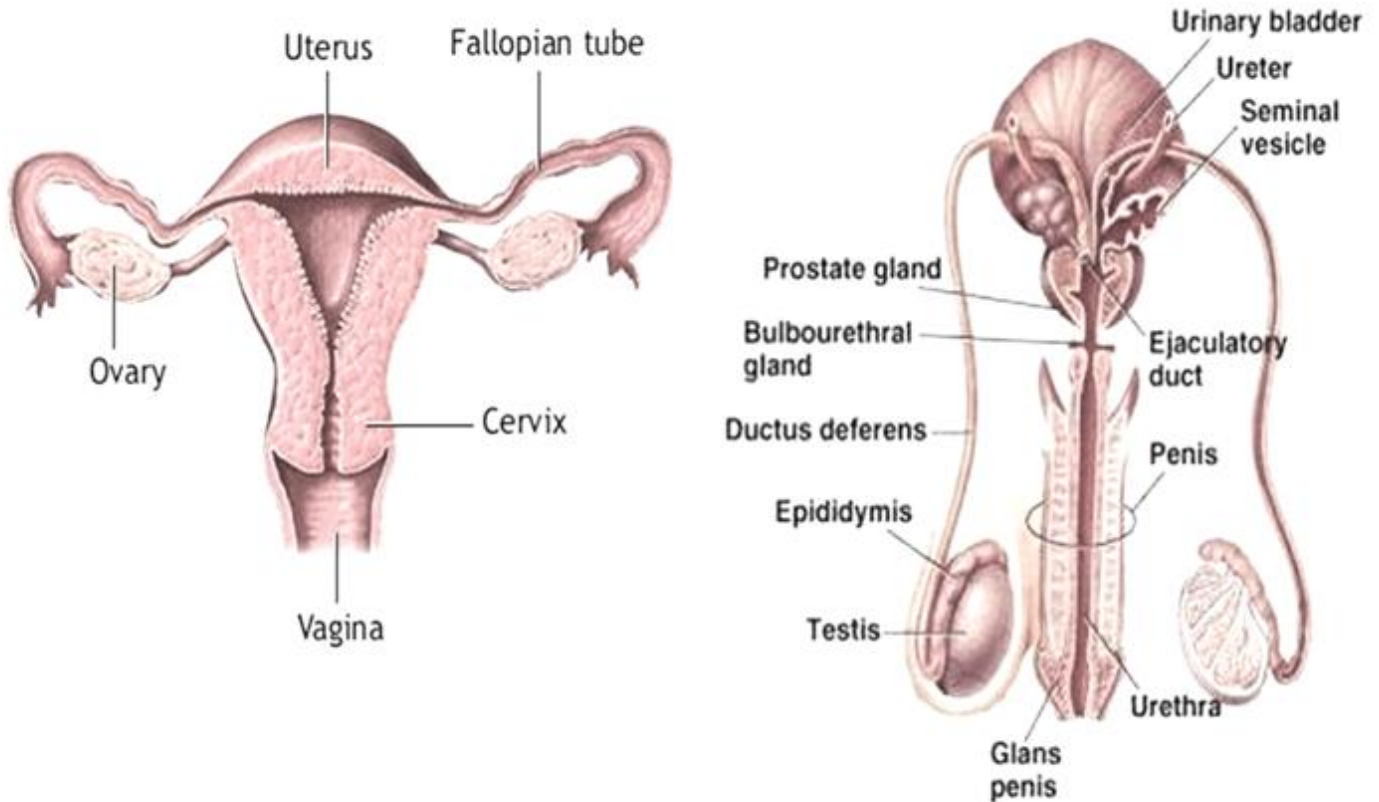


8th Lecture

Physiology of Breast



PHYSIOLOGY TEAM – 430

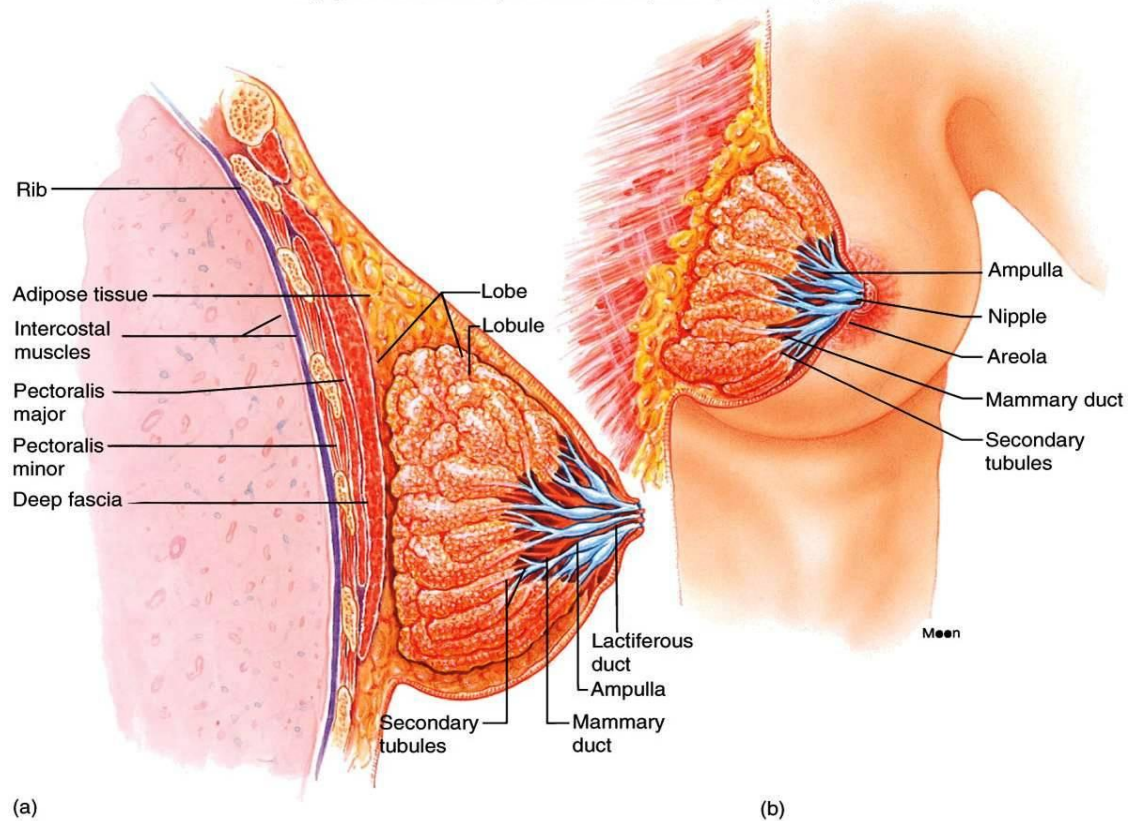
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- **General anatomy of the breast:**

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- Lobules contain the **alveoli**; an alveolus is formed of two types of cells, the **alveolar epithelial** “milk producing cells > to the lumen of the alveolus” and the surrounding **myoepithelial cells** “contraction and ejection of milk through the duct”
- Each breast consists of **4~20 lobes** of secretory tissue
 1. Each lobe has **one lactiferous duct**
 2. Lobes (and ducts) arranged **radially**
 3. Lobes composed of **lobules**
 4. Lobules comprise **alveoli**
- **Alveolus:** microscopic unit made up of alveolar cells with an open lumen for **collection of secreted milk**
- **Alveolar cell (epithelial cell):** basic cell **producing milk** in the **mammary gland**
- **Myoepithelial cell:** **muscle-like cell** surrounding the alveolus; **contracts to express milk** from the alveolar lumen
- **Ductal System:**
 - Alveolar Tubule
 - Secondary tubule
 - Mammary duct
 - Ampulla (lactiferous sinus)
 - Lactiferous duct

➤ **Blood capillaries** surround the alveolus to carry the nutrients that are required for milk production.

- **Breast development (mamogenesis):**

During puberty	During pregnancy
<ul style="list-style-type: none"> - Estrogen stimulates proliferation of ducts and deposition of fat. - Progesterone stimulates development of lobules and alveolar secretory changes. 	<ul style="list-style-type: none"> - Complete development of glandular tissue. - Only in pregnancy the breast reaches its full development.

- **Role of endocrine system:**

- Endocrine system plays a major role in synchronizing development (mamogenesis) and function (lactogenesis) of mammary gland with reproduction.
- Three categories of hormones:

(1) Reproductive hormones (Endocrine)	<ul style="list-style-type: none"> • Estrogen • Progesterone • Prolactin • Oxytocin • HPL (Human placental lactogen)
(2) Metabolic hormones (Endocrine)	<ul style="list-style-type: none"> • Growth hormone • Corticosteroids • Thyroxine • Parathyroid hormone • Insulin
(3) Mammary hormones (Autocrine)	<ul style="list-style-type: none"> • Growth hormone • Prolactin • Leptin • Parathyroid hormone-related protein

1) Reproductive hormones: (They have direct effect on mamogenesis)

A. Estrogen: (from the placenta)

- Growth & branching of ductal system. (with GH)
- Fat deposition in the stroma.

B. Progesterone: (from the placenta)

- Growth of lobule-alveolar system. (Budding of alveoli and secretory changes in epithelial cells)

Although estrogen and progesterone are essential for physical development of the breasts; they inhibit actual secretion of milk.

C. Prolactin: (from anterior pituitary)

- Its level increases during pregnancy. (10-20 times)
- Its main function is milk production.
- Sudden drop in Estrogen & Progesterone after delivery allows milk production.
- It is controlled mainly by hypothalamic hormone PIH (Prolactin inhibitory hormone - Dopamine)

D. Human placental lactogen: (from the placenta)

- Facilitate mamogenesis.
- Delay milk production.

- **Lactogenesis:**

- It is cellular changes by which **mammary epithelial cells** are converted from a **nonsecretory** state to a **secretory** state.
- In **two** stages:

Lactogenesis 1:

(Cytologic and enzymatic differentiation of alveolar epithelial cells) *Preparation*

Starts in **mid-pregnancy** and characterized by **expression of many genes** involved in **synthesis of milk components** (increases in **uptake transport systems** for amino acids, glucose, and calcium required for milk synthesis).

- Hormones involved:

1. **Progesterone**. (suppresses milk secretion)
2. **Prolactin** and/or placental lactogen.
3. **Growth hormone**.
4. **Glucocorticoids**. (Cortisol)

Lactogenesis 2:

(Copious secretion of all milk components)

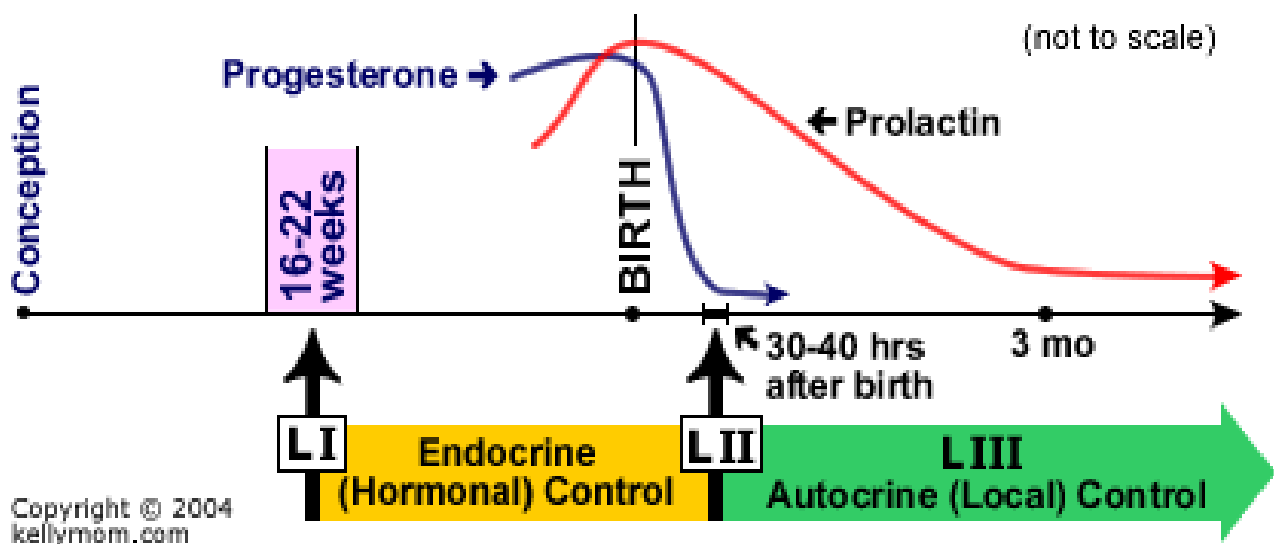
Around parturition withdrawal of **progesterone + high level of prolactin** leads to:

- Further **increase** in **expression of milk protein genes**.
- Glands absorb increased quantities of **metabolic substrates** from the blood.
- **Movement of cytoplasmic lipid droplets** and casein into alveolar lumina.
- Transfer of **immunoglobulins**.
- **Secretion of colostrum** followed by milk.
- **Suckling stimulates** further increase in **expression of genes** involved in milk secretion with expansion of alveolar epithelium.
- Lactation is maintained by **removal of milk**.
- **Hormones involved:**
 1. **Prolactin**. (milk production)
 2. **Oxytocin**. (milk let-down)

What is colostrum?

It is a form of milk produced by the mammary glands in day four of lactation. It contains antibodies to protect the newborn against diseases as well as being lower in fat and higher in protein than ordinary milk.

- **Stages of lactogenesis:**



➤ Notice that stage one starts prior to giving birth while stage 2 occurs after birth.

2) Metabolic hormones (direct effect):

A. GH:

- Can be produced **locally**. (Also considered a mammary hormone)
- Its secretion is **stimulated by progesterone**.
- Increases production of **IGF-1 by the liver**.
- Mediate **cell survival** and **ductal growth**.

B. Corticosteroids:

- **Increases** during **pregnancy**. (Fivefold)
- Involved in **breast development**. (Permissive action on milk protein synthesis)

C. Thyroxin:

- Essential for **milk production**.
- Thyroxin & TSH level **decreases during lactation**.
- TRH (Thyrotropin releasing hormone) **increases** leading to **stimulation of Prolactin**. (Nasal administration to treat inadequate lactation)

D. Insulin:

- **Low** during **lactation**. (Making glucose stays longer in blood for milk production)
- **Shunt of nutrients** from storage depots to milk synthesis.

3) Mammary hormones

A. GH:

- Progesterone stimulates its secretion.

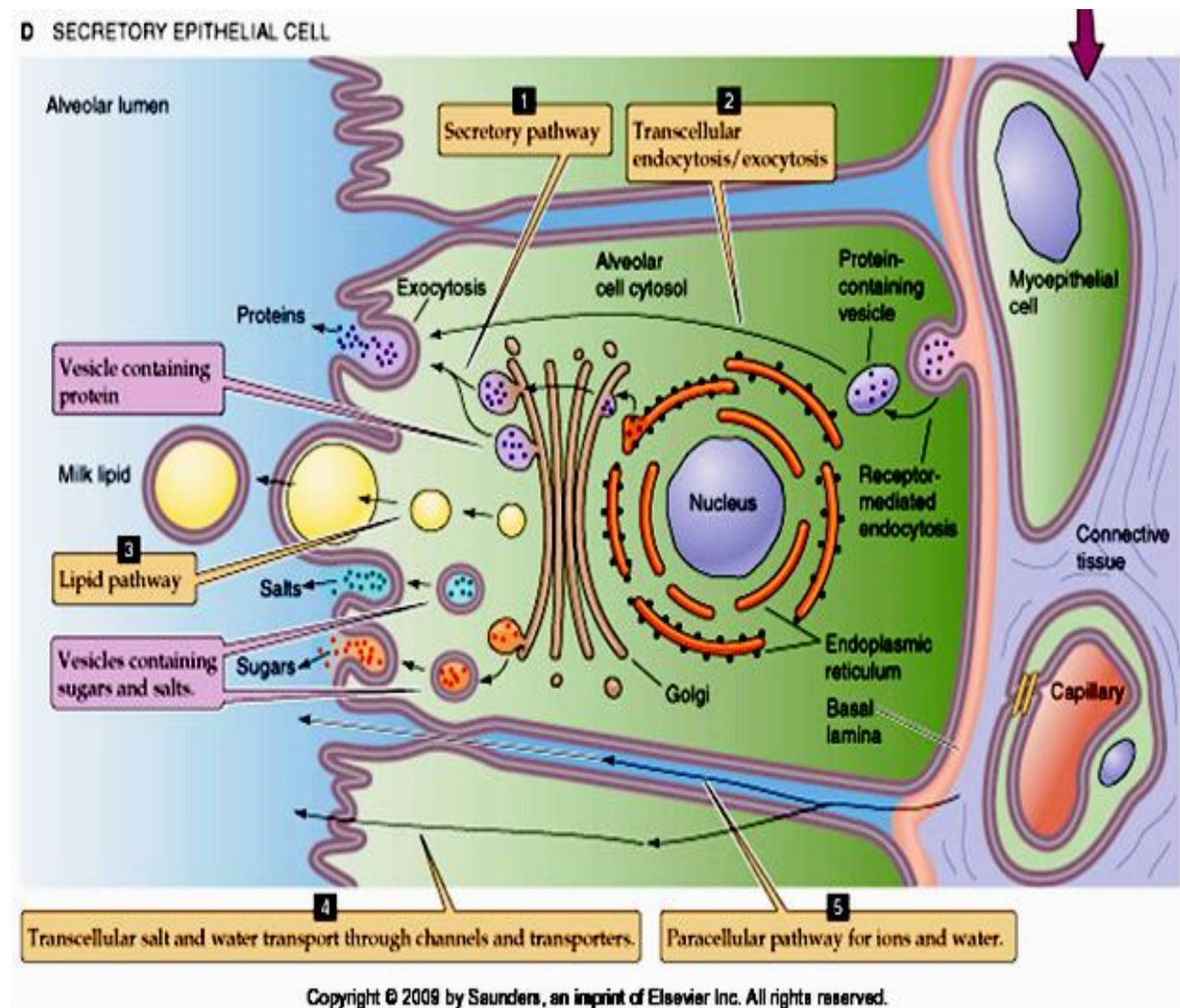
B. Leptin:

- Increases during pregnancy. (Increase adipose tissue)
- Decreases with lactation

C. PTHrP (PTH-related hormone):

- Increases during lactation.
- Mobilizes bone calcium.
- Increase in alkaline phosphatase.

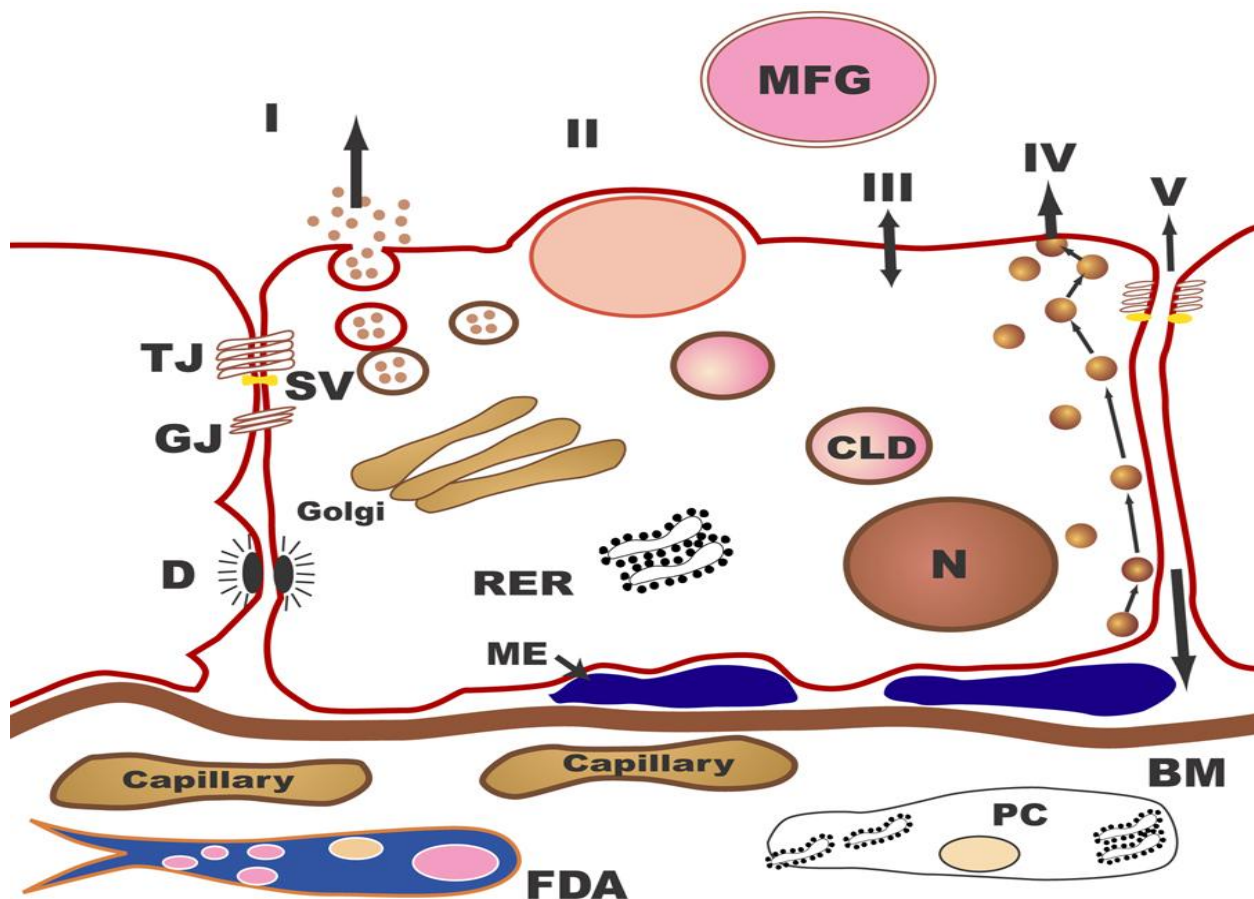
• The pathways for milk secretion and synthesis by the mammary epithelial cell:



Milk production is a "use it or lose it" process.

The **more** often and effectively the **baby nurses**, the **more milk** will be **produced**

- Milk production <100 ml/day in day 1 postpartum.
- Milk production by day 3 reaches 500 ml/day.
- Milk composition changes dramatically ($\downarrow \text{Na}^{+2}$ & Cl^{-}) due to **closure of tight junctions** that block paracellular pathway.



SV = Secretory vesicle. RER = Rough endoplasmic reticulum. BM = Basement membrane.
MFG = Milk fat globule. CLD = Cytoplasmic lipid droplet. N = Nucleus. PC = Plasma cell.
FDA = Fat-depleted adipocyte. TJ = Tight junction. GJ = Gap junction. D = Desmosome.
ME = Myoepithelial cell.

1. Exocytosis of **milk protein**, **lactose**, and other **components** of the aqueous phase in **Golgi-derived secretory vesicles**.
2. **Milk fat secretion** via the **milk fat globule**.
3. Direct **movement of monovalent ions**, **water**, and **glucose** across the **apical membrane** of the cell.
4. **Transcytosis** of **components** of the **interstitial space**.
5. The paracellular pathway for plasma components and leukocytes. **Pathway V** is open only **during pregnancy**, **involution**, and in **inflammatory states** such as **mastitis**.

- **Galactopoeisis:**

- Galactopoeisis is defined as the **maintenance of lactation** once lactation has been **established**.

➤ **Role of Hormones:**

1. **Prolactin:**

- **Milking-induced surge** is a direct link between the **act of nursing** (or milk removal) and the **galactopoeitic hormones** involved in maintaining lactation.

2. **Growth Hormone:**

- Support increase in **synthesis** of **lactose**, **protein**, and **fat** in the **mammary gland**.

3. **Glucocorticoids:**

- **Galactopoeitic** in physiological doses.

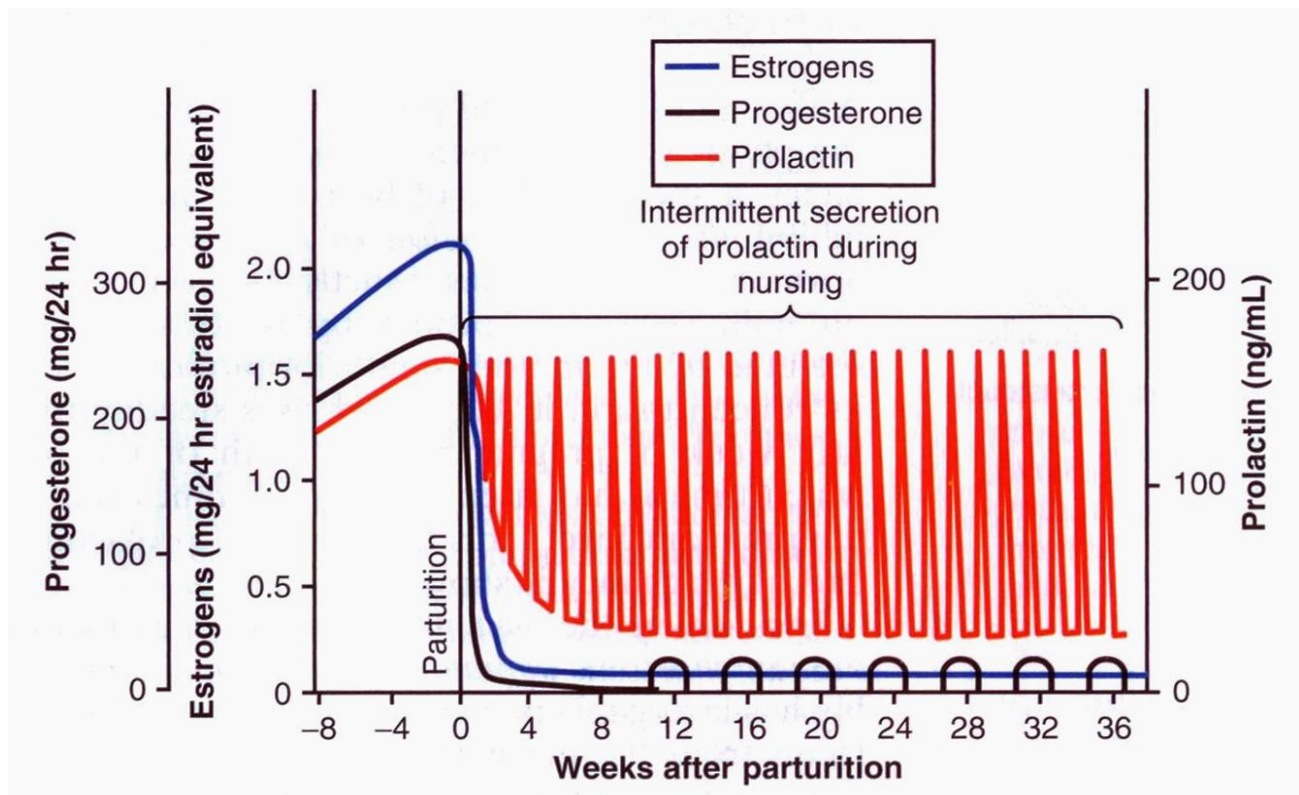
4. **Thyroid Hormones:**

- **Galactopoeitic**.

5. **Ovarian Hormones:**

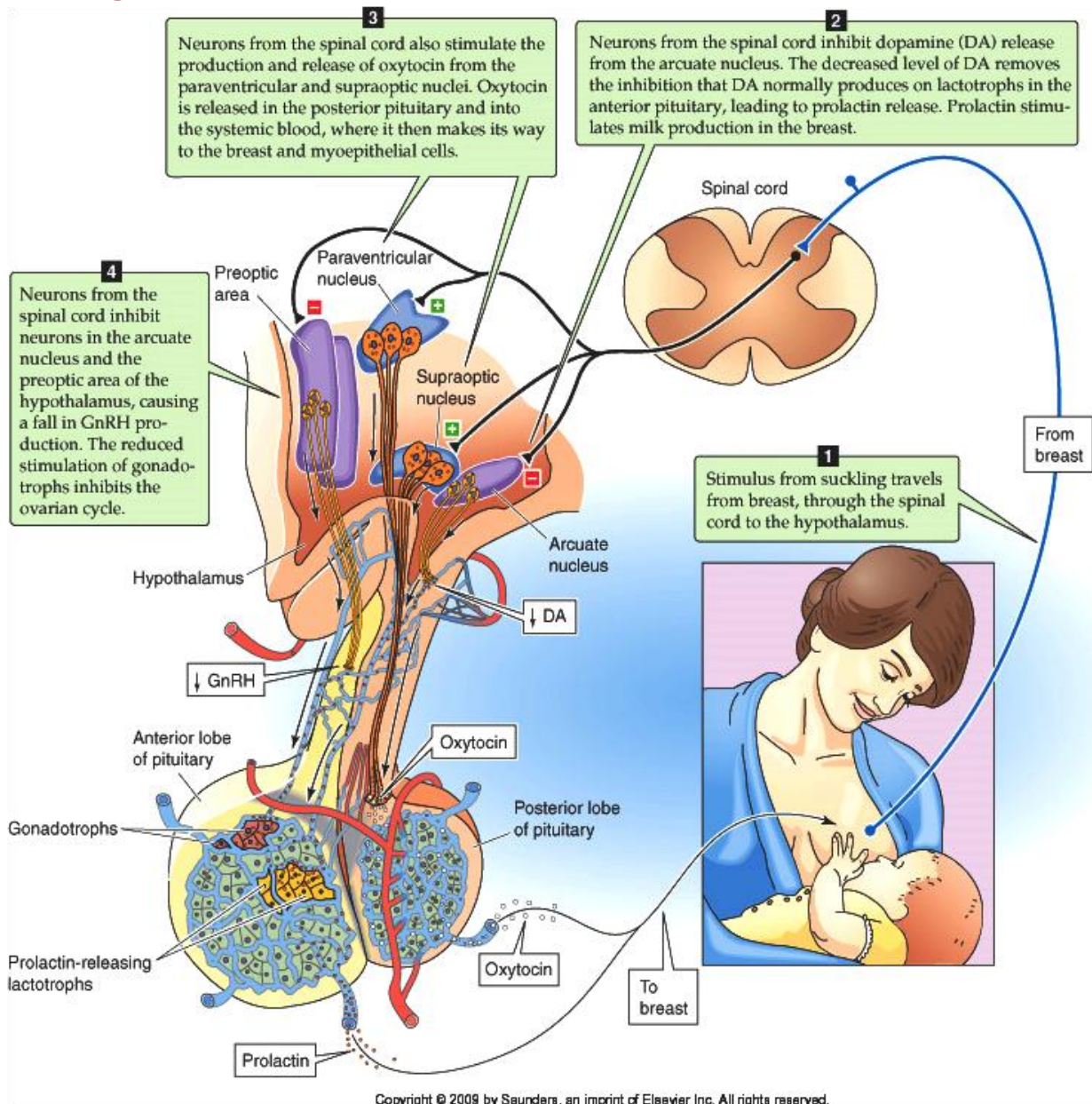
- **Estrogen** in very **low** doses is **galactopoeitic**.
- **Progesterone alone has no effect on galactopoeisis** because there are **no progesterone receptors** in the mammary gland during lactation.

If a woman is lactating and she wants to take contraceptives (Progesterone) it won't affect milk production (It won't inhibit the action of prolactin) why? Because once lactating has been established progesterone receptors will disappear.



- Notice that after pregnancy P & E levels drop, while prolactin has multiple surges based on the action of suckling of the baby.

• Suckling reflex:



• Secretory Activation:

- The most **critical time** in the establishment of lactation is its **onset**, during the transition from **pregnancy to lactation**, a period now called **secretory activation** (previously termed lactogenesis stage II). Secretory activation takes place **after birth** in women. Most **lactation problems** arise during **this period** as the result of **stress of childbirth** or **problems with the mechanics of suckling**. If unresolved these problems can lead to **lactation failure**.
- The major **inhibitor of milk production** during **pregnancy** is **progesterone**.
- Once **birth occurs**, a developed mammary epithelium, the continuing presence of **high levels of prolactin**, and a **fall in progesterone** are necessary for the onset of **copious milk secretion**.
- Thus **removal of the placenta**, the **source of progesterone** during pregnancy in women, has long been known to be necessary for the **initiation of milk secretion**.
- Conversely, **retained placental fragments** with the potential to **secrete progesterone** have been reported to **delay secretory activation**.
- **Progesterone receptors** are **lost** in **lactating mammary tissues**.

- **Milk "Letdown":**

- Milk letdown is the **evacuation** of milk from the **alveolar lumen** to the **duct system**
- ✓ **Nerves** receive stimuli at the **end of nipple**
- ✓ **Stimuli** is received in the **posterior pituitary**
- ✓ **Oxytocin** is **released** from **pituitary** into blood
- ✓ **Blood circulation** brings **oxytocin** to **mammary tissue**
- ✓ **Targets** are the **myoepithelial cells** that **contract**

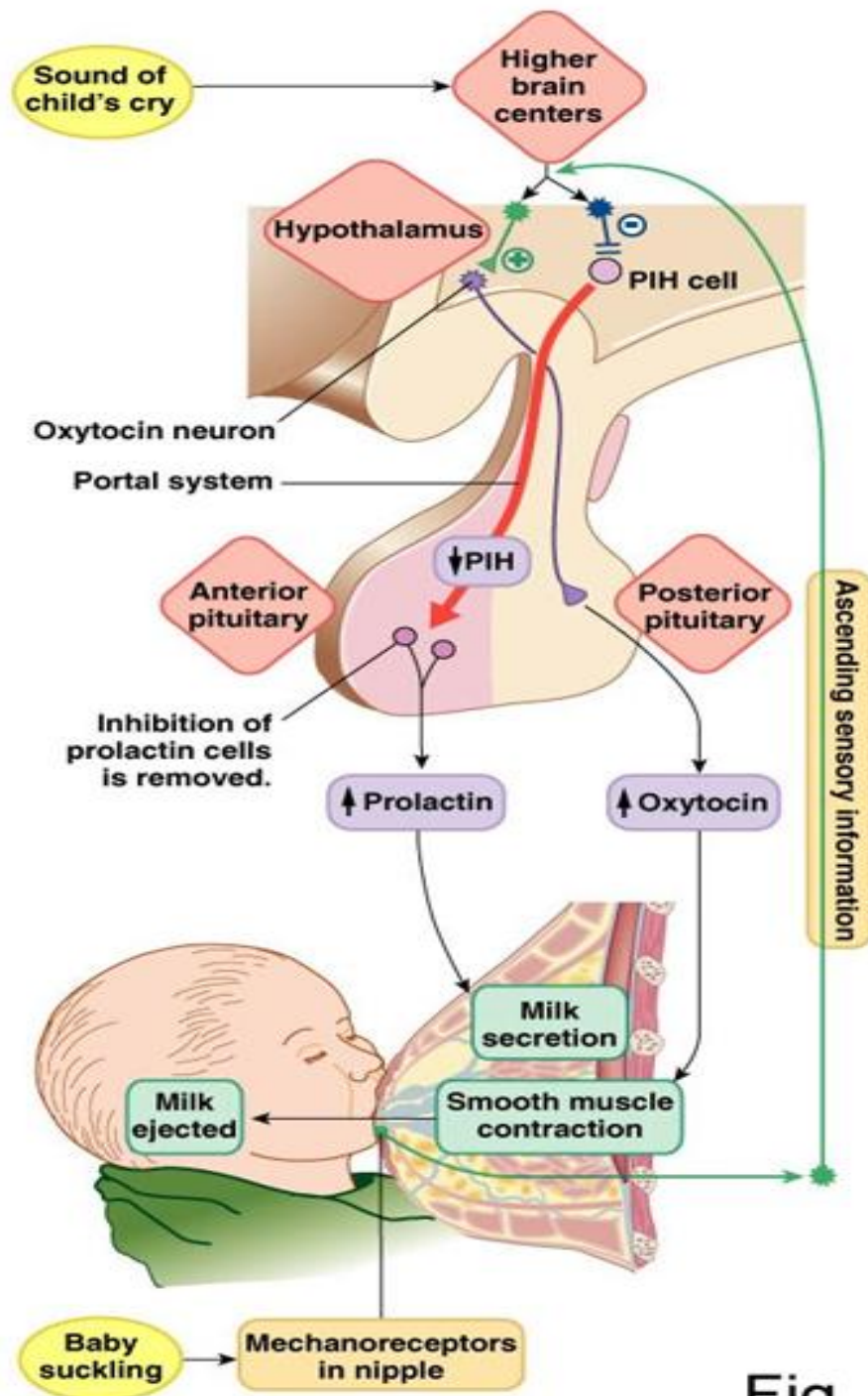
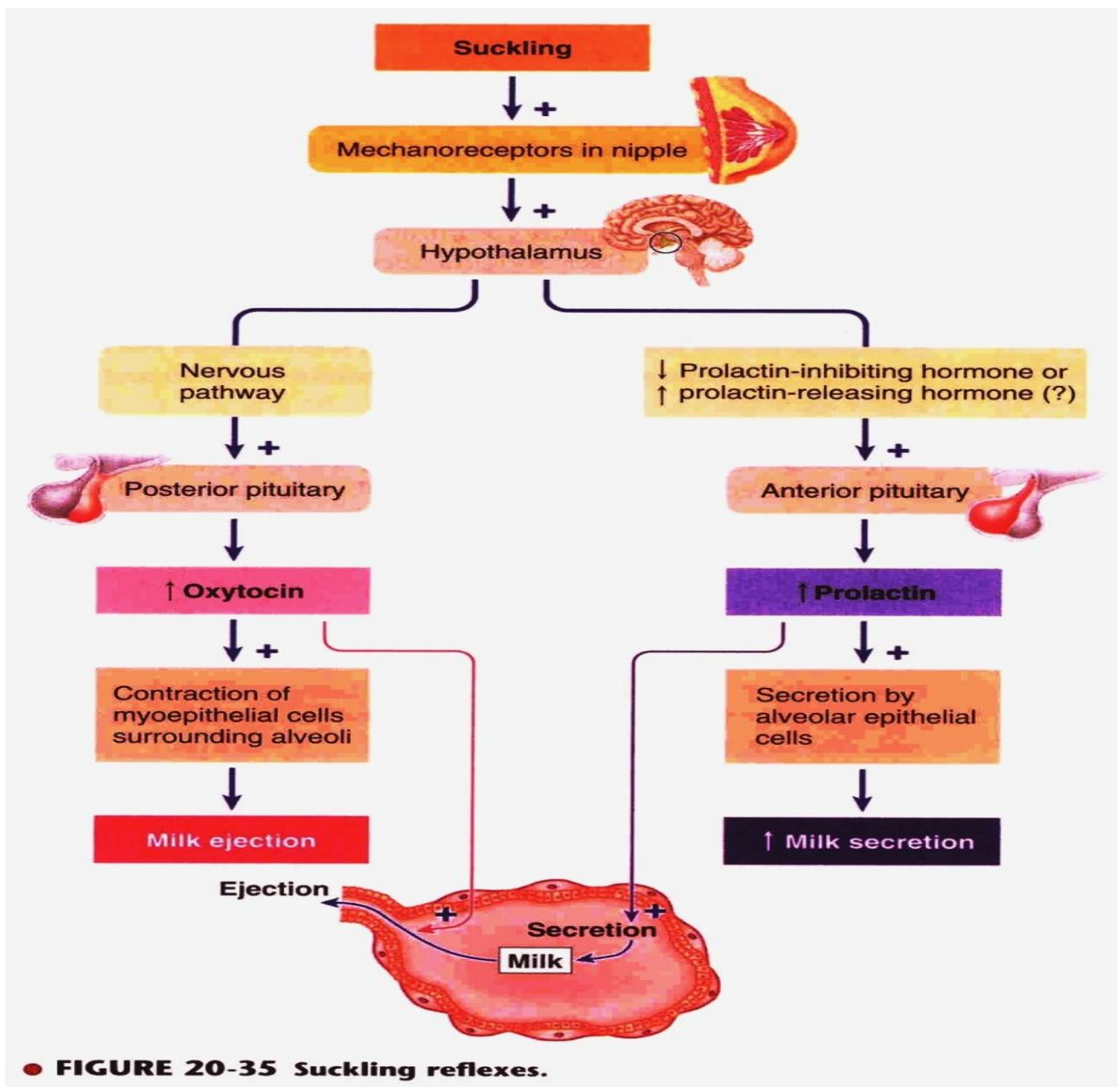


Fig. 26-23

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● **AAP Recommendations: (American Academy of Pediatrics):**

1. Exclusive **breastfeeding** for the **first six months of life**.
2. **Continued breastfeeding** for at least **one year**, 'As long as is desired by mother and child'.