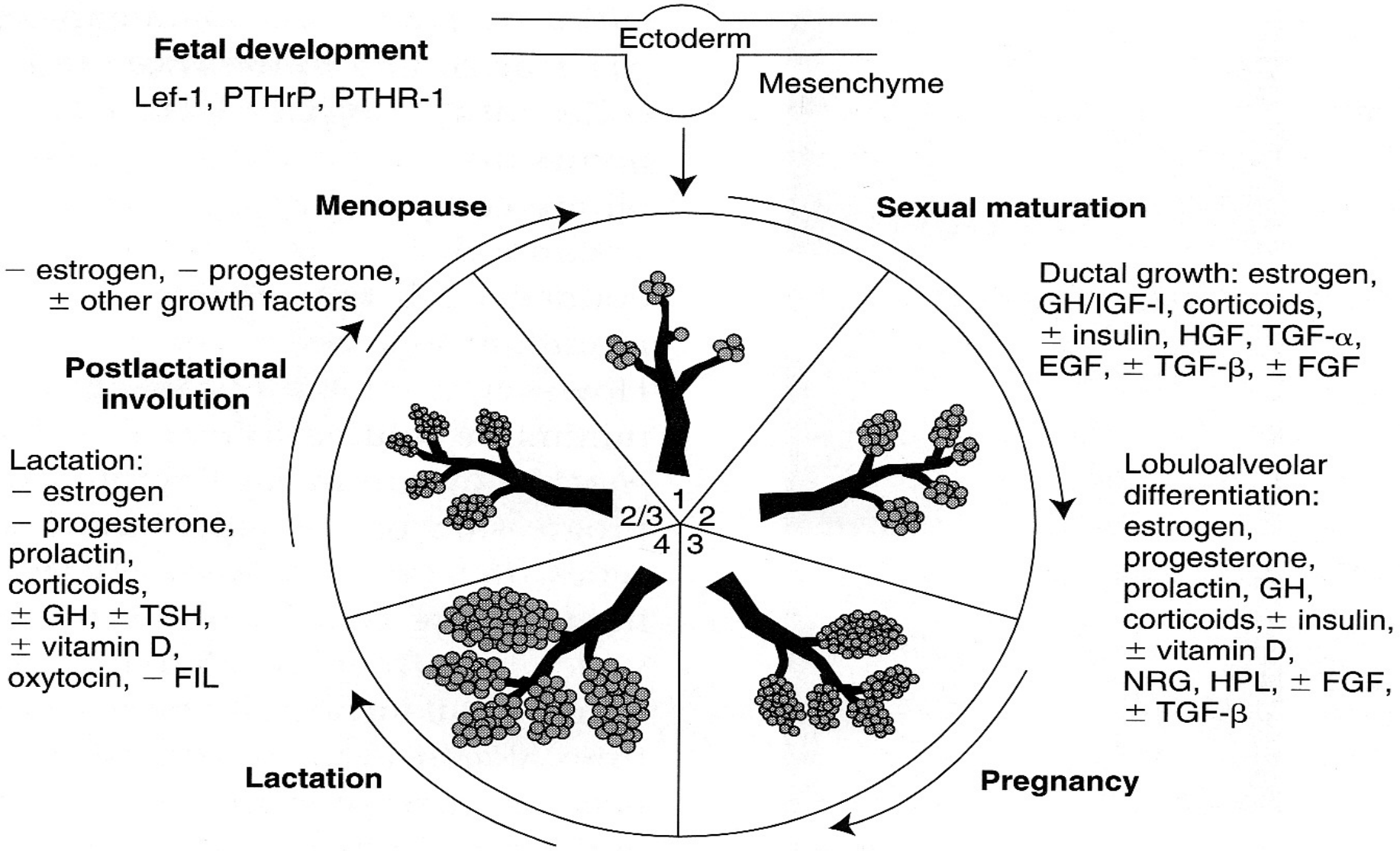


Image made available by a generous grant from Bristol-Myers Squibb



- Epithelial system of ducts & lobuloaveolar secretory units embedded in mesenchymal derived fat pad

Regulatory influences on breast development



생후 유선 발달

- 유관의 형태 발생기
- 소엽-폐포 발달기
- 수유기
- 유선의 퇴행성 변화

Witch's milk

- Prolactin stimulates newborn breast secretion
- Water, fat, debris
- 80~90% of infants
- Dissipates within 3 to 4 weeks
- lactocele

유관의 형태 발생기

- 생후 4주~사춘기
- 뇌하수체호르몬의 영향
- 종말부배아(terminal end bud, TEB)
- 세포증식과 자연사간의 균형

상피잔류물

- (+) 임신 중의 태반 경유 모성호르몬
- (±) 원인불명의 국소인자
- (-) 태반경유 HCG, 태반경유 인히빈, 태아 테스토스테론

사춘기 유방 발달과정

- (+) 성장호르몬, 에스트로겐, 프로게스테론, 프로락틴, 인슐린, 글루코코르티코이드, IGF-I, HGF
- (+?) TGF-α
- (-) TGF-β
- (±) 기타 성장인자

비정상적 유방 발달

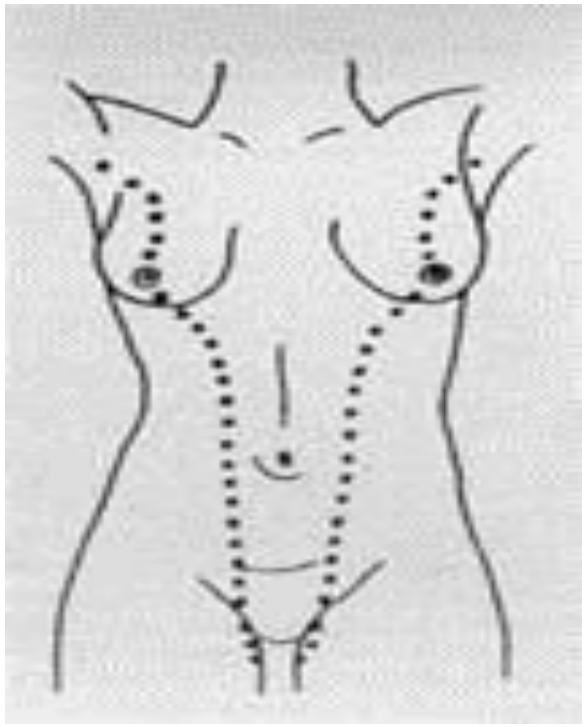
선천성 장애

- 다유두증 (Polythelia, Accessory nipple, Supernumerary nipples)
- 다유방증 (Polymastia, Supernumerary breast)
- 유방형성장애 (hypoplasia) / 무유방증 (Amastia)
- 무유두증 (Athelia)

후천성 발달장애

- 약물 유발성 큰 유방증
  - D-페니실라민
    - 윌슨병, 류마티스관절염, 범발성강피증 치료제

다유방증 (Accessory mammary tissue, Polymastia)



- Most often located in the axilla, may swellduring pregnancy

다유두증 (polythelia)

- Most common on the thorax below healthy breasts

Premature thelarche

- Breast development before age of 8 yrs without concomitant signs of puberty
  - Usually bilateral, within the first 2 years of life
  - Persistence or increase in the breast tissue present at birth
    - Initial : maternal influence
    - Persistence of breast tissue : infant hormone

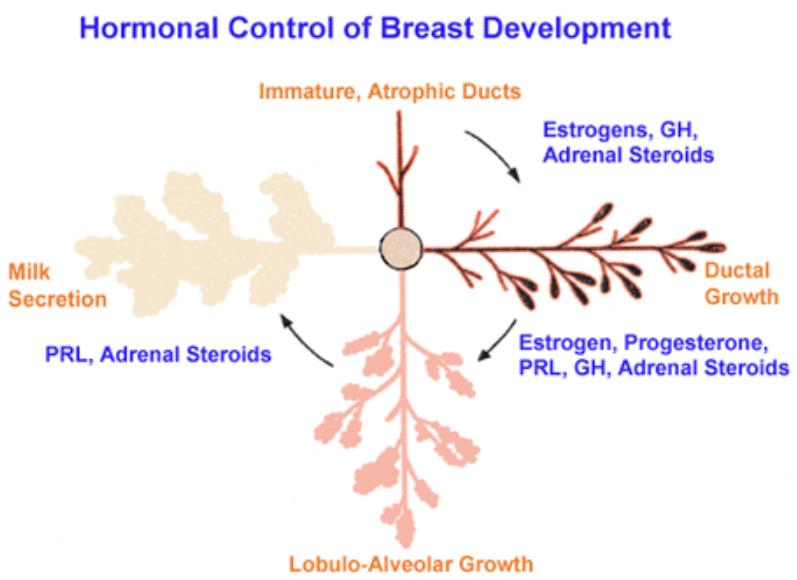
      (elevated FSH, LH, estradiol)
  - Resolves within 3 to 5 years with no adverse sequelae

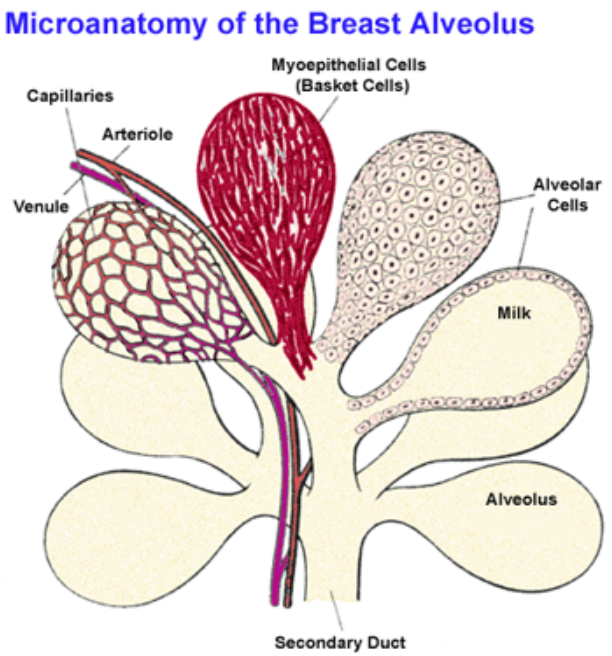
- Second period of premature thelarche
  - After 6 years of age
  - Unclear, before the rise in estrogen levels
  - Serum androgen, free estrogen, altered FSH
  - Puberty occurs at the usual time
  - Bone age is normal : no further evaluation is needed

Puberty

Ductal growth phase

- Ducts elongate, ductal epithelium thicken, peripheral connective tissue increases
- Stem cells in the ductal tree form club-shaped terminal end buds(TEBs)





(Modified from Austin & Short (ed) *Reproduction in Mammals, Book III: Hormonal Control of Reproduction,* Cambridge University Press: Cambridge, UK, 1984.)

Types of Breast Lobules

Type 1
Breast at birth

Type 2
Breast after puberty

Type 3
Breast with pregnancy after 32 weeks

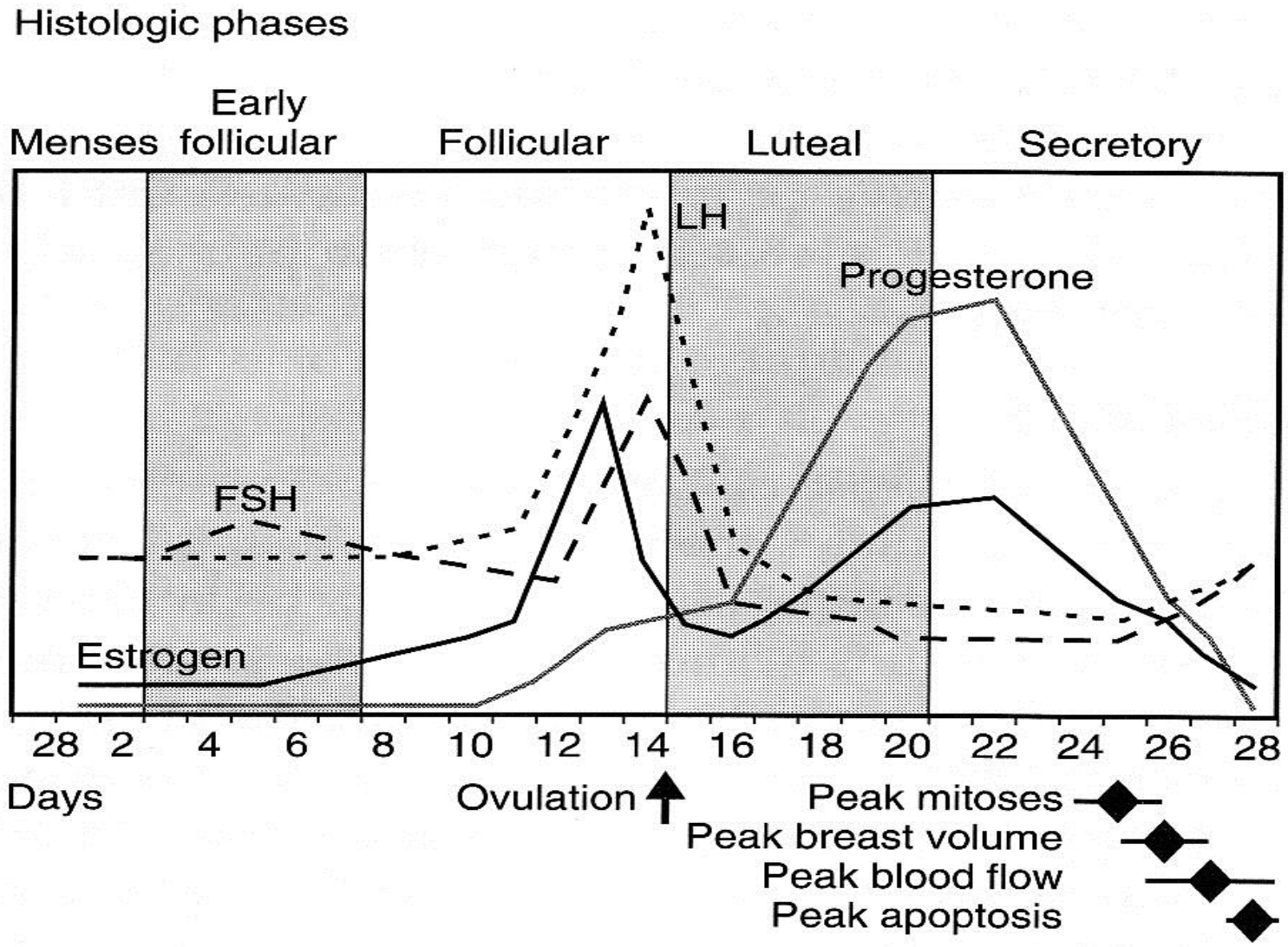
Type 4
Breast with milk

Hormone

- “Estrogen window”
  - Anovulatory cycles for the first 1 to 2yrs after menarche
  - Ductal growth phase
- Estrogen
  - The major hormonal influence on the breast at the onset of puberty
  - Potent mammogen, primarily stimulates dutal growth but also, increases fat deposition and contributes to later phases of development

- GH
  - By enhancing stromal secretion of IGF-I
  - Increase elongation and growth at the TEB
- Progesterone
  - Not essential in early ductal growth
  - Essential for lobuloalveolar growth
    - Prolactin, GH, estrogen, glucocorticoid
  - Fullness and tenderness premenstrually
- PRL
  - Integral to lobuloalveolar development
  - Facilitating P4 action

Breast changes during menstrual cycle



Clinical correlates

- Normal variants
  - Initial unilateral development
  - Asymmetric
- Adolescent, juvenile hypertrophy
  - Postpubertal continuation of epithelial and stromal growth (3-8 kg)
  - Usually no systemic hormonal imbalance
  - Reduction mammoplasty / total mastectomy with reconstruction
  - Bromocryptine, tamoxifen, danazol, medroxyprogesterone

Pregnancy

소엽-폐포 발달기

- 임신기
- 기질의 지방층 증식
- β-casein, WAP(whey acidic protein) 유전자 합성
- 프로게스테론, 프로락틴

임신 중 유방 변화

- (+) 프로락틴, 에스트로겐, 프로게스테론, 태반유선자극호르몬, 태반성장호르몬
- (+) EGF, Amphiregulin, FGF, CSR-1, Snt-4
- (-) TGF-β, 유유읽물산성단백질

Hormone

- Estrogen, progesterone, PRL, HPL
  - Prolactin
    - Increases beginning at 8 weeks and continue to rise
    - Lobuloaveolar differentiation
  - HPL
    - 30 times the concentration of PRL
    - may contribute to the prolactin effects
  - Estrogen
    - Induce the differnetiation of ant. pituitary lactotrophs
    - Enhance PRL gene expression
    - Suppress the secretion of PRL inhibiting factor (dopamine)

- Progesterone
  - Primes the breast for lactation
  - Inhibition of initiation of lactogenesis
  - Reduces the binding and antagonizes the positive effects of PRL at its receptor
  - Suppress production of milk protein casein

Clinical correlates

- Gravid hypertrophy
  - Rapid and massive enlargement during pregnancy
  - May appear during a second pregnancy

Figura 1 - Em visão lateral nota-se a ação das volumosas mamas sobre a estrutura músculo-esquelética das espáduas. Gravidez na 28ª semana.

- Early parity has a protective effect against breast cancer
  - Lob 1
    - The most undifferentiated lobule
    - Highest rate of proliferation
    - Highest expression of ER, PR
    - Highest angiogenic index (AI)
    - No expression of protease inhibitors
  - Lob 1 in nulliparous women (prime target) were higher proliferating rate than that of parous women

Lactation

수유기

- 생식호르몬
  - 에스트로겐, 프로게스테론, 프로락틴, 태반유선자극호르몬, 옥시토신
- 대사호르몬
  - 성장호르몬, corticosteroid, 갑상선호르몬, 인슐린
- 옥시토신
  - 근육상피세포수축, 유즙분비 유도
- 갑상선호르몬, 성장호르몬
  - 영양분 흡수 조절, IGF-I 분비 증가

수유기

- (+) 옥시토신
- (-) TGF-β, FIL, β-lactoglobulin
- (±) 프로락틴

Hormone

- PRL
  - Principal hormone for the synthesis of milk proteins and the maintenance of lactation
  - PIF, progesterone : prohibits PRL
- Glucocorticoids
  - Along with prolactin, differentiate mammary epithelium and stimulate milk synthesis and secretion
  - Progesterone : glucocorticoid antagonists
  - After birth, PRL, in concert woth glucocorticoids, is able to initiate lactogenesis II

- Oxytocin
  - Responsible for release of stored milk (milk let-down)
  - Secreted from posterior pituitary by a sensory stimulation from the nipple/areola complex
  - Crying/ pain and embarrassment
  - Stimulate contraction of the myoepithelial cells
- GH, placental lactogen
  - Interchangeable in function with PRL
  - Pituitary dwarfism, removal of pituitary adenoma, low levels of placental lactogen : normal pregnancy and breastfeeding

Clinical correlates

- Delayed onset of lactation (lactogenesis II)
  - Lack of infant suckling
  - Unscheduled Cesarean delivery
  - Vaginal delivery with prolonged stage 2 labor
  - Obesity
  - Retained placenta : progesterone
  - Type-1 DM

Inadequate milk production

- Smaller breasts : increasing the frequency & the degree of emptying
- Minimal breast growth during pregnancy : compensatory growth during the 1st month postpartum
- Low level of prolactin : metoclopramide, oral TRH
- Sheehan's syndrome

Galactorrhea

- Inappropriate secretion of milky fluid in the absence of pregnancy or breast feeding more than 6 months
- Stress from exercise, surgery, sexual intercourse or sleep : inhibit PIF release
- Drug-induced : resolve within 3-6 mo.
- Pituitary tumor, hypothyroidism
- Adrenal insufficiency, Cushing syndrome, acromegaly, renal failure, lung/renal tumor(ectopic PRL)
- In patients with prolactin levels less than 100 ng/ml and no evidence of a pituitary tumor, no treatment is needed

Menopause

유선의 퇴행성 변화

- 수유 중단 후
- 1단계
  - 엽 정체, 소실세포 (acinar cell) 자연사
- 2단계
  - Prolactin 감소
  - 임신기 전 상태로 재구성
  - TGF-b3 mRNA, STAT3, IGFBP5

퇴화

- (-) 다수호르몬 철회
- (-) TGF-β

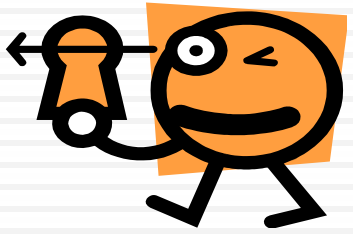
- Glandular epithelium : apoptosis
- Interlobular stromal tissue : decrease and replacement by fat
- Intralobular tissue : replaced by collagen

⇒ Reduction of the number of ducts and lobules

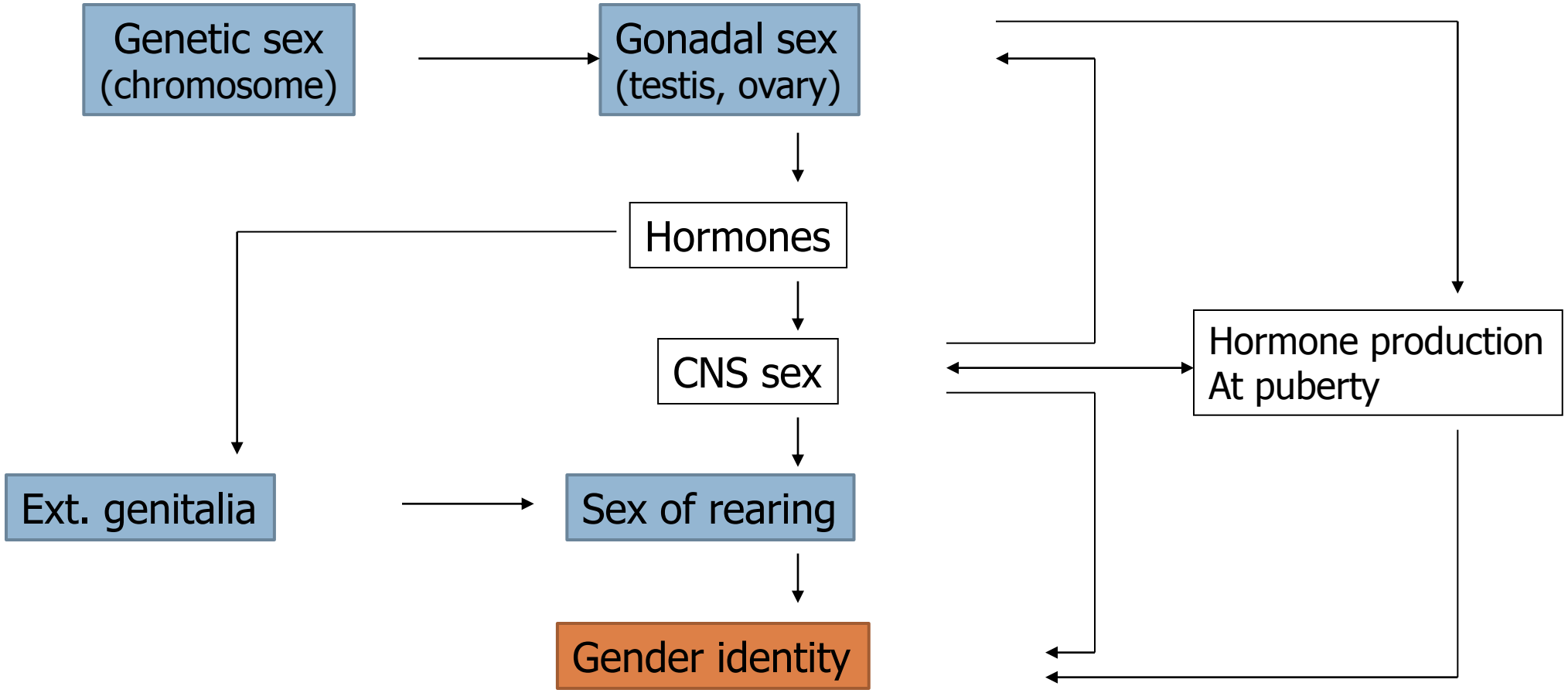
Clinical correlates

- Return to high percentage of Lob 1
  - More susceptible to interaction with carcinogens

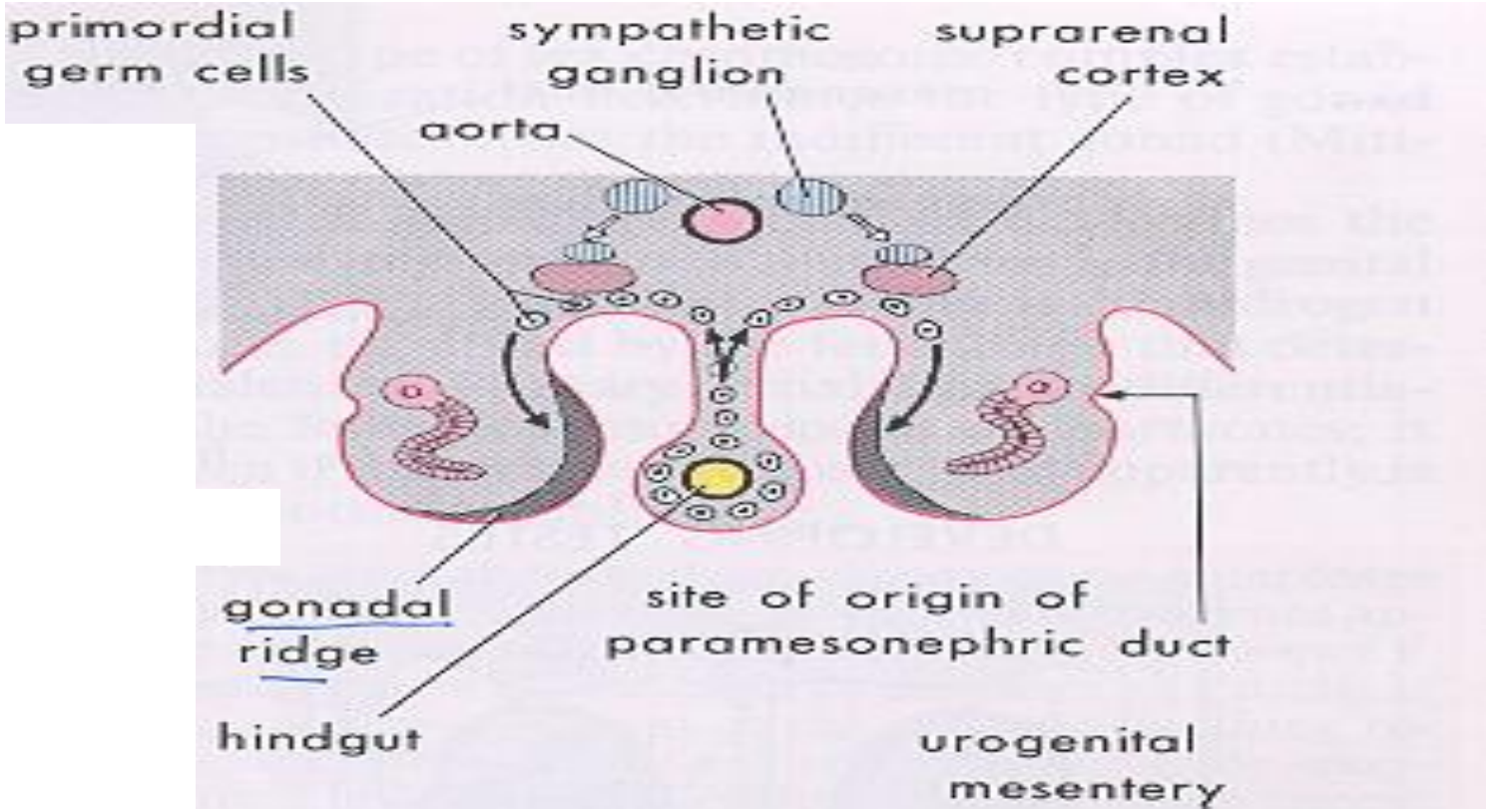
Normal Sexual Development



Normal sexual development



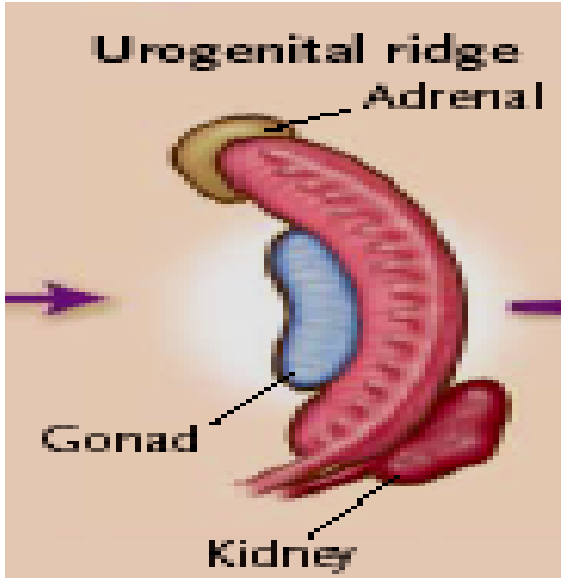
Gonadal Differentiation (I)



Migration of primordial germ cells into gonadal ridge
: 4 – 6 weeks of gestation

Gonadal Differentiation (II)

6-7 weeks of gestation

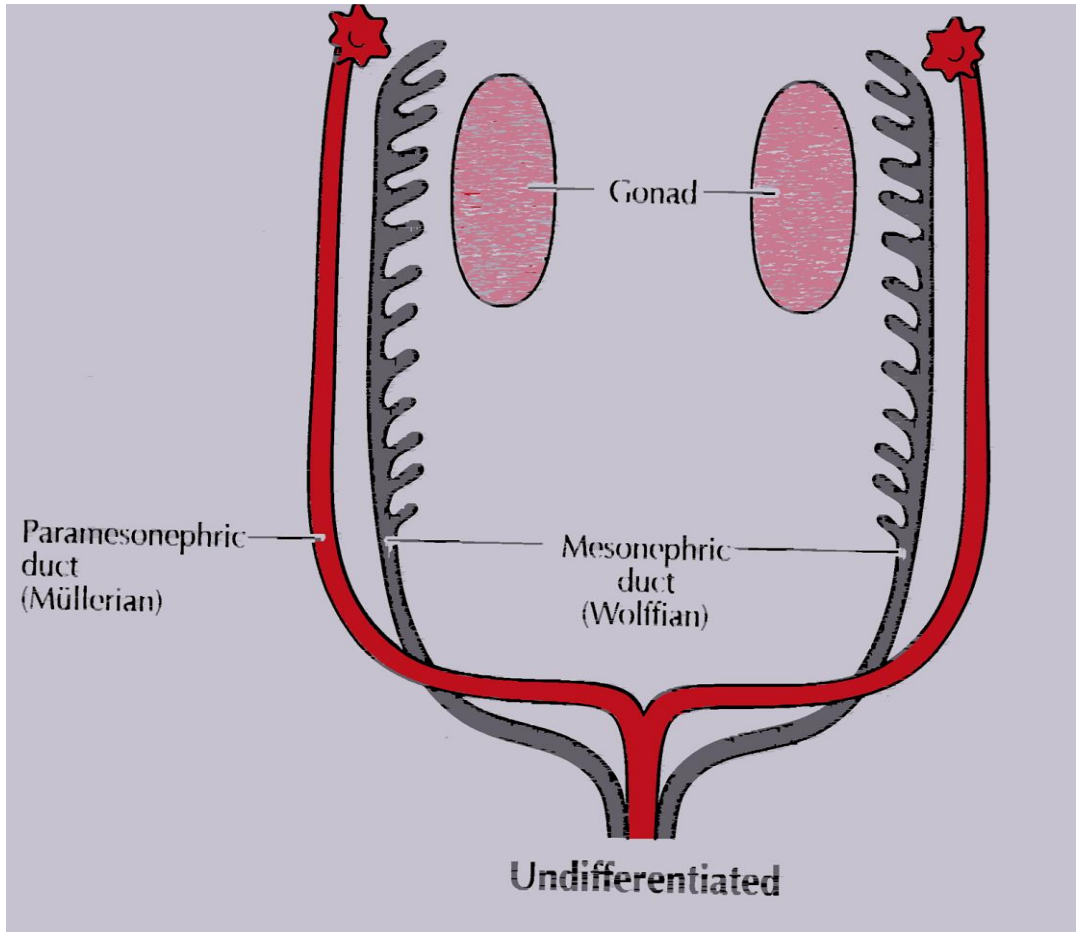


Indifferent gonad

Y chromosome
SRY(+) → testis

If SRY(-)
2 weeks later → ovary

Ductal Differentiation(I)



Wolffian duct

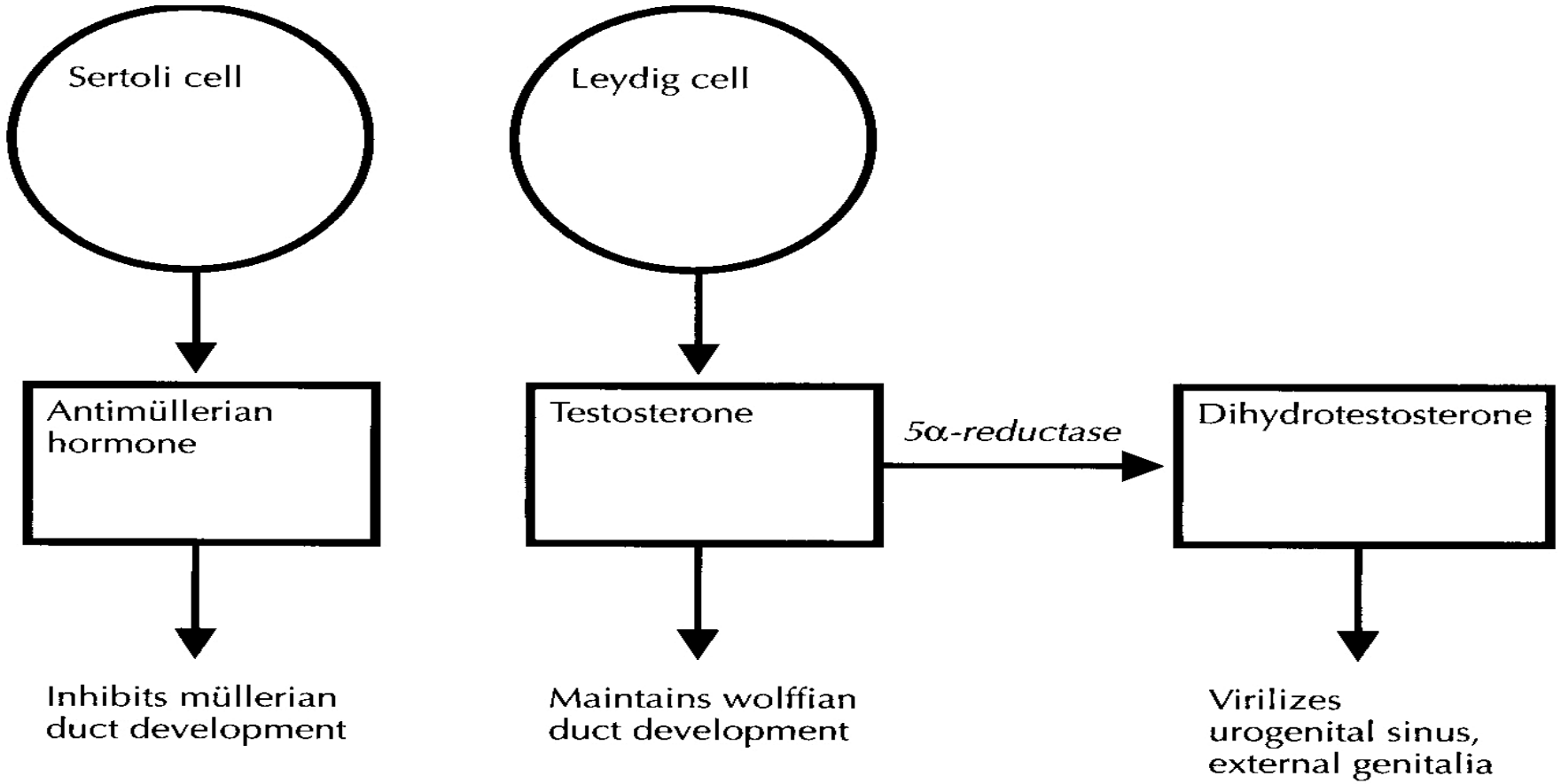
: epididymis, vas deferens, seminal vesicle

Müllerian duct

: fallopian tube, uterus, upper vagina

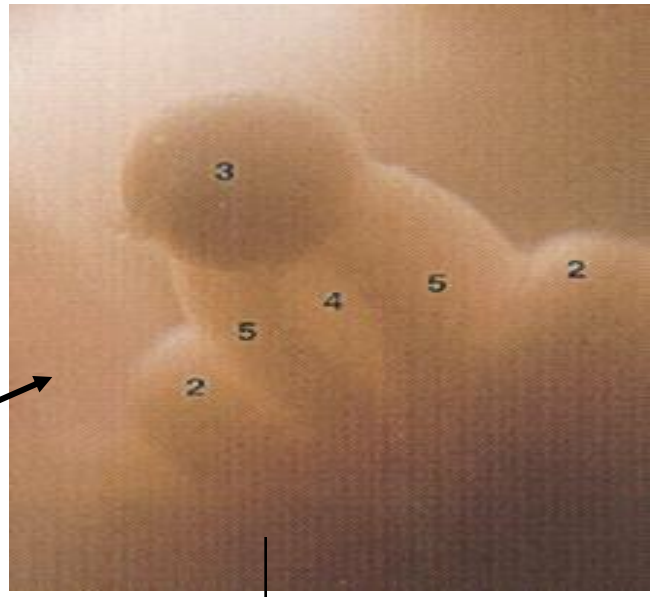
Ductal Differentiation(II)

- Testis : 8 weeks of gestation



Ext.Genitalia Differentiation

- Genital tubercle(3)
- Urogenital sinus(4)
- Labioscrotal swelling(2)

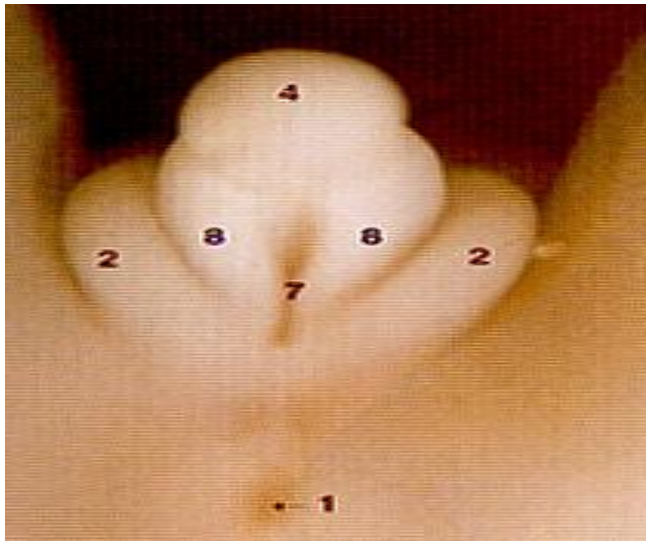


5. Urogenital folds

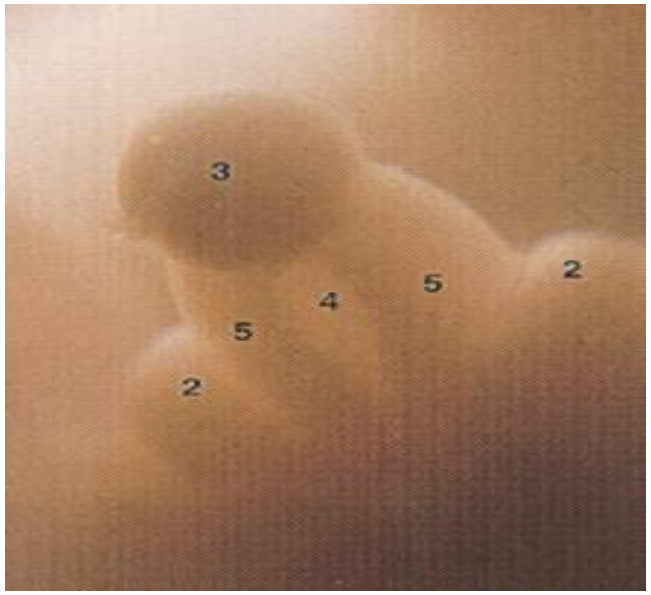
Testosterone, DHT
- 8 - 9 wks of gestation
- begin 1 wk later

Masculinization

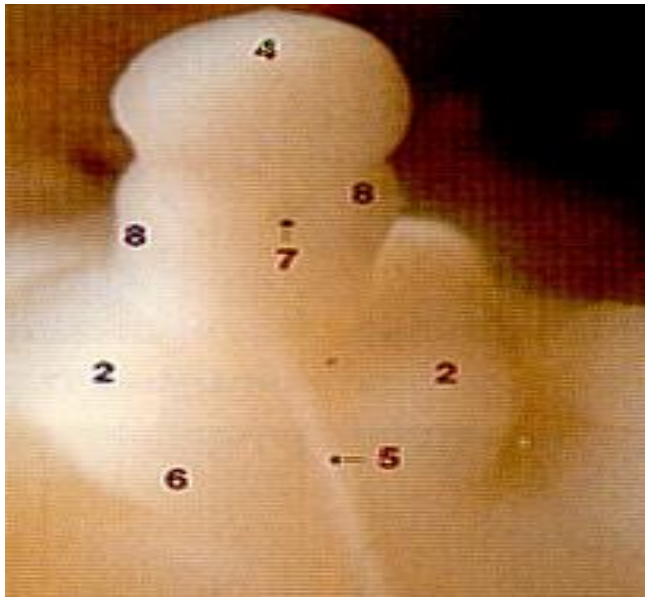
External Genitalia Differentiation (male)



Indifferent stage



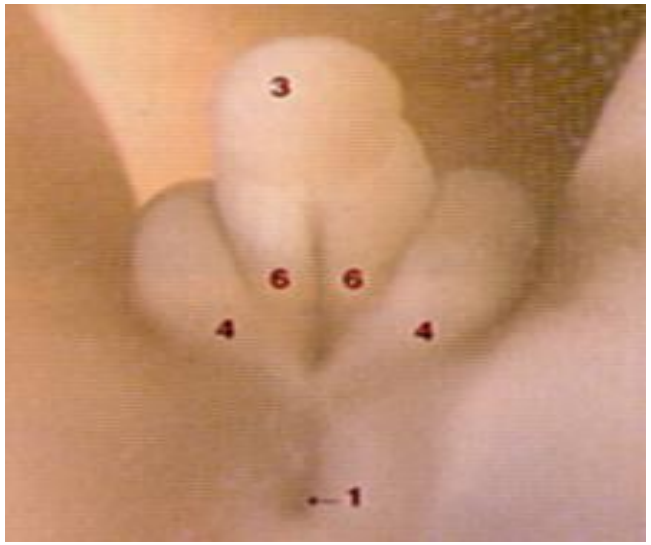
9 weeks



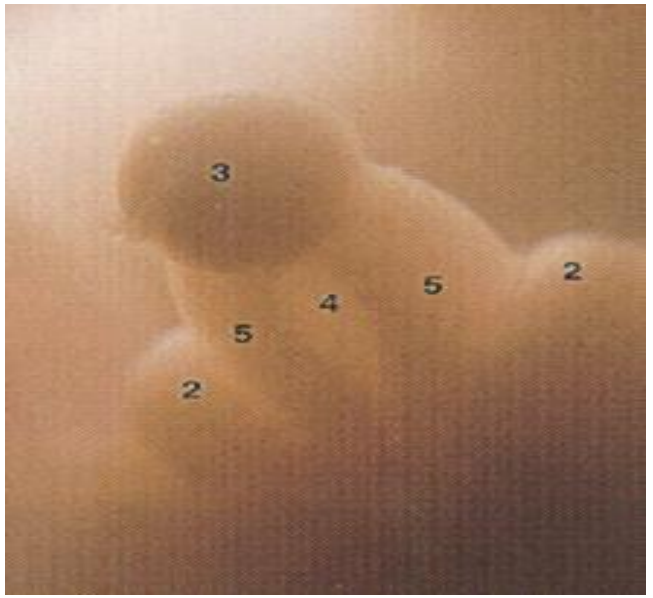
10 weeks

2. Labioscrotal swelling : scortum
4. Glans
7. Urethral groove
8. Urogenital folds

External Genitalia Differentiation (female)



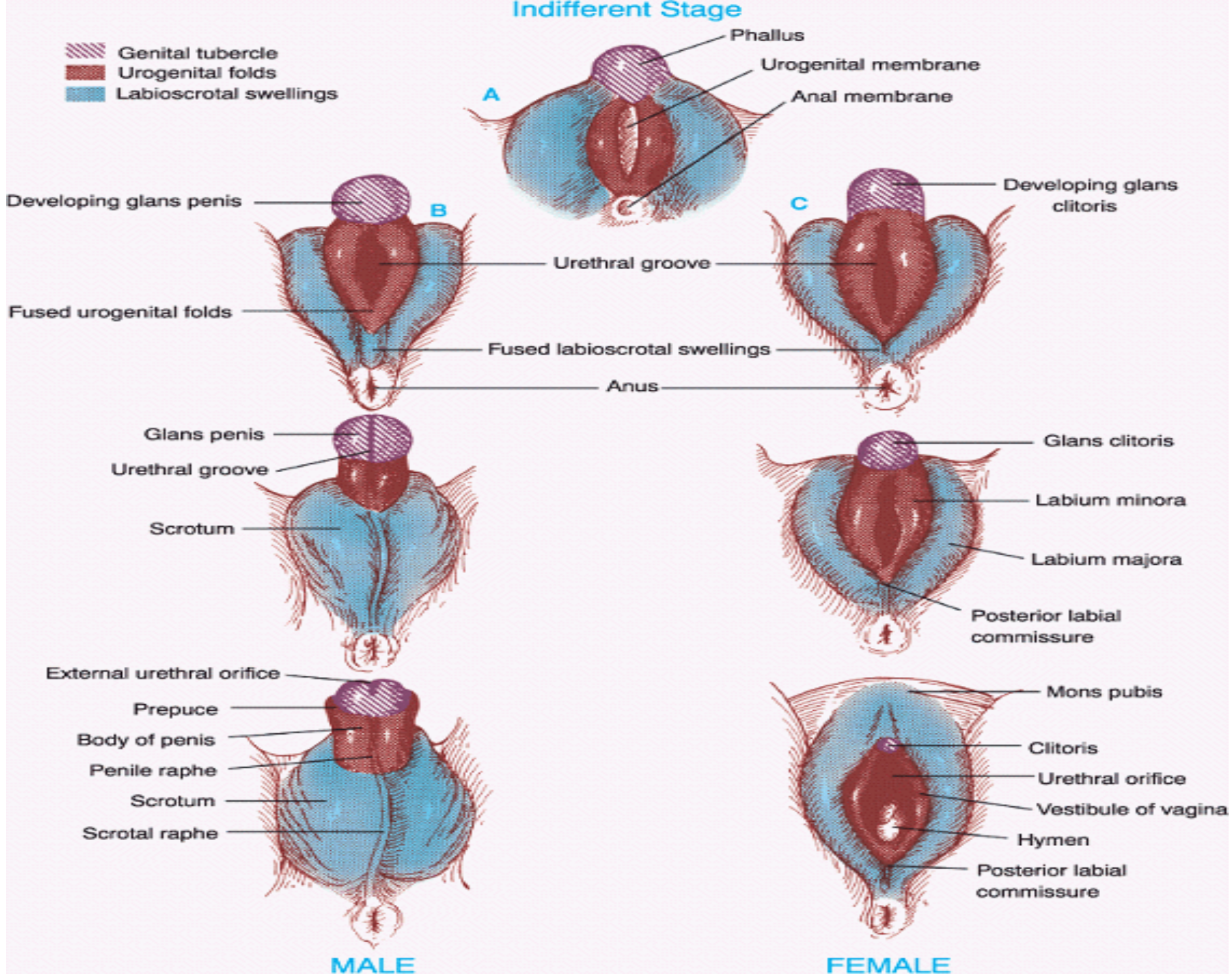
Indifferent stage



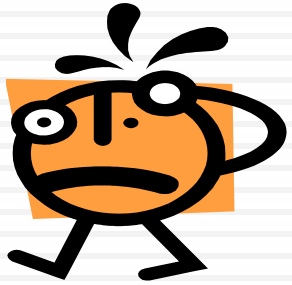
9 weeks

12 weeks

3. clitoris
4. Labioscrotal swelling : labia majora
6. Urogenital folds: labia minora


Indifferent Stage
Genital tubercle
Urogenital folds
Labioscrotal swellings
A
Phallus
Urogenital membrane
Anal membrane
B
Developing glans penis
Urethral groove
Fused urogenital folds
Fused labioscrotal swellings
Anus
C
Developing glans clitoris
Glans penis
Urethral groove
Scrotum
External urethral orifice
Prepuce
Body of penis
Penile raphe
Scrotum
Scrotal raphe
Glans clitoris
Labium minora
Labium majora
Posterior labial commissure
Mons pubis
Clitoris
Urethral orifice
Vestibule of vagina
Hymen
Posterior labial commissure
MALE
FEMALE

Abnormal Sexual Differentiation



Abnormal Sexual Differentiation

- Chromosome
- Gonad
- Int. genitalia
- Ext. genitalia

XX

Ovary

XY (SRY)

Testis

AMH

Testosterone

Exposure to Androgen
9-14 gest. wks

defect

Female pseudohermaphroditism

Male pseudohermaphroditism

Congenital Adrenal Hyperplasia

- Chromosome
- Gonad
- Int. genitalia
- Ext. genitalia

XX

Ovary : AMH(–), testosterone(–)

Müllerian duct (+)

(Fallopian tube, uterus, upper vagina)

Excessive Androgen by adrenal cortex (10-12 weeks)

Mascualized external genitalia

; *fusion of labioscrotal folds. clitorical enlargement, change of vagina & urethra*

Congenital Adrenal Hyperplasia

- 21-Hydroxylase (P450c21) deficiency
  - 95% of CAH
  - the most frequent cause of sexual ambiguity
  - the most common endocrine cause of neonatal death
  - salt-wasting, simple virilizing, non-classical type
- 11β-Hydroxylase (P450c11) deficiency
  - 5-8% of CAH
- 3β-Hydroxysteroid dehydrogenase deficiency

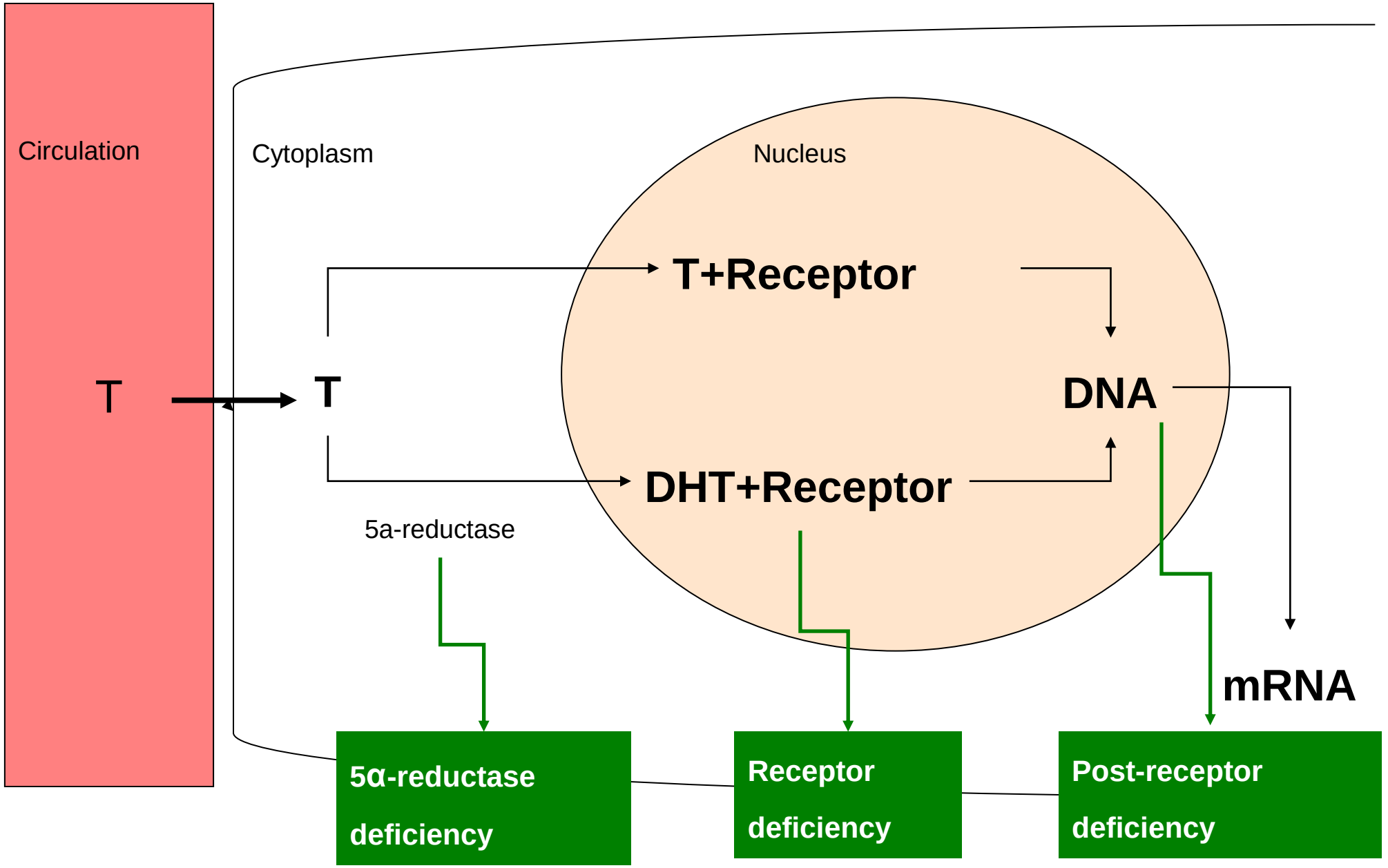
Abnormal Sexual Differentiation

Disorder of fetal endocrinology

1. Masculinized females (Female H.)
   - Congenital adrenal hyperplasia
   - Elevated androgen in the maternal circulation
   - Aromatase deficiency
2. Incompletely masculinized males (Male H.)
   - Androgen insensitivity syndrome
   - 5α –reductase deficiency
   - Testosterone biosynthesis defect
   - Gonadotropin resistant testes
   - Anti-Mullerian hormone deficiency

Androgen Insensitivity Syndrome

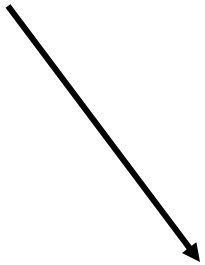
- Complete
- Incomplete
- 5α-reductase deficiency


Circulation
Cytoplasm
Nucleus
T
T
T+Receptor
DHT+Receptor
DNA
mRNA
5a-reductase
5α-reductase deficiency
Receptor deficiency
Post-receptor deficiency

Androgen Insensitivity Syndrome

- Chromosome — XY
- Gonad — testis : AMH(+), testo.(+),Fc (–)
- Int. genitalia — Müllerian(–), Wolffian(variable)
- Ext. genitalia

Insensitivity to Androgen

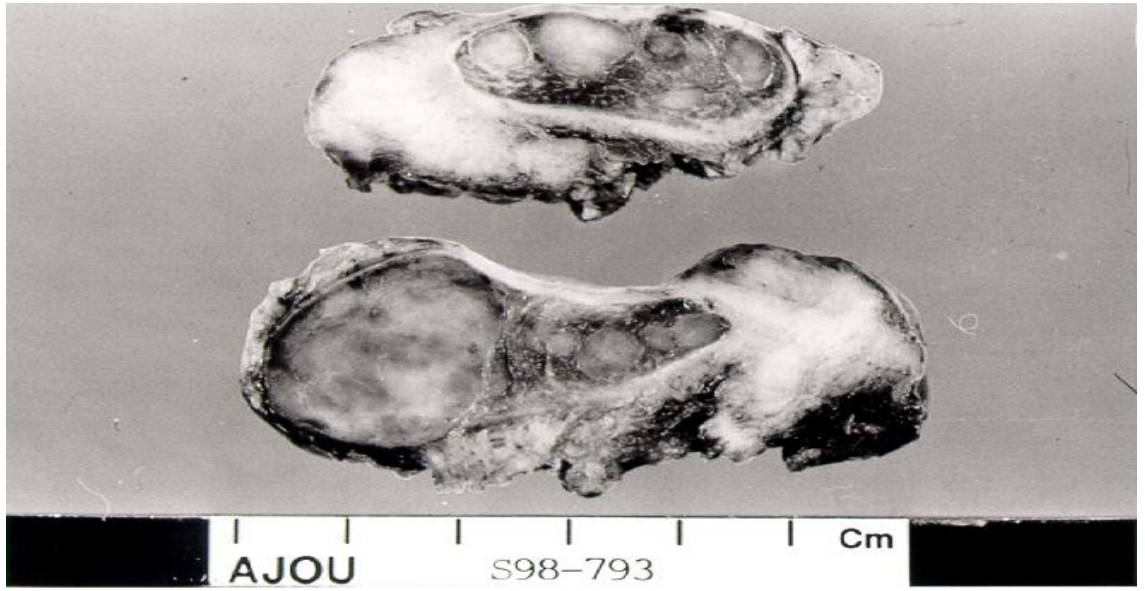


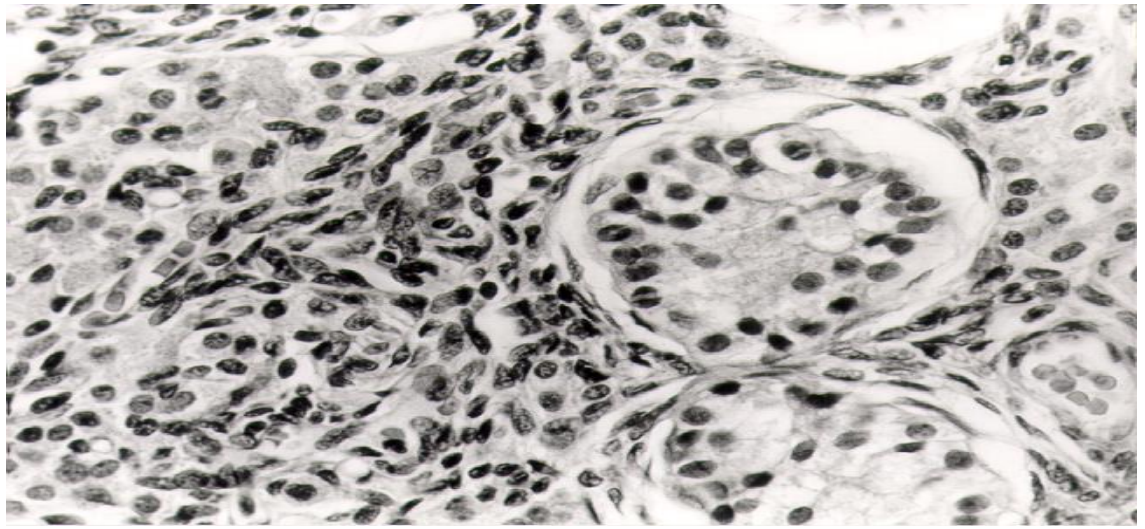
female phenotype(complete) to male phenotype

Androgen Insensitivity Syndrome

Complete	Incomplete	Reifenstein syndrome	Infertile male

Female ⟷ Ambiguous genitalia ⟷ Male





numerous immature seminiferous tubules
Leydig cells in interstitium

Hormone treatment of patients without ovaries

- Function of secondary sexual characteristics
- Promote the achievement of the full height potential.
- Increase in bone density in adolescent

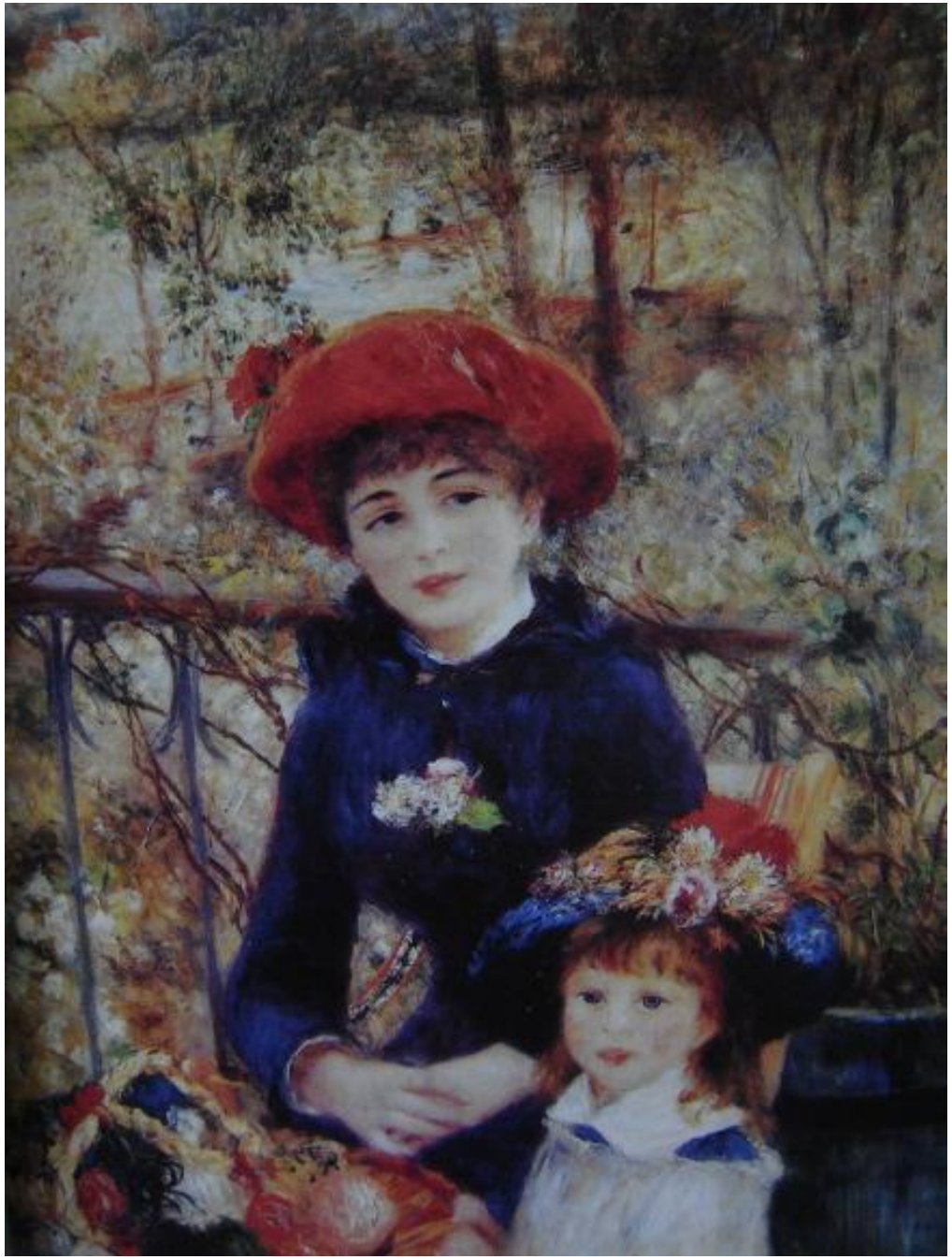
- Start at age 12-14 age with unopposed estrogen
  (0.3mg conjugated estrogens or 0.5mg E2)
- After 6Mo-1yr, sequenial program
  (0.625mg conjugate estrogen or 1.0mg E2
  + 5mg MPA for 14days)

Dx. of ambiguous Genitalia

Rule out CAH !!

- life threatening(vomiting, diarrhea, dehydration, shock)

- FHx, maternal medication
- Physical exam.
  gonad, phallus length & diameter, urethral meatus, labioscrotal fold fusion, vagina, vaginal pouch, urogenital sinus
- pelvic US (detect uterus, ovary, undescened testis)
- Lab. (karyotype, hormones etc.)



감사합니다