

Estrogens

C_{18} Steroids

- Types: Estradiol E_2 , Estrone E_1 & Estriol E_3
most potent
most predom. LH least potent
FSH
- Secretion: Cholesterol $\xrightarrow{\text{Theca cells}}$ Androgen $\xrightarrow{\text{Granulosa cells}}$ Estradiol

- Sources: Ovary 2 peaks
 Placenta
 Adrenal cortex

Preovulatory just before ovul.	Midluteal Mid luteal
Graafian follicle Granulosa & theca cells	C. luteum Lutein cells
380 $\mu\text{g/dl}$	250 $\mu\text{g/dl}$ <small>Smaller longer</small>

- Transport: Free 2% N.B estradiol production in men 50 $\mu\text{g/day}$
 Bound 98% Albumin 60% Globulins 38%

- Metabolism: Liver
 • Oxidised or conjugated
 • Estradiol \longrightarrow Estriol & estrone.

- Mechanism of action:
 • Genomic $(\uparrow\uparrow \text{DNA} \ \& \ \uparrow\uparrow \text{mRNA})$
 • Non genomic $(\uparrow\uparrow) \longrightarrow -- \text{FSH} \ \& \ \text{LH via mem R}$

Actions

- 1 Embryonic life $\left\{ \begin{array}{l} \text{♀ Full develop. of uterus \& \ vagina.} \\ \text{♂ masculine \& \ brain} \longrightarrow \text{♂ sex behavior} \end{array} \right.$
- 2 Prepuberal $-- \text{GRTH due to hypoth. hypersensitivity}$
- 3 Non-pregnant adult

- A Target organs **Discuss**
- B General metabolism

- 1 Ptn anabolism: Bones & Genitalia
- 2 Maturation of ossific centres, $\uparrow\uparrow$ osteoblastic activity & union of epiphysis & Growth spurt.
- 3 Anti insulin
- 4 $--$ cholesterol & VD by nitric oxide.
($--$ myocardial relaxation before menopause)
- 5 Salt & H_2O retention \longrightarrow premenstrual dysphoria

- C Endocrinal glands
- 1 $\uparrow\uparrow$ size of pituitary gland.
- 2 Regulation of gonadotropins **Discuss** $(-ve \ \& \ +ve)$
- 3 $\uparrow\uparrow$ angiotensinogen, TBG & CBG

note estrogen receptors $\left\{ \begin{array}{l} \alpha : \text{Hypoth, pituitary, uterus, kidney \& \ adrenal, testis \& \ epidy} \\ \beta : \text{Bladder, Brain, Bone, prostate \& \ pulm (lungs)} \end{array} \right.$

Actions of estrogen on target organs

1 Primary sex organ

- Growth of ovarian follicles.
- LH surge → ovulation & CL formation.

2 Secondary sex organs

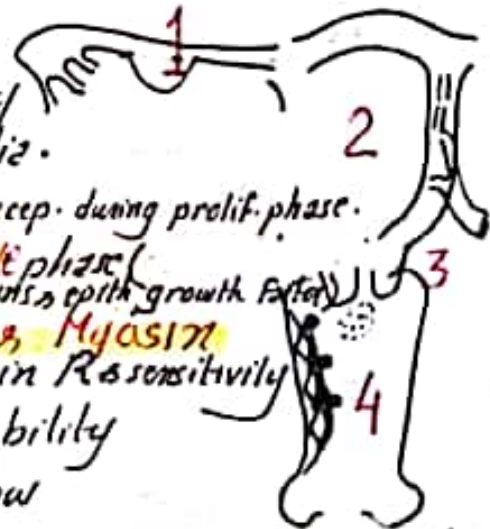


① Fallopian tube ++ mobility
++ activity & NO of cilia.

② Uterus max NO of estrogen Recept. during prolif. phase.

- endometrium Proliferative phase
via ++ growth factors (somatomedins, epith. growth factor)

- myometrium ++ Actin & Myosin
++ oxytocin R sensitivity
++ excitability
++ bl. flow



③ Cervix thin alkaline mucous (thinnest at ovulation)

Stretched into long threads (Spinnbarkeit test)
Fern like pattern when dry.

④ Vagina Stratification & keratinization & thick mucous

Glycogen → lactic acid (kill bacteria)

⑤ Breast Enlargement & fat deposition & ++ bl. flow

Duct & Nipple
Aeolae: pigmentation, especially early pregnancy

3 Secondary sex characters

① Hair -- body ++ scalp
pubic ▽ base upwards

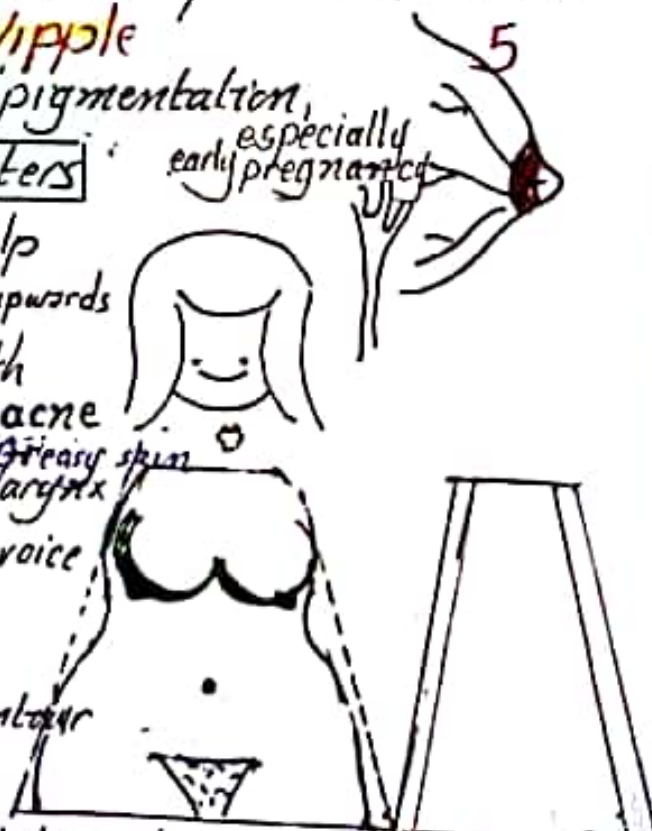
② Skin soft & smooth

③ Voice sebaceous g. -- acne
N.B. excess → dry skin -- Greasy skin
no effect on larynx

i.e. High pitched child voice

④ Body narrow shoulders
broad pelvic
fat, rounded contour

⑤ Behavioural libido
make up of ♀



[note] pubic & axillary hair growth by adrenal androgen.

Progesterone

.C21 Steroid

- Sources Corpus luteum and placenta
small amount from ovarian follicles & adrenal cortex
- Important intermediate in ALL tissues secreting steroid hormones
- In C luteum, granulosa cells secrete progesterone by themselves or theca cells provide pregnanolone.

Plasma level in follicular phase 0.9 ng/ml
++ 20 time to L. peak Mittluteal 18 ng/ml

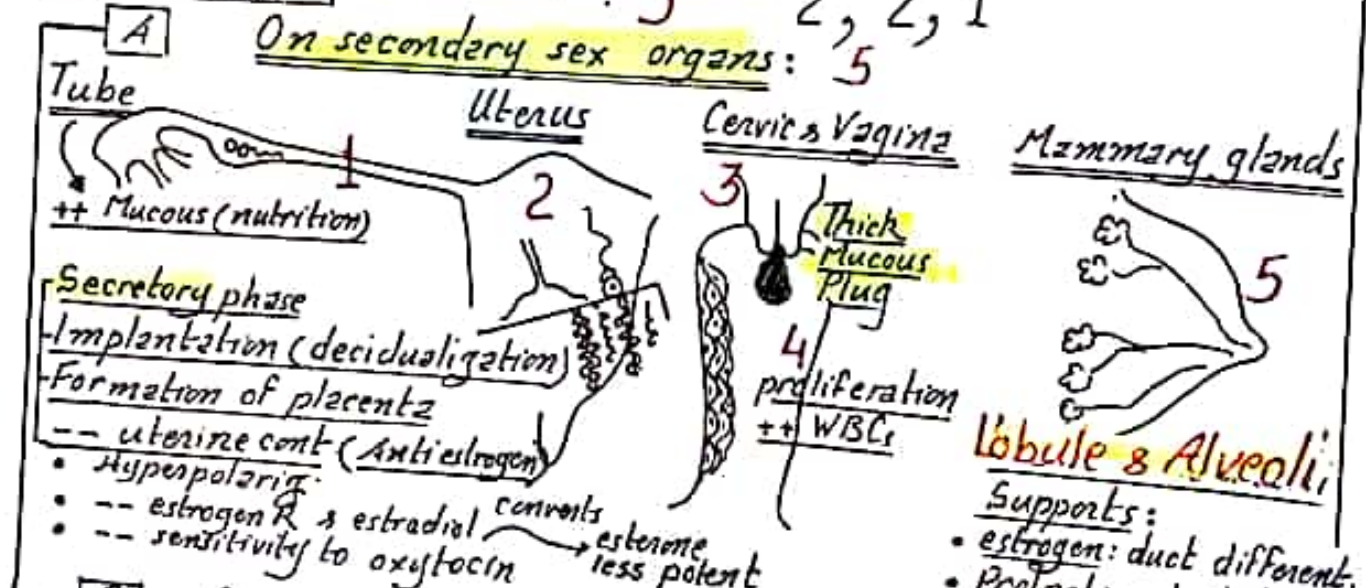


- Transport Free 2%
Bound 98% Albumin 80% Globulins 18%
- Metabolism Liver converted to pregnandiol & excreted in urine.
- Mechanism of action. Genomic

Progesterone releases its receptor from heat shock ptn.
→ exposure of DNA binding domain of receptors (A & B)

Actions

On secondary sex organs: 5, 2, 2, 1



B On prim sex organ:
 - minute amount augments LH surge
 - Large amount -- LH → -- ovulation
 stim resp → -- PCO₂
 ++ 0.5°C at ovulation & end 1/2 of cycle

C On respiration:
D Thermogenic:
basal body temp

E Electrolyte balance:
 • Prog. like gluco. & mineralo. on DCT → Na & H₂O retention
 • Prog. on large dose competes with aldost. → Na & H₂O excretion

Abnormalities of ovarian Functions

- 1 Prim hypogonadism Ovaries : Congenital absence or diseases
- 2 Secund. " Hypoth or pit : diseases



1 Prepuberal Manifestations 2 Post-puberal hypogonadism

<ul style="list-style-type: none"> • prim. amenorrhoea & sterility • remain infantile • don't appear • Tall (delayed epiphyseal fusion) 	<u>Ovaries</u> <u>Secund. sex organs</u> <u>Secund. sex characters</u> <u>Bones & muscle</u>	Secund. amenorrhoea & sterility regress regress osteoporosis & wasting
---	---	---

Estrogen secreting ovarian tumours

- 1 - Child → precocious pseudo puberty
- 2 - After menopause : granulosa cell tumour.

Abnormalities of ovarian cycle.

Aneovulatory cycles

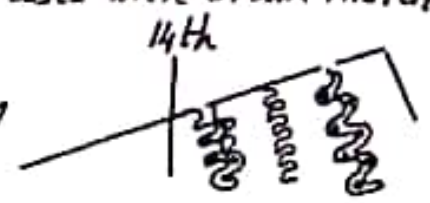
- Definition : failure of ovulation.
- Causes :

- Physiological 1st few cycles at puberty & last cycles at menopause
- Pathological
 - 1 Lack of sufficient LH surge
 - 2 Lack of ovarian response to LH
 - 3 ++ prolactin or stress → -- GnRH.

- Characteristic : NO C. luteum → NO progesterone leading to
 - Absence of Secretory changes in endometrium
 - Short cycles Mature Graffian follicle regresses with ovum inside.

Diagnosis of ovulation :

1. Endometrial biopsy : Secretory pattern
2. Folliculometry by sonar
3. Midcycle LH surge by blood hormonal assay
4. Rise of body temp 0.5°C in 2nd 1/2 of cycle
5. ++ progesterone in plasma & Mittelschmerz pain i.e. lower abdomen pain at ovulation due to peritoneal irritation



Amenorrhoea

- 1 primary : associated with immature sexual signs e.g. small breast

b secondary stoppage of cycles after normal cycles.

Causes

- 1 pregnancy main cause.
- 2 emotional stress or systemic diseases.
- 3 Hypoth., pituitary or ovarian diseases.
- 4 Menopause.

3 Hypomenorrhea ↓ Amount of menstrual blood.

4 Oligomenorrhea: ↓ Frequency of menstruation.

5 Metrorrhagia: bleeding between periods.

6 Menorrhagia: Abnormal profuse menstrual flow.

7 Dysmenorrhea: Painful menstruation.

Menopause

Permanent stoppage of sexual cycles in ♀ (45-55)

Cause Decrease number of OVA (primordial follicles)

→ ↓ estrogen → no surge or inhibition of FSH & LH

Hormonal changes

↓ Estrogen
↓ Progesterone

-ve →

↑ GnRH

↑ FSH
↑ LH
but no surge

↑ androgen



Manifestations = Postpubertal Hypogonadism

1 Secondary amenorrhoea & sterility.

2 Second. sex organs & characters gradual regress

3 Osteoporosis due to -- estrogen anabolic effect.

4 Hot flushes 25% of women (Cause is unknown)

5 Psychic disorders anxiety, irritability, depression & dyspnea

ttt

1 Small doses of estrogen

2 Milk & vitamin D to avoid osteoporosis

3 Psychotherapy.

testosterone in old age

Contraception

Temporary prevention of pregnancy

- 1 Natural family planning (fertility awareness 80-90% success)
 - a Symptothermal method midcycle pain, ++ temp & thin cervical mucus
 - b Safe period (rhythm method) no intercourse 3 days before & 3 days after ovulation

2 Hormonal suppression contraceptive pills

a Single hormone therapy

1 Estrogen pills daily for 3 W/month

-- GnRH & inhibit ovulation

2 Synthetic progesterone pills (progestin)

Thick cervical mucus *sperms* can't penetrate

Atypical secretory endometrium

It is effective for 5 Years

b Combined hormone therapy (progestin & estrogens 3W/M)

- **Fertilization** Fusion of sperm with mature ovum
- **Time** 14th - 16th day of ovarian cycle
- **Site** Ampulla of Fallopian tube.
- **Preparatory steps for fertilization**

① 2nd meiotic division begins arrested in metaphase.

Ovum's corona radiata picked by fimbriae of F. tube.

- Ovum retains capacity for fertilization 12-14 hours

- Sperm " " " " 1-2 days

② Ascent of spermatozoa to ampulla takes 1 hour

aided by a Alkaline seminal fluid = vaginal acidity



b Vagina: semen coagulates

c Cervix thin secretion by estrogen

d Uterus & F tube cont → -ve p

a Only 50-100 sperm reach ovum.

Fertilization involves:

- ① **Chemoattraction** of sperm by ovum substance.
- ② **Adherence** of sperm to ZP₃ receptors
Mediated by fertilin (ptn on surface of sperm head)
→ Acrosomal reaction (discuss)
- ③ **Break down of fusion area** with release of sperm nucleus into ovum cytoplasm
- ④ **Fusion leads to**
 - 1) **Prevention of polyspermy by**
 - - membrane potential of ovum
 - ++ IP₃ in oocytes → Ca release → exocytosis of small granules → release of enzyme → hardening ZP
 - 2) **Completion of 2nd meiotic division**

● Preimplantation

- ① Zygote : mitotic division within ZP (zona pellucida)
 - ② Zygote descends in F tube to uterus within 3-5 days
blastomere (2 cell stage) → morula (50-100 cells)
 - ③ Implantation in uterus takes 2-4 days
Morula contains fluid filled cavity separating cells into:
 - Inner cell mass forms Embryonic tissue
 - Outer cell mass forms Trophoblast
 - ④ ZP shedding by lytic factor (plasmin) released from decidual cells
- N.B If cells divide into 2 separate group → identical twins
- ⑤ Pinopodes Finger like protrusion from endometrial cells approximate embryo & uterine epith close to each other

● Implantation

- Time 6th - 8th days after ovulation.

- Three steps :

- ① Apposition of blastocyst with endometrial epith.
It occurs at site of rupture of ZP
- ② Adhesion of microvilli from trophoblasts to uterine epith. It involves ligand receptor.
→ dislodging of uterine epith from basal lamina
- ③ Invasion Trophoblast: rapidly proliferates and differentiates into - inner cytotrophoblast

Placenta

- Disc : 22 cm in diameter 2-2.5 cm thickness
500 gm in weight

- Feto Maternal organ

a Fetal placenta develops from blastocyst

b Maternal placenta ,, from uterine tissue

- Placental permeability

Low in early months, then progressive increase
then decreases by end of pregnancy

- Placental barrier includes

1 Outer Syncytial trophoblast.

2 Middle Mesenchymal layer

3 Inner Cytotrophoblast

4 Wall of Fetal capillaries

- Placental Circulation

Maternal blood flow 600-700 ml/min. at term

Sluggish flow due to small blood lakes

& Geometry of maternal bl. vs (lateral spread then reverse)

Exchange between fetal capillaries in placental villi

& maternal sinuses branches of uterine arteries

- Maternal placental fetal unit

Placenta can't form steroidal hormones

• Mother supplies placenta by cholesterol

• Fetal liver & adrenal glands provides placenta with
enzymes e.g 16 & 17 α hydroxylase.

& androgen to form estrogens

So maternal estrogen level indicates fetal well being :3

- Placental Functions

① Diffusion of Gases

Ⓐ O₂: Maternal PO₂ 50-60 mmHg
Fetal PO₂ 20-30 mmHg

O₂ transport to fetus is facilitated by:

- 1 HbF has 20-30% more **affinity** than HbA
- 2 Fetal Hb has 50% more **conc** than maternal Hb
- 3 **Bohr** effect i.e. Fetal CO₂ ↓ affinity of maternal Hb to O₂
- 4 High **CO** relative to fetal weight

Ⓑ CO₂: PCO₂ in fetal blood is 3-5 mmHg higher than in maternal blood.

This is sufficient for CO₂ diff since **solubility** of CO₂ : O₂ **20 : 1**

PCO₂ in maternal blood is low due to resp stim. by **progesterone**

② Diffusion of nutrients

a CHO glucose diffuses by **facilitated diffusion**

Glycogen is stored in placenta.

b Fat diffuses slower than ... glucose

c Pln aa is transported by **active transport**

d Minerals Na⁺, K⁺, Cl⁻ by **simple diffusion**

Ca⁺⁺, PO₄⁼⁼, Fe⁺⁺ by **active transport**

c Vitamins Fat soluble with fat

H₂O soluble by **SD** except riboflavin

③ Diffusion of excretory products \ C by AT

e.g. urea & creatinine

Impermeable

Toxins
Ig M
ABO antibodies
Bacteria

permeable

Antitoxins
Ig G passive immun.
Rh antibodies
Viruses Drugs
↳ malformation

⑤ Endocrinal functions of placenta ⑤ main hormones

Major endocrinal role.

Influence Mother } physiol. Ovarian, Uterine & Mammary
Fetus

A Steroid hormones secreted by syncytial trophoblasts

① Progestins e.g progesterone

2 Major roles during pregnancy:

a Support of the endometrium for fetal survival

Placental progestins can maintain pregnancy after removal of both ovaries

b ↓ contractility of uterine smooth ms (antagonises estrogen)
By end of pregnancy ↓ progestins / estrogen ratio → Parturition

Other actions

a ↓ FSH & LH → prevents ovulation during pregnancy

b breast Alveo lobular system

② Estrogens Major Placental estrogen is estriol.

Increases to maximum by end of gestation

2 Major roles

a Stimulates growth of myometrium (actin & myosin)

Prepares uterus for parturition by ↑ oxytocin receptors & antagonises progestins

b Stimulates mammary gland development & its duct system

Other actions

- 1 ↓ FSH & LH → prevents ovulation during pregnancy.
- 2 Helps in relaxation of pelvic ligaments & cervical softening

B Plac hormones

Influence Mother endocrinal system &
Fetal metabolism.

① Human chorionic gonadotropins hCG Glycoprotein

Produced by fetal trophoblast cells

Detected in blood 6 days after conception

in urine 14 days after conception

Reaches a peak 7-9 Weeks of pregnancy

Alpha subunit like LH mainly but also FSH & TSH & β subunit

It has no -ve feed back with progesterins & estrogens

It indicates pregnancy

Actions

- 1 Ovaries maintains CL & pregnancy
- 2 Testis of fetus secretion of testosterone 3Ds
- 3 Uterus Helps growth of endometrium, implantation & placental formation
- 4 Prevents fetal rejection

② Placental lactogen = human placental lactogen = hCS

Actions not well understood = GH & Prolactin

- 1 Mobilizes energy substrate for fetal use e.g glucose
- 2 Plac deposition
- 3 Breast development prior to parturition.

③ Relaxin

Sources Placenta & CL

Actions

- 1 Acts synergistically with progesterone to maintain preg.
- 2 Relaxes pelvic ligaments at end of pregnancy to aid parturition

Other hormones secreted during pregnancy

- 1 Pituitary glands is stimulated by placental hormones
↑ ACTH, TSH & Prolactin
↓ FSH & LH
- 2 Thyroid ↑ T_3 & T_4
- 3 Parathyroid ↑ PTH (maintain Ca^{++})
- 4 Adrenal cortex ↑ Gluco & Mineralocorticoids
- 5 Pancreas ↑ Insulin

Notes

Continuation of pregnancy by prevention of regression of CL via HCG of trophoblast
Corpus luteum remains 60 days, then placenta takes its re

Failure to reject fetal graft is due to

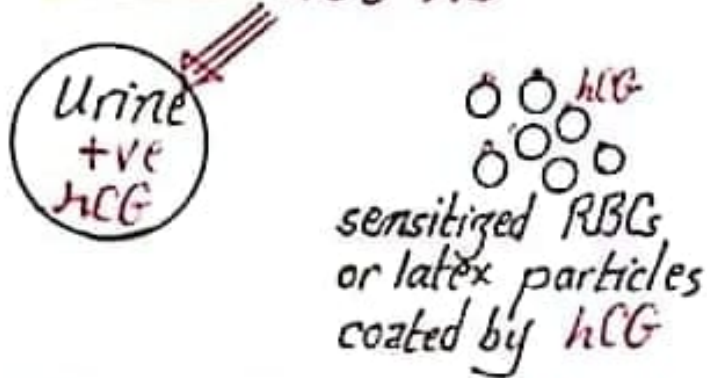
- 1 Expression of HLA-G by placental trophoblast instead of MHC class I, II
- 2 FAS-ligand on surface of placenta

Pregnancy tests

Depend on detection of **hCG** in urine or blood

① Agglutination (immunological) tests rapid specific

a Indirect hCG Ab



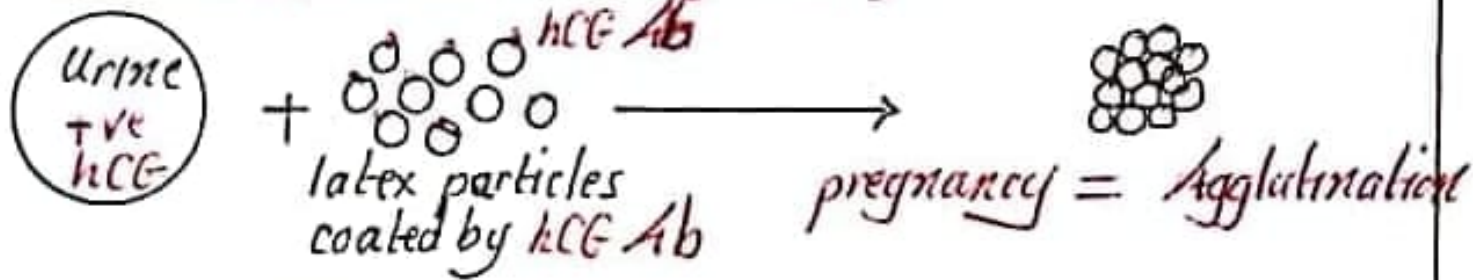
Pregnancy = No agglutination

hCG Ab



No pregnancy = Agglutination

b Direct agglutination (coagulation)



② Radioimmuno assay

used for polypeptide β subunit receptors of hCG

Stages of labour

- 1st U cont. till fully dilated cervix
- 2nd Expulsion of baby from birth canal
- 3rd Expulsion of Placenta and fetal membranes.

Parturition = labour = delivery

Expulsion of fetus & placenta.

It requires strong coordinated uterine contractions
Helped by voluntary abdominal contractions

Multifactorial \longrightarrow \uparrow uterine contractions

① Hormonal factors

a \uparrow estrogen / progesterone ratio

At 7 months estrogen continues to increase
progesterone decreases or constant

b Oxytocin Fetal & Maternal sources

Direct cont or Indirect cont via PGs

estrogen \uparrow synthesis & sensitivity of oxytocin receptors

c Prostaglandins From decidua & fetal membranes

- Direct U. contraction Induce oxytocin action

- Softens dilates & thins out uterine cervix

d Fetal hypothalamic pituitary adrenal axis \uparrow U. contractions

② Mechanical factors

a Stretch of U. muscles \longrightarrow U. contraction,

b Stretch of Cervix \longrightarrow U. contraction.

c +ve feedback mechanisms

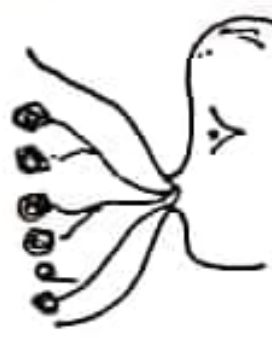

1 Cervical stretch \longrightarrow U. cont \longrightarrow more cervical stretch

2 Cervical stretch \uparrow oxytocin more cervical stretch

Ferguson Reflex

● Lactation

Breast development starts at puberty. completed during pregnancy.

<u>Growth</u>		<u>Secretion</u>		<u>Milk ejection</u> milk let down	
Duct system	Lobules & alveoli				
<u>Estrogen</u>	<u>Progesterone</u>	<u>Prolactin</u>	<u>Oxytocin</u>		
Enlargement stroma & fat ↑ blood flow Pigmentation of areola (early preg)		stim. by Suckling			
Duct & Nipple		Lobules & alveoli		Secretion	Milk let down
<u>Aided by</u> Prolactin, Growth H, Insulin & Glucocorticoids		hCS			

Colostrum 1st W after birth contains more Ig & Pln

Milk 2nd & 3rd W contains more lactose & fat (high Calorie)

Initiation of lactation 5th M of gestation Small amount of milk
 After labour, expulsion of placenta → ↓ estrogen & progesterone
 → removal of inhibitory effects of estrogen on prolactin
 estrogen & prolactin synergise each other on breast growth
 antagonise on lactation.

Effect of lactation on menstrual cycles

Prolactin \longrightarrow -- GnRH \longrightarrow no ovulation \downarrow estrogen & progesterone

May amenorrhoea for 25-30 W

50% of cycles in 1st 6 M anovulatory

Chiari Fermmel syndrome rare

= Persistence of lactation & amenorrhoea in unnursing ♀ after delivery

Cause Persistence Prolactin secretion \longrightarrow \downarrow FSH & LH

Notes Nonpregnant ♀ having galactorrhoea & amenorrhoea with high prolactin level due to pituitary tumour or injury of pituitary stalk \longrightarrow \downarrow PIIH

Hormones & cancer

- 35% of breast cancer in women of childbearing age are estrogen dependent.

So, symptoms are improved not cured for months or years by removal of ovaries or drugs inhibiting actions of estrogen

- Some of prostate cancer are androgen dependent is regress temporarily after removal of testes or Ht with GnRH agonists in doses cause down-regulation of GnRH receptors on gonadotrops \longrightarrow \downarrow LH \longrightarrow \downarrow testosterone