

Hormones affecting the breast

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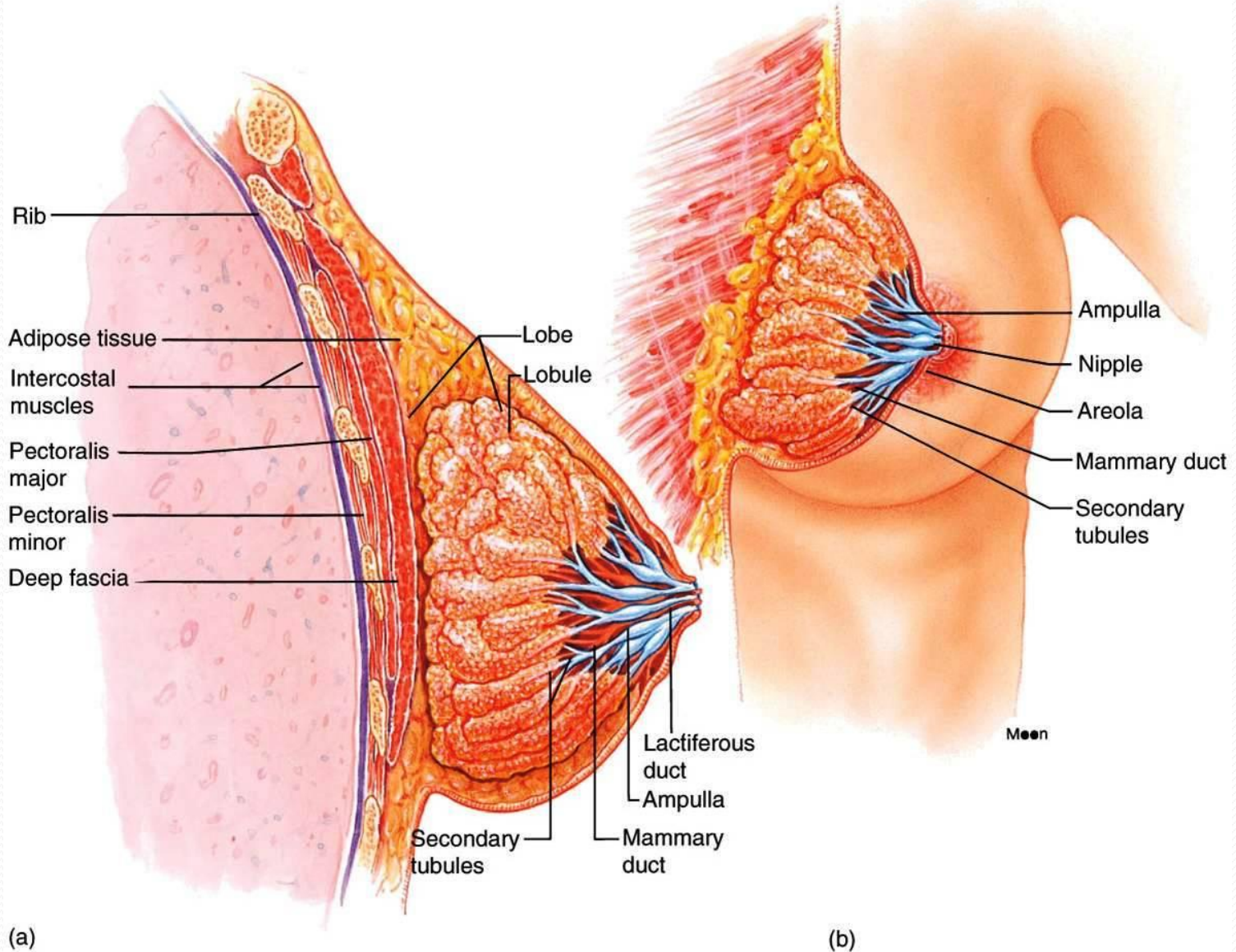
Objectives

- Physiological anatomy of the breast
- Physiological changes during breast development (**Mamogenesis**)
- Physiological changes during lactation (**Lactogenesis**) and their physiological action
- Phases of lactogenesis.
- Physiological changes during **Galactopoeisis**.
- Endocrine and autocrine control.
- **Involution** (the termination of milk production).

Small group activity

- What is the structure of human breast?

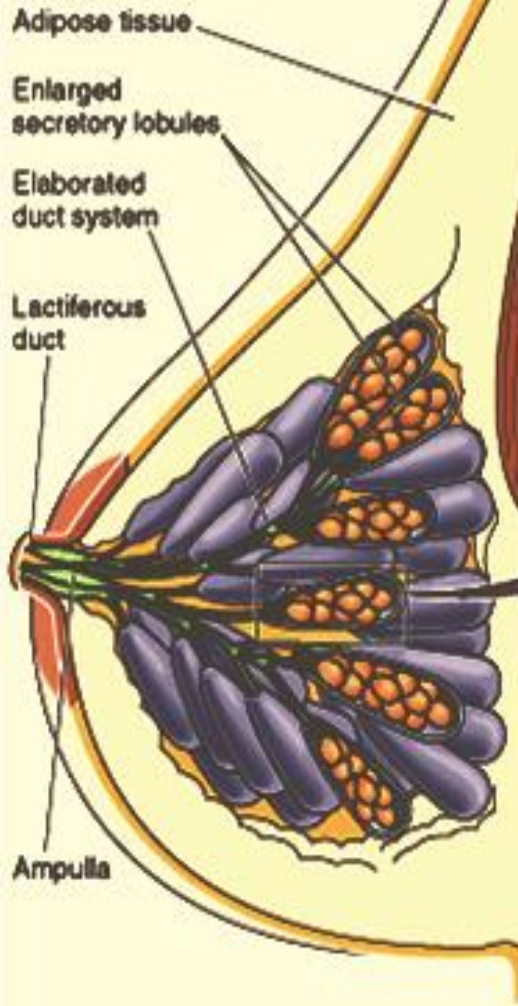




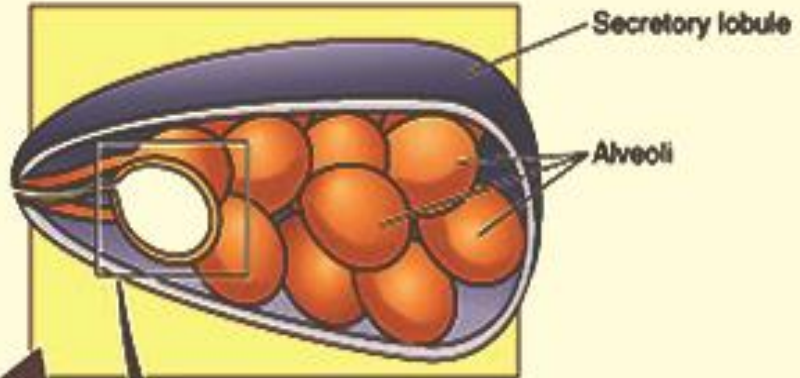
(a)

(b)

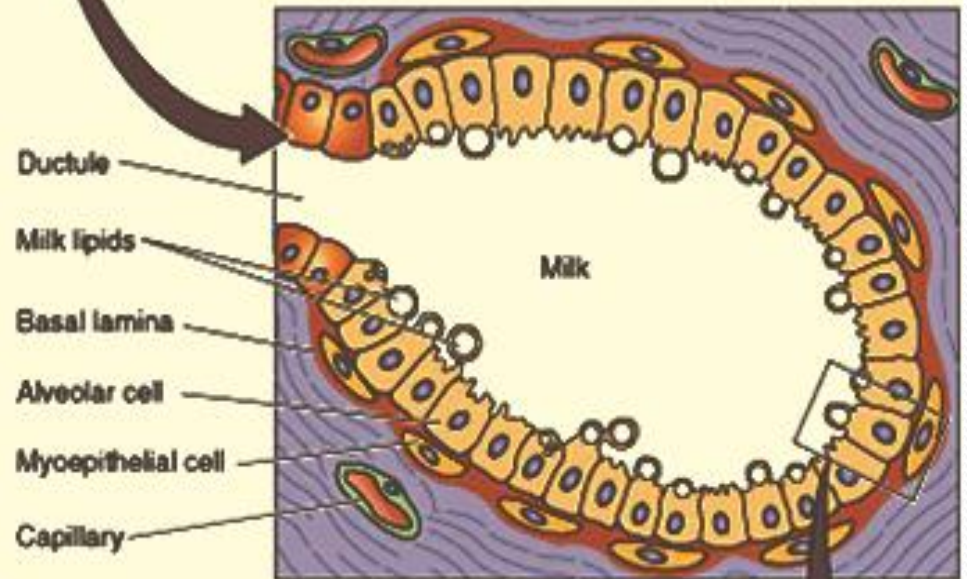
A LACTATING BREAST



B LOBULE



C ALVEOLUS



Small group activity

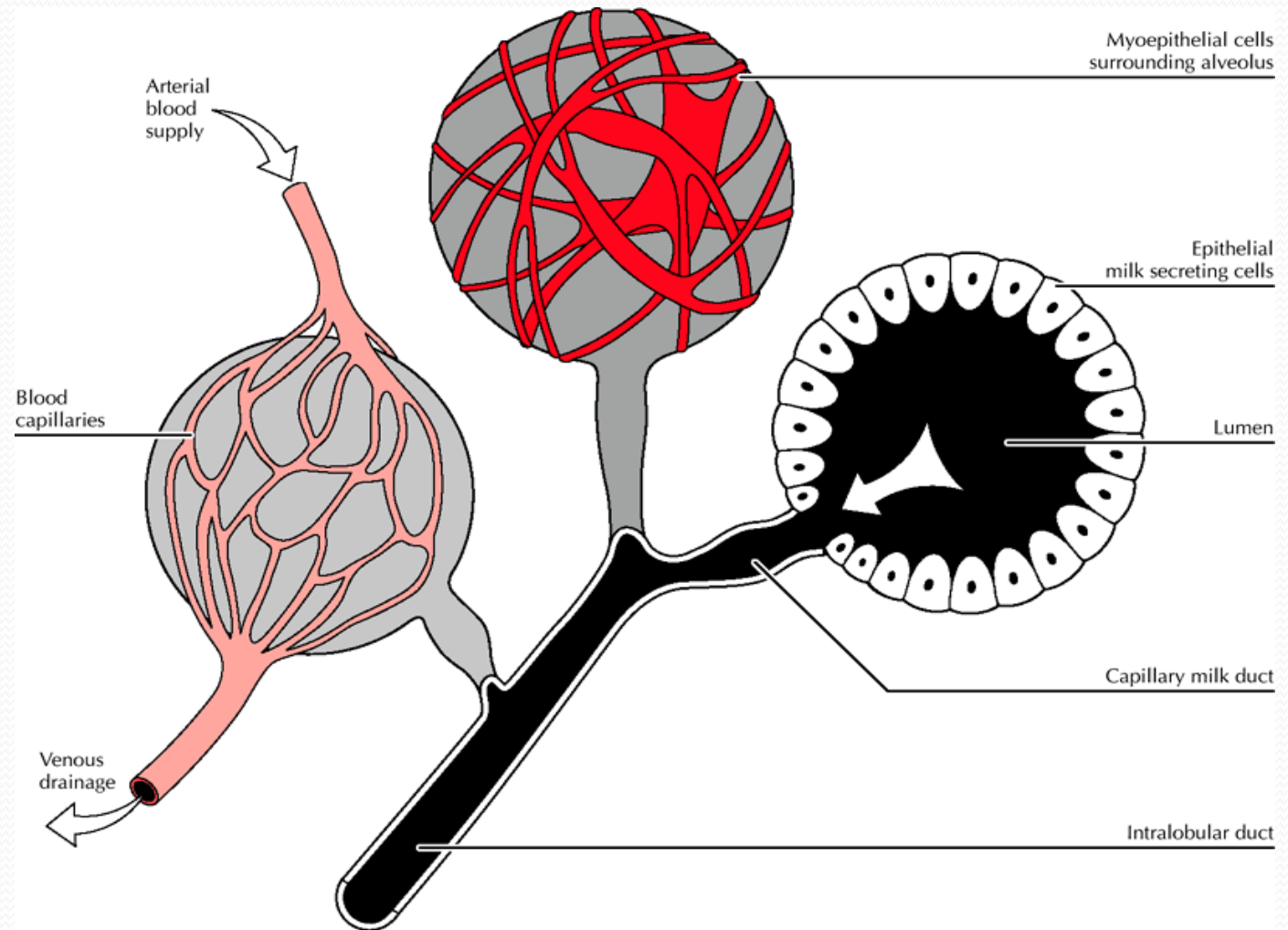
- Where does milk come from?

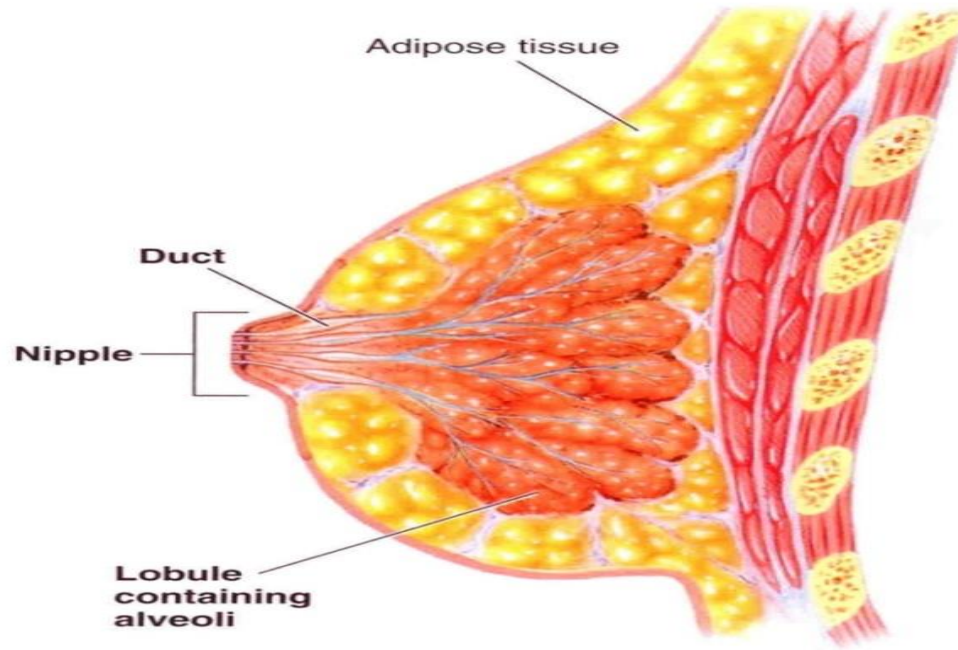


Theories

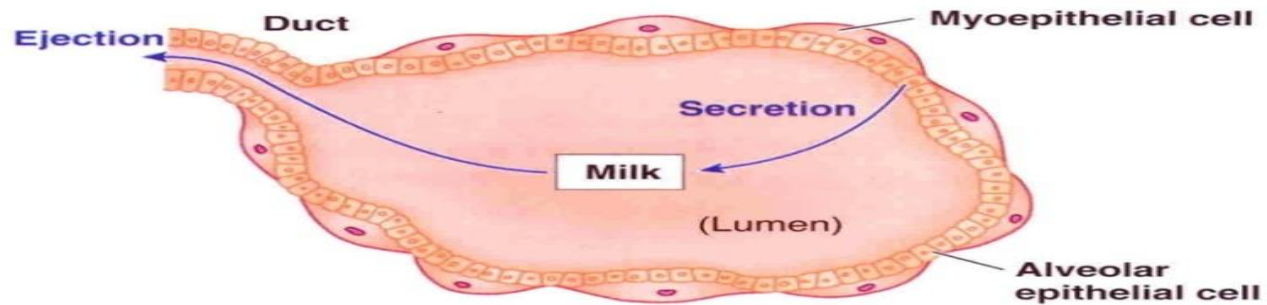
- **Uterine milk theory:** Vessel connecting the uterus to the breast (diversion of menstrual blood to the breast)
- **Chyle theory:** Milk is derived directly from chyle (milky fluid of emulsified fat absorbed from the intestinal tract into lymphatic system).
- **Synthesis theory:** Milk is formed from substrates carried to the gland in the blood

Where does milk come from?





(a) Internal structure of mammary gland, lateral view



(b) Alveolus within mammary gland

- **FIGURE 20-34 Mammary gland anatomy.** The alveolar epithelial cells secrete milk into the lumen. Contraction of the surrounding myoepithelial cells ejects the secreted milk out through the duct.

Mamogenesis

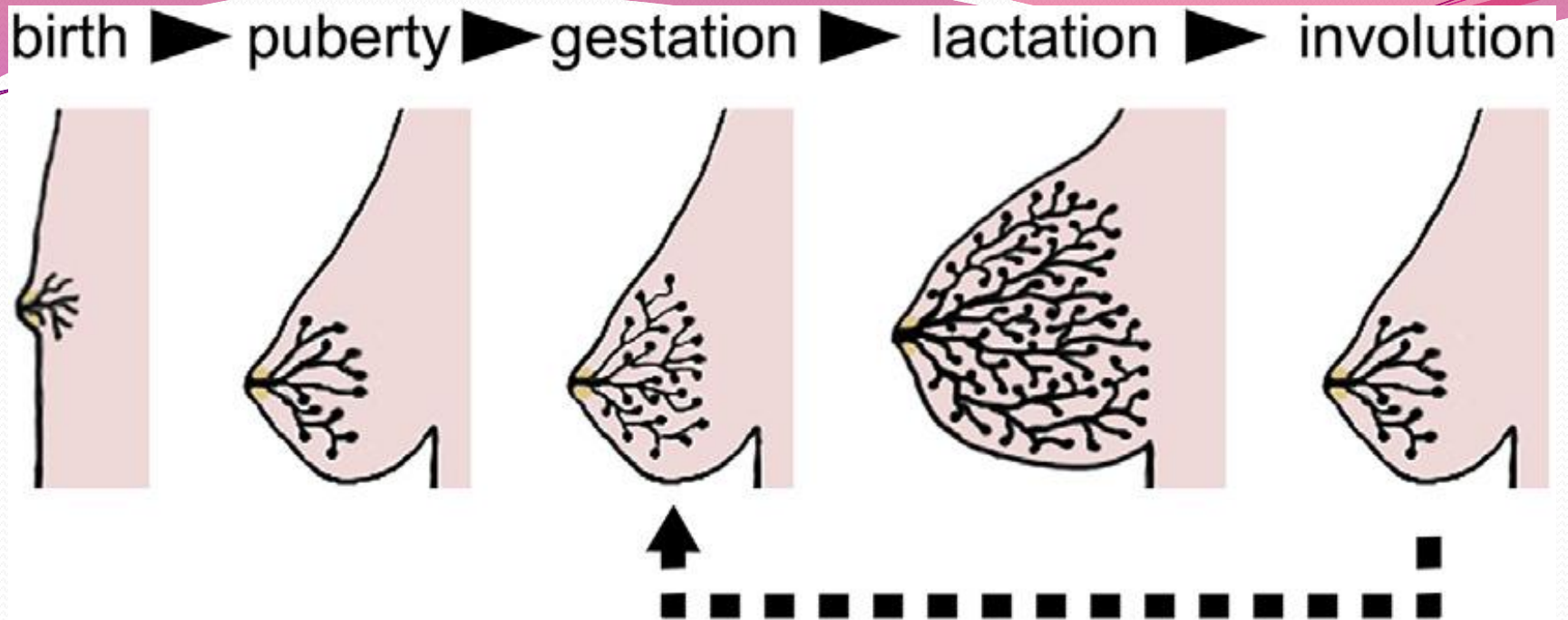
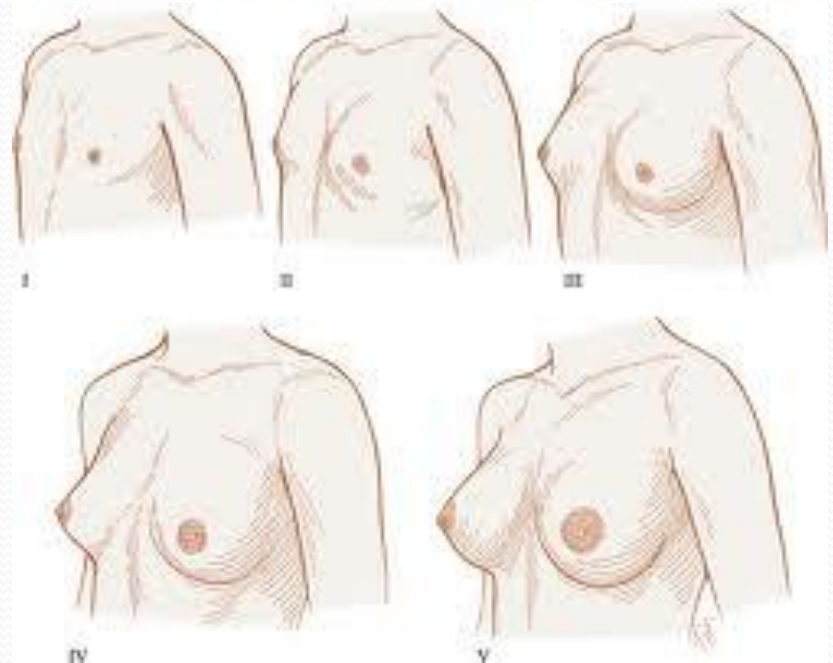
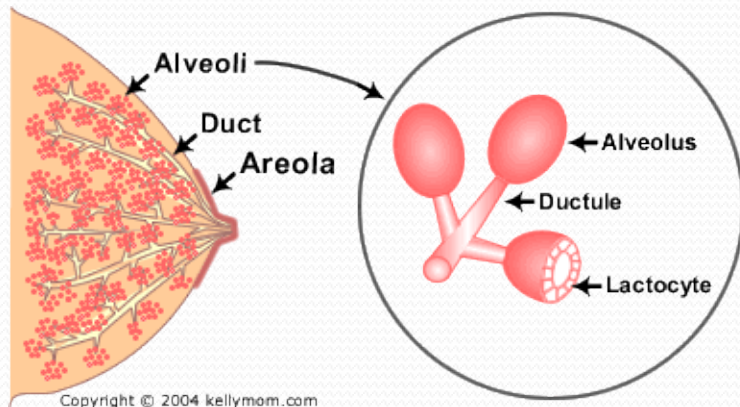


Fig. 1. Mammary gland development. The postnatal development of female mammary tissue occurs in several steps regulated by hormones. **At birth**, the mammary epithelium consists of limited ducts. **At puberty**, high levels of circulating hormones stimulate both the proliferation of the mammary epithelial cells (MECs) and the enlargement of the surrounding fat pad. At the onset of **pregnancy**, epithelial ducts elongate, branch and alveoli develop. During **lactation**, the mammary epithelium reach its maximal development containing numerous alveoli, which produce huge amounts of milk. Upon **weaning**, milk production ceases, the mammary alveoli regress (**involution**) and the mammary epithelium returns to a non-pregnant state.

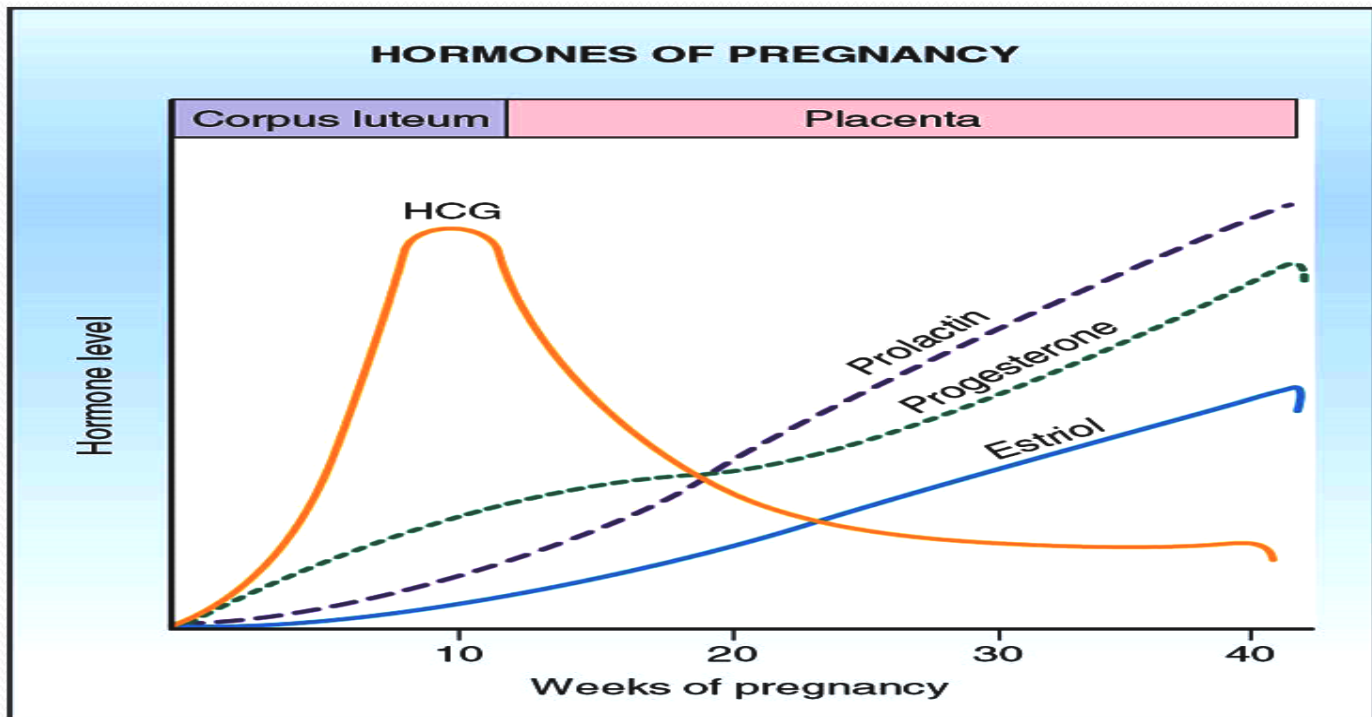
Breast development (mamogenesis)

- During puberty
 - Estrogen stimulate proliferation of ducts and deposition of fat
 - Progesterone stimulate development of lobules



Breast development (mamogenesis)

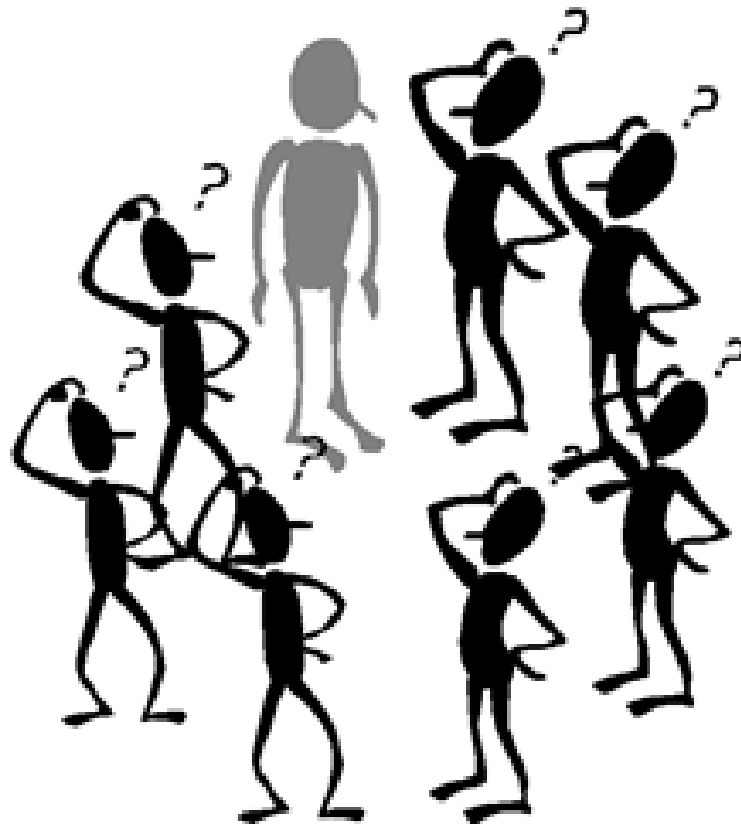
- During pregnancy
 - Complete development of glandular tissue



Breast development (mamogenesis)

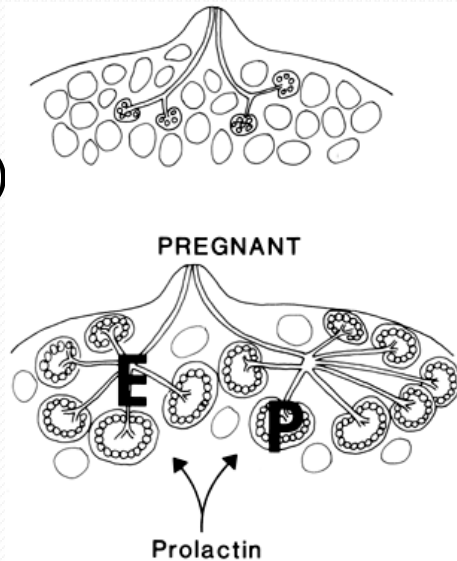
- Endocrine system plays a major role in synchronizing development (mamogenesis) and function (lactogenesis) of mammary gland with **reproduction**
- Three categories of hormones:
 - **Reproductive hormones** (endocrine)
 - Estrogen, progesterone, prolactin, oxytocin and hPL
 - **Metabolic hormones** (endocrine)
 - GH, corticosteroids, thyroxin, PTH and insulin
 - **Mammary hormones** (autocrine)
 - GH, prolactin, parathyroid hormone-related protein (PTHrP) and leptin

Size of the breast & lactation



Breast development (mammogenesis)

- **Reproductive hormones** (direct effect)
 - **Estrogen** (placenta)
 - Growth & branching of ductal system (with GH)
 - Fat deposition in the stroma
 - **Progesterone** (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

Breast development (mamogenesis)

- **Prolactin** (anterior pituitary)
 - Its level increases during pregnancy (10-20 times)
 - Its main function is milk production
 - Sudden drop in E & P after delivery allows milk production
 - It is controlled mainly by hypothalamic hormone
 - **PIH (Dopamine)**
- **Human placental lactogen** (placenta)
 - Facilitate mammogenesis
 - Delay milk production

Lactogenesis

Lactogenesis

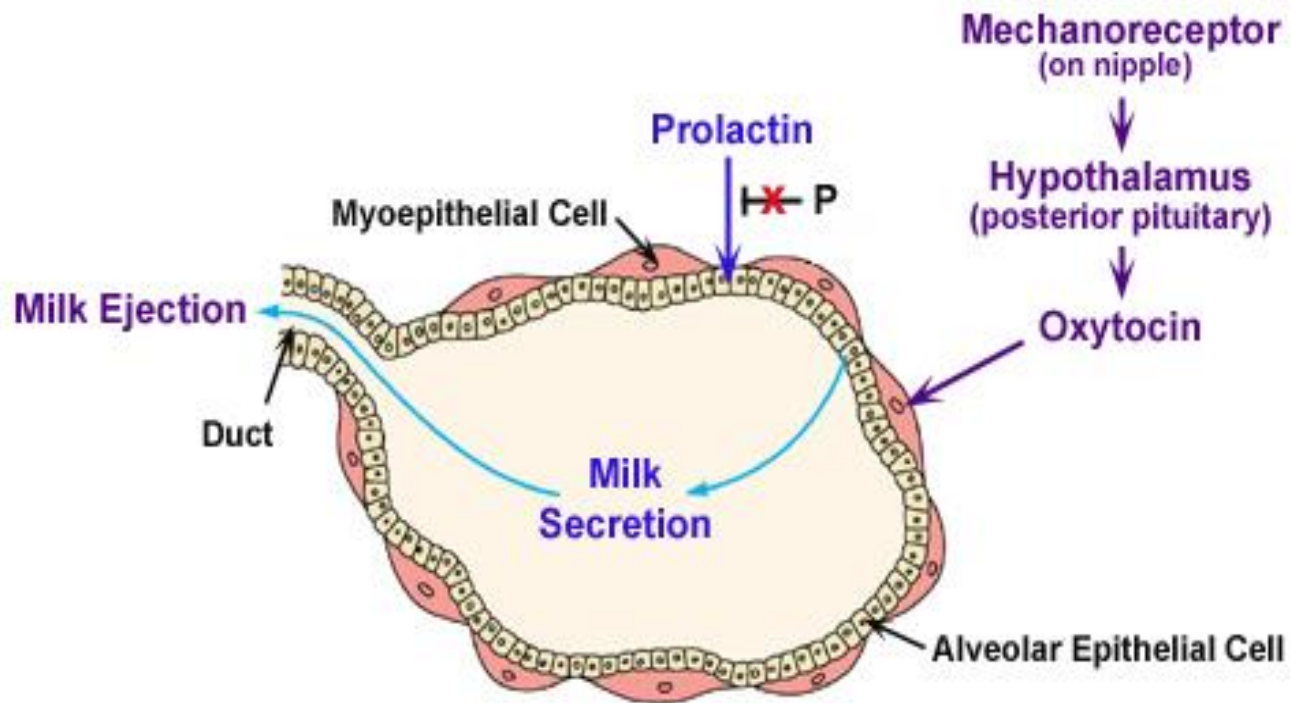
- Lactogenesis: cellular changes by which mammary epithelial cells are converted from a non secretory state to a secretory state: 2 stages
- **Lactogenesis 1**: (Cytologic and enzymatic differentiation of alveolar epithelial cells).
 - Starts in **mid pregnancy** and characterized by expression of many genes involved in synthesis of milk components (increase in the 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

- **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

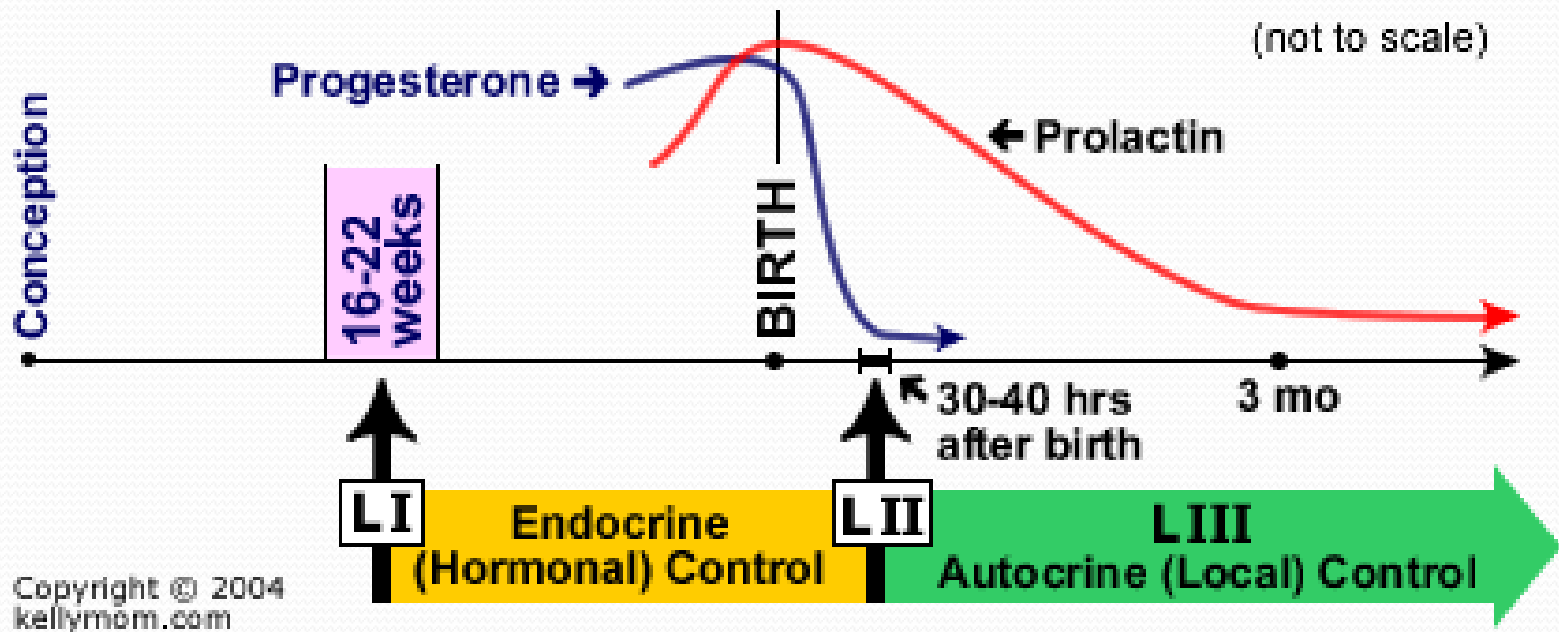
Lactogenesis

- Lactogenesis 2:
 - Suckling stimulates further increase in expression of genes involved in milk secretion with expansion of alveolar epithelium
 - Lactation is maintained by removal of milk
 - 2 hormones involved
 - Prolactin (milk production)
 - Oxytocin (milk let-down)



Alveolus of Mammary Gland

Stages of lactogenesis



Mamogenesis

Lactogenesis

Galctopoesis



Hormonal regulation of lactogenesis

- 1) **Metabolic hormones** (direct effect)
 - **GH**
 - Its secretion is stimulated by progesterone
 - Increases production of IGF-1 by the liver and locally.
 - Mediate cell survival and ductal growth
 - **Corticosteroids**
 - Increases during pregnancy (five fold)
 - Involved in breast development (permissive action on milk protein synthesis)

Hormonal regulation of lactogenesis

- **Thyroxin**

- Essential for milk production
- Thyroxin & TSH level decreases during lactation
- TRH increases leading to stimulation of PRL (nasal administration to treat inadequate lactation)

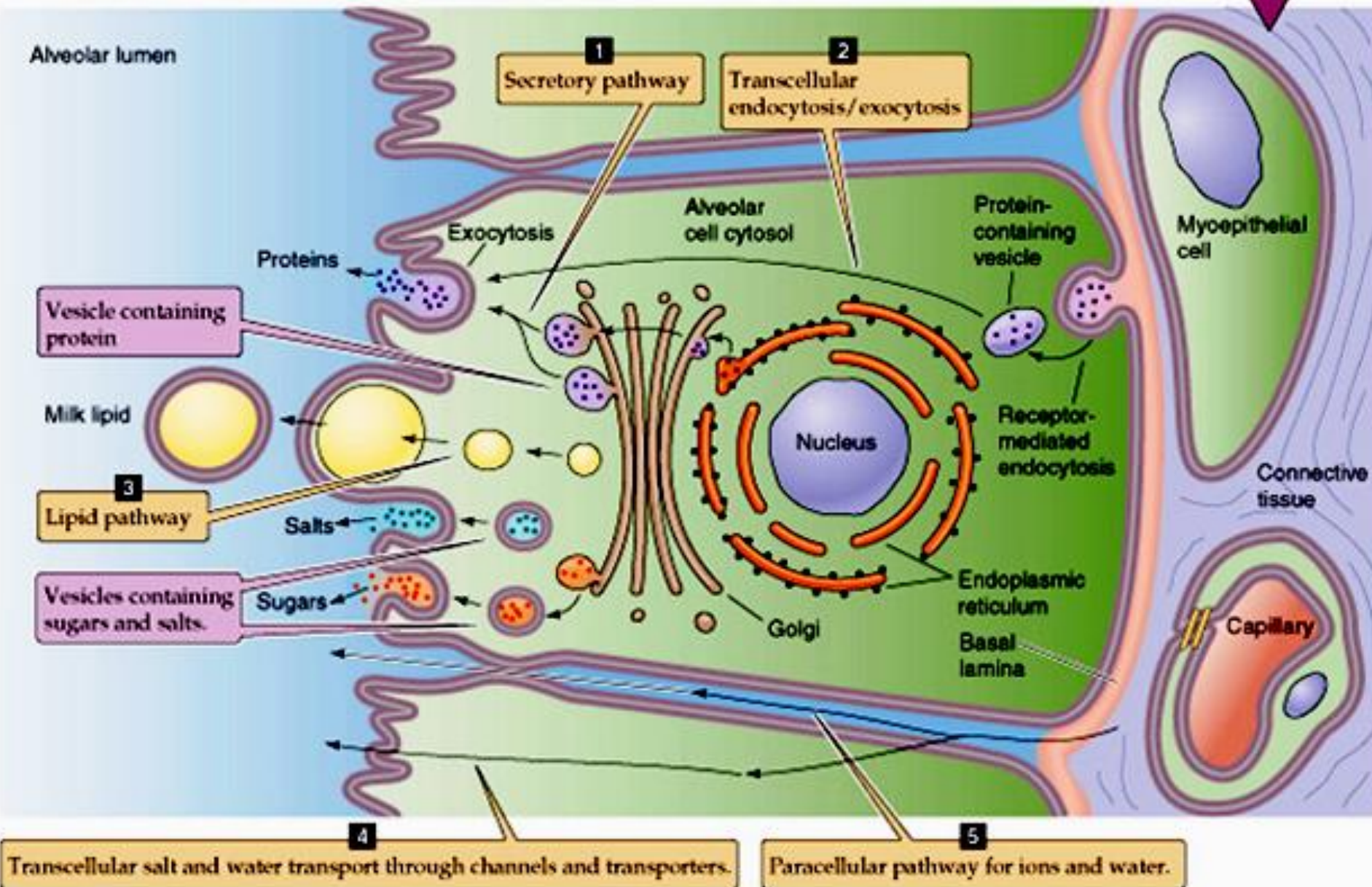
- **Insulin**

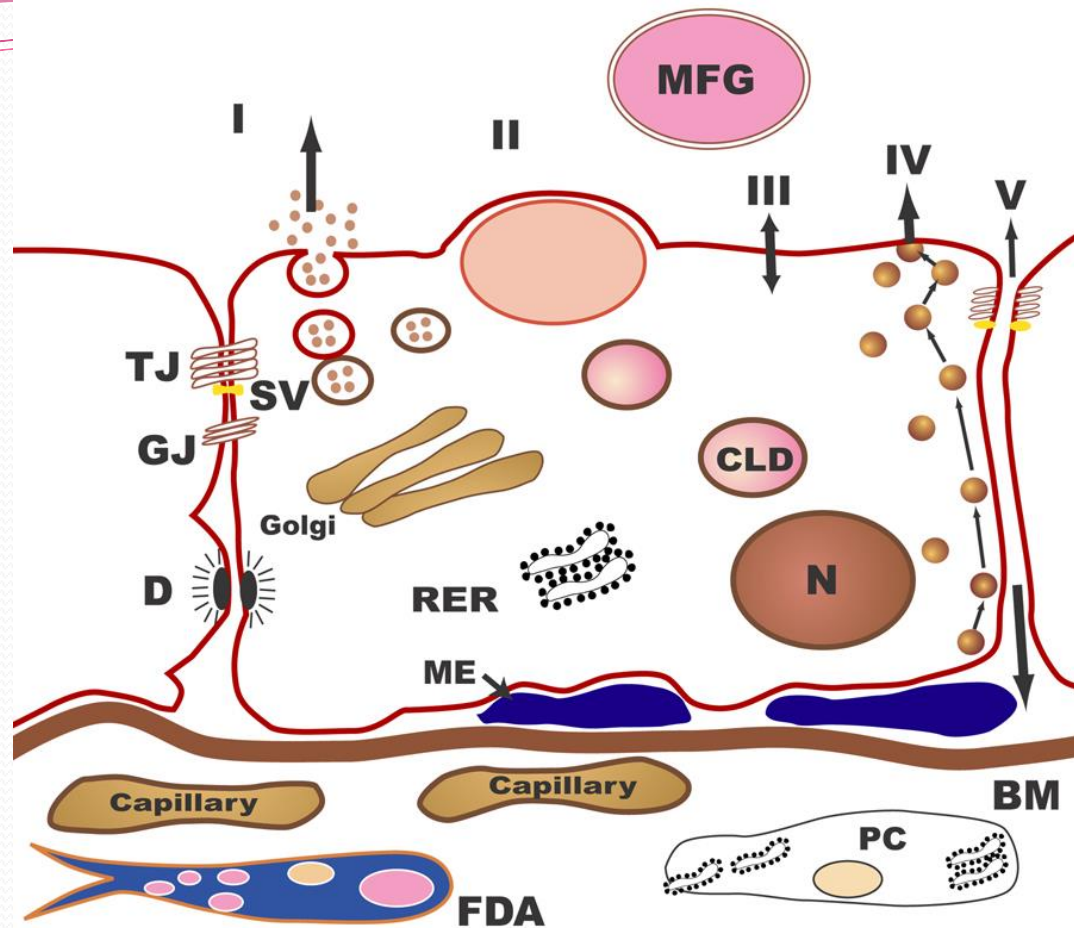
- Low during lactation
- Shunt of nutrients from storage depots to milk synthesis

Hormonal regulation of lactogenesis

- 2) **Mammary hormones**
 - **GH**
 - Progesterone stimulates its secretion
 - **Leptin**
 - Increases during pregnancy (increase adipose tissue)
 - Decreases with lactation
 - **PTHrP**
 - Increases during lactation
 - Mobilizes bone calcium
 - Increase in alkaline phosphatase

D SECRETORY EPITHELIAL CELL





The pathways for milk secretion and synthesis by the mammary epithelial cell. I: Exocytosis of milk protein, lactose, and other components of the aqueous phase in Golgi-derived secretory vesicles. II: Milk fat secretion via the milk fat globule. III: Direct movement of mono valent ions, water, and glucose across the apical membrane of the cell. IV: Transcytosis of components of the interstitial space. V: The paracellular pathway for plasma components and leukocytes. Pathway V is open only during pregnancy, involution, and in inflammatory states such as mastitis. 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.

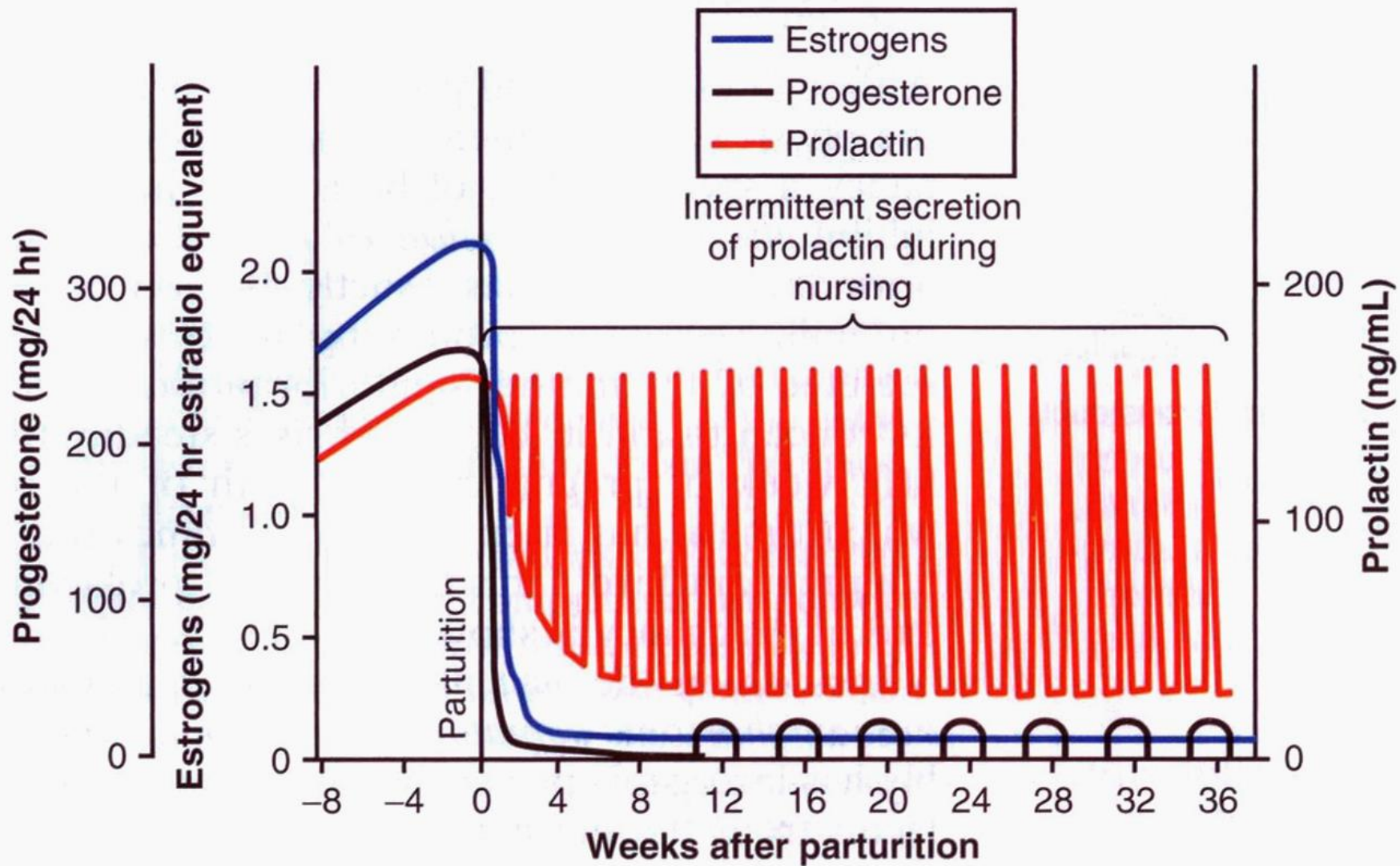


Galactopoeisis

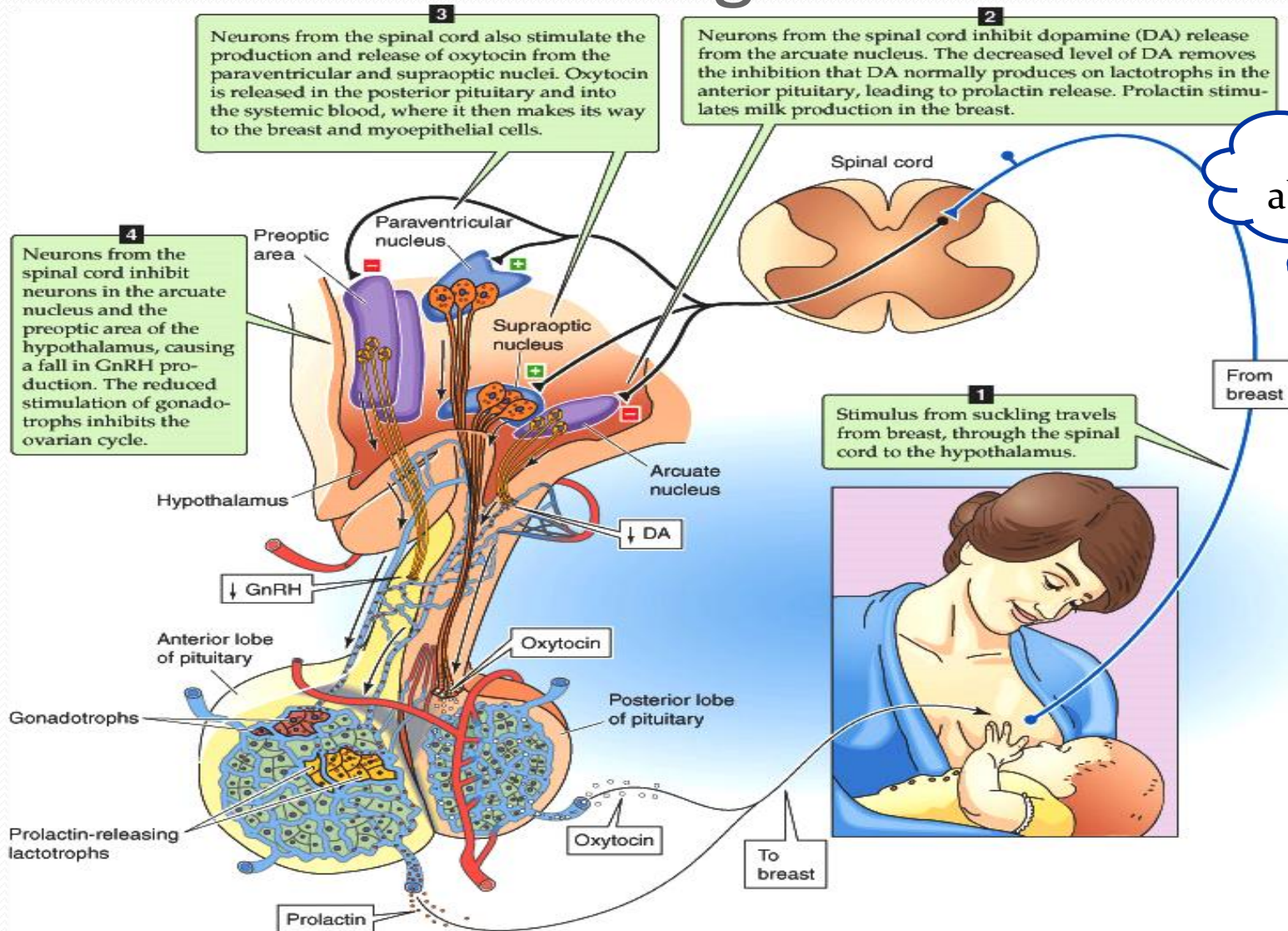
Galactopoeisis

- **Definition:** Galactopoeisis is defined as the maintenance of lactation once lactation has been established.
- **Role of Hormones**
 - **Prolactin:** milking-induced surge is a direct link between the act of nursing (or milk removal) and the galactopoeitic hormones involved in maintaining lactation.
 - **Growth Hormone:** support increase in synthesis of lactose, protein, and fat in the mammary gland
 - **Glucocorticoids:** galactopoeitic in physiological doses

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



Suckling reflex



What about---



Suckling reflex

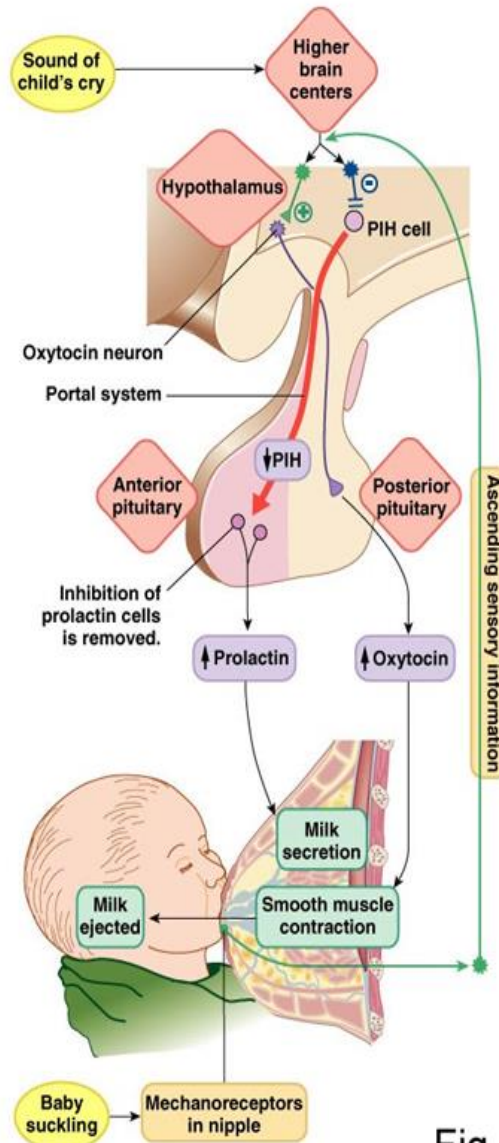


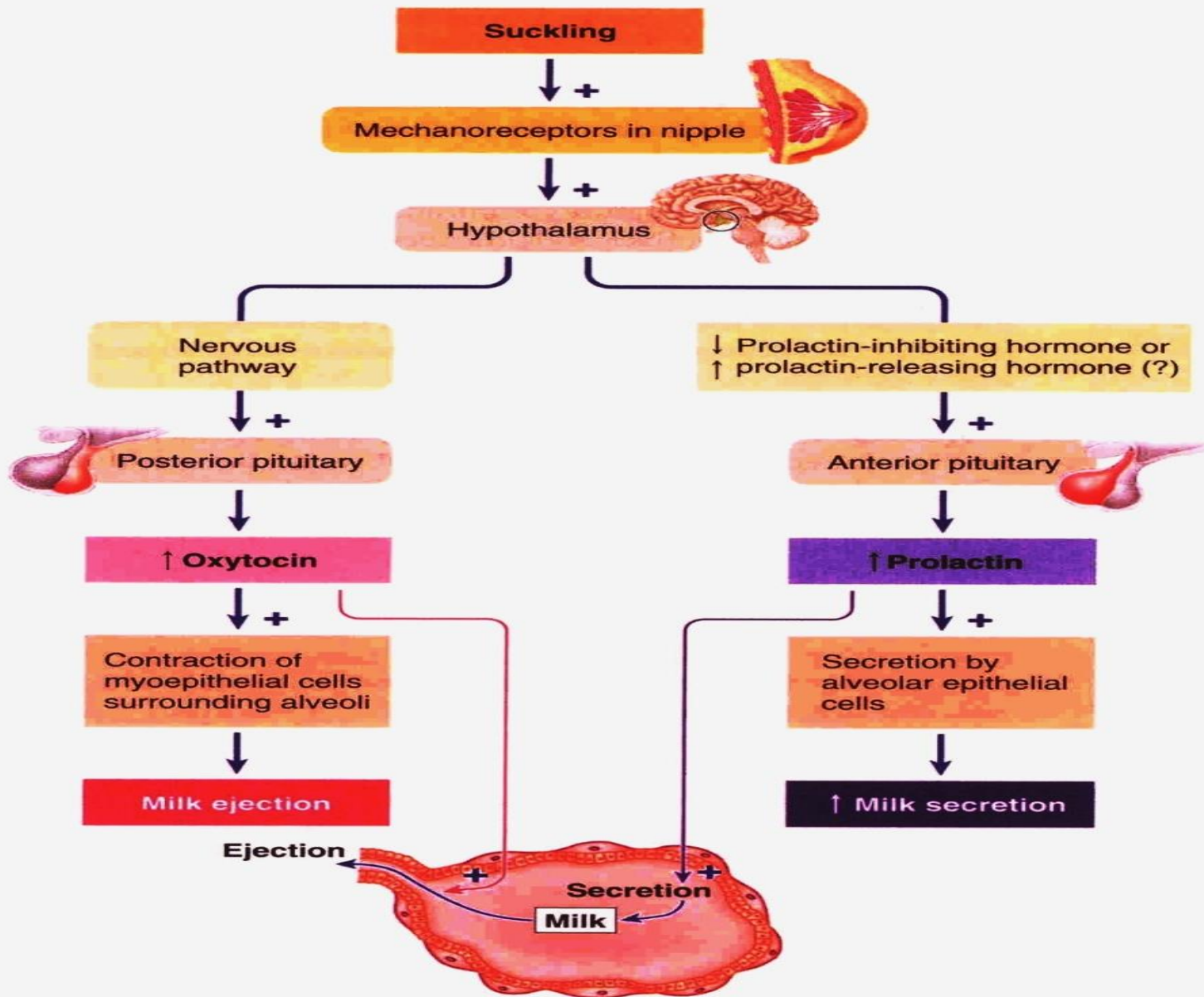
Fig. 26-23

- 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 Na⁺& Cl⁻) due to closure of tight junctions that block paracellular pathway



● **FIGURE 20-35 Suckling reflexes.**

- يقول تعالى(والوالدات يرضعن أولادهن حولين كاملين لمن أراد أن يتم الرضاعة) (البقرة . [233]:
- وفي إشارة علمية دقيقة أخرى للقرآن الكريم نراه يحدد مدة الرضاعة بما يقرب من الحولين ، في الآية رقم (14) في سورة لقمان : (ووصينا الإنسان بوالديه حملته أمه وهنا على وهن وفصاله في عامين) ،
- والآية (15) في سورة الأحقاف : [حملته أمه كرهاً ووضعته كرهاً وحمله وفصاله ثلاثون شهراً]
- ويفهم من هذا أن إرضاع الحولين ليس حتماً ، بل هو التمام ، ويجوز الاقتصار على ما دونه ، كما أشارت الأحكام الإسلامية الخاصة بالرضاعة إلى ذلك ، اعتماداً على قوله تعالى(فإن أراداً فصلاً عن تراضٍ منهما وتشاورٍ فلا جناح عليهما) الآية 233 البقرة .

AAP Recommendations

- Exclusive breast feeding for the first six months of life
- Continued breast feeding for at least one year, 'As long as is desired by mother and child'



Failure of breast feeding



قَالَ إِنَّمَا أَشْكُو بَثِّي وَخُزْنِي إِلَى
اللَّهِ وَأَعْلَمُ مِنَ اللَّهِ مَا لَا تَعْلَمُونَ

يوسف : ٨٦

