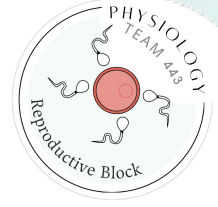










L6-Hormones affecting Breastfeeding

Reproductive physiology



Objectives



-  **Physiological anatomy of the breast**
-  **Physiological changes during breast development (Mammogenesis)**
-  **Physiological changes during lactation (Lactogenesis)**
-  **Recognize Phases of lactogenesis.**
-  **Physiological changes during Galactopoiesis.**
-  **Describe Endocrine and autocrine control of lactation.**
-  **Involution (the termination of milk production).**
-  **Explain the physiological basis of suckling reflex and its role in lactation.**



Click here for the team channel!



**This Lecture was presented by:
PROF.MOHAMMED ALOTAIBI & Dr.Hana Alzamil.**



Editing File



﴿ تِلْكَ الْجَنَّةُ الَّتِي نُورِثُ مِنْ عِبَادِنَا مَنْ كَانَ تَقِيًّا ﴾

إضغط هنا لتسمع الآية بصوت فضيلة الشيخ بدر التركي

Introduction

Structure of the human breast

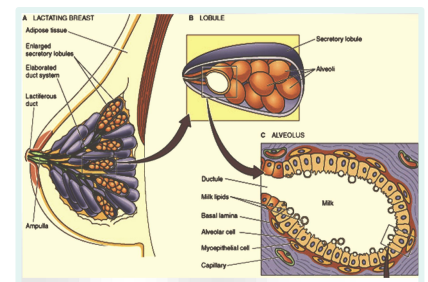
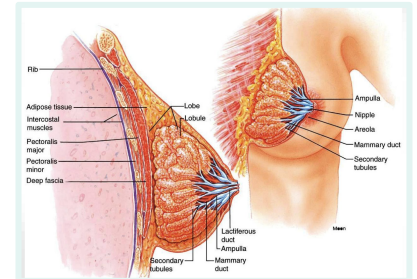
Lobule-Alveolar system

The function of the alveolar epithelial cells is to remove nutrients from the blood and transform these nutrients into the components of milk.

Ductal system

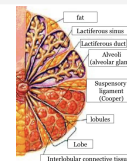
1. Alveolar tubule
2. Secondary tubule
3. Mammary duct
4. Ampulla (lactiferous sinus)
5. Lactiferous duct

The structure of the breast and mammary glands



Each breast consists of 15-20 lobes of secretory tissue:

1. Each lobe has one lactiferous duct
2. Lobes (and ducts) are arranged radially
3. Lobes are composed of lobules
4. Lobules are composed of alveoli (around alveoli → myoepithelial cells for → milk ejection)



Male slides

- » The fundamental secretory unit of the breast is the alveolus.
- » Where does milk come from? ↓ These are old theories

❖ Uterine milk theory:

Vessel connecting the uterus to the breast (diversion of menstrual blood to the breast).

لأن الدورة متجهها فكانوا يعتقدون ان الدم راح للـ breast

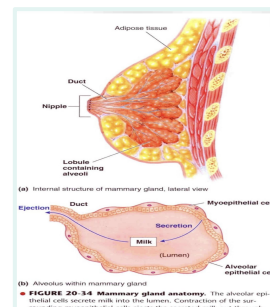
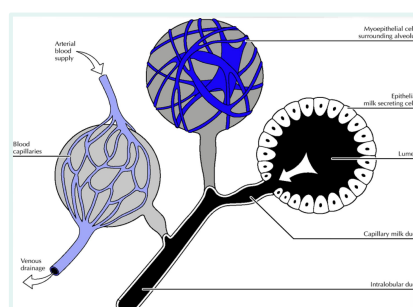
❖ Chyle theory:

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.
This is the new and the acceptable theory.

Female slides



Stages of Mammary gland development

أهم جزء بالمحاضرة: "تعرف كل حاقه من دول معناها ايه؟ وايه الهرمون اللي بيعملها؟"

Stages of Mammary Gland Development

Male slides

1-Mammogenesis (priming):

Q: Normal adult Female, Not pregnant or lactating, is she ready for lactation?
No, Further anatomic development (**mammogenesis/priming**) and Histologic development (**Lactogenesis I**).

Growth and development of mammary gland to a functional state.

2-Lactogenesis

(initiation of milk secretion **Lactogenesis 2**)
Lactogenesis I, Lactogenesis 2 → small amounts (not enough for the Baby), so galactopoiesis is needed.

3-Galactopoiesis

(maintenance of milk secretion in the postpartum period) طوال فترة الرضاعة

4-Involution

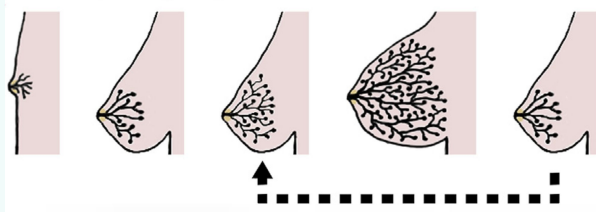
(cessation of milk production)

1-Breast Development

Breast Development (Mammogenesis)

Female slides

birth ► puberty ► gestation ► lactation ► involution



Mammary gland development

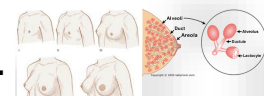
Estrogen → Gross development
Progesterone → Microscopic structures (lobules, ducts).
الاستروجين والبروجيسترون يتعاونان في Priming، حل البرولاكتين يشارك في Priming؟ ايوا ولكن دوره مش مهم، ايه؟
لو كان البرولاكتين اعلى ويساهم بعملية Priming بيسبب Galactorrhea وهذا ما يحصل في Female إلا في الأمراض!

The postnatal development of female mammary tissue occurs in several steps regulated by hormones.

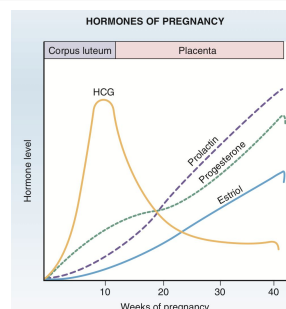
- ➔ At birth, the mammary epithelium consists of *limited* ducts.
- ➔ At puberty, high levels of circulating hormones stimulate both the proliferation of the mammary epithelial cells (MECs) and the enlargement of the surrounding fat pad.

During puberty:

- ➔ Ovarian Hormones stimulate mammary growth.
- ➔ Estrogen stimulate proliferation of **ducts** الكبيرة and deposition of **fat**.
- ➔ Progesterone stimulate development of **lobules**.



- ➔ At the onset of pregnancy, epithelial ducts elongate, branch and alveoli develop.
- ➔ During pregnancy → Complete development of glandular tissue.
- ➔ During lactation, the mammary epithelium reach its maximum development containing numerous alveoli, which produce huge amounts of milk.



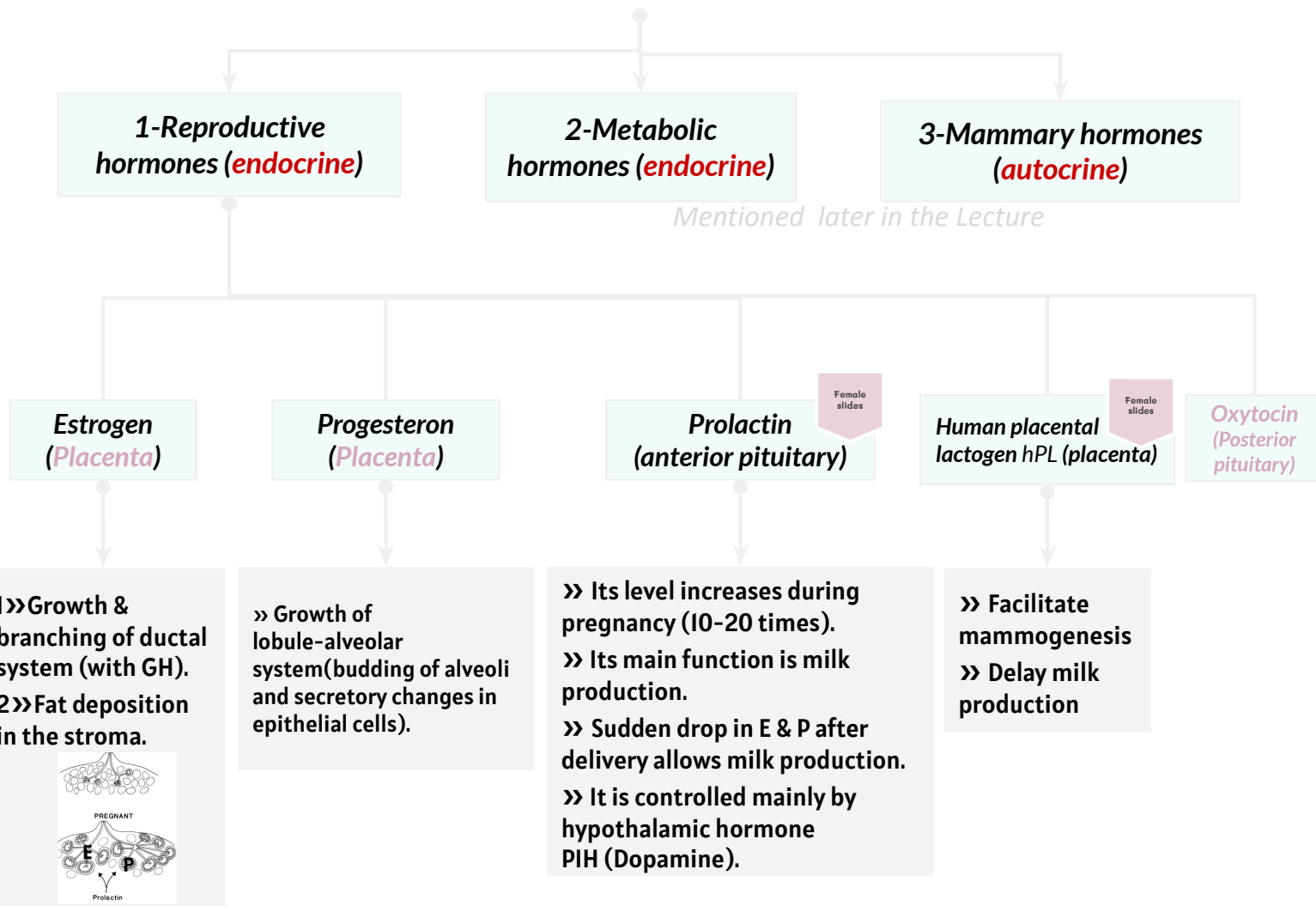
- ➔ Upon weaning الفطام, milk production ceases, the mammary alveoli regress (**involution**) and the mammary epithelium returns to a non-pregnant state.

Hormones affecting female breast

Endocrine system plays a major role in synchronizing development (mammogenesis) and function (lactogenesis) of mammary gland with reproduction.

Mammogenic Hormones (promoting the proliferation of ductal and alveolar cells) [ductal & alveolar morphogenesis] (Prolactin, Estrogen, Progesterone, Growth Hormone, Cortisol).

Three categories of hormones:



Although estrogen and progesterone are essential for physical development of the breasts, they **inhibit** actual secretion of milk during pregnancy by interacting with prolactin receptors.

Progesterone (mainly) & Estrogen
Have STRONG inhibitory effect on prolactin **secretory** function
يقولوا لا: العمل priming مثل ما انت عايز، لكن increase secretion !

2-Lactogenesis

Steps of Lactogenesis

- ❖ **Lactogenesis:** Cellular changes by which **mammary** alveolar epithelial cells are converted from a non secretory state to a secretory state (**initiation of milk secretion**).
- ❖ **Lactogenic hormones** (promoting initiation /onset of milk production by alveolar cells)
- ❖ **Involves 2 Phases/ 2 Stages:**
 - **Lactogenesis I**
 - **Lactogenesis 2** Lactogenic Hormone: Prolactin ثم prolactin ثم Prolactin

#Check pic1+2

Lactogenesis I

Cytologic (histological) and enzymatic differentiation of alveolar epithelial cells.

◆ Starts in **mid pregnancy** (bcz increased Prolactin, Pregnancy has Inhibitory effect on Dopamine!) and characterized by expression of many (**but not all**) genes involved in synthesis of milk components. (This increases the uptake transport systems for amino acids, glucose, and calcium required for milk synthesis). but very low in (Iron, Vit C, vit D, vit K)

◆ **Hormones involved:**

1. **Prolactin (PRL) and/or Placental lactogen (hPL) / (hCS) functions like GH+PRL**
2. **Progesterone** (suppresses milk secretion)
"قافل على نفس البرولاكتين لذلك ما فيش secretion of milk"
3. **Growth hormone**
4. **Glucocorticoids (Cortisol)**

further differentiation is inhibited by high levels of progesterone from the placenta.

-(Progesterone+PRL→ Alveologenesis)

-Production and secretion of milk components in this stage are restricted to a limited number of alveolar epithelial cells with incompletely developed secretory mechanisms.

Lactogenesis 2

Copious **secretion** of all milk components, **starts 2-3 days postpartum**

◆ Around parturition (**postpartum**), **withdrawal of progesterone** + high level of **prolactin** leads to:

1- Further increase in expression of milk protein genes.

2- **Glands absorb increased quantities of metabolic substrates from the blood.**

3- Movement of cytoplasmic lipid droplets and casein into alveolar lumen.

4- Transfer of immunoglobulins خصوصاً IgA.

5- 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 due to switch from endocrine to autocrine control of milk production.**

-Switch from endocrine to autocrine control of milk production

◆ **Two hormones involved: Prolactin (milk production) Oxytocin (milk let-down)**

Hormones involved

Male slides

Lactogenic Hormone: Prolactin ثم prolactin ثم Prolactin

All are required to facilitate the mobilization of nutrients and minerals.

(Lactogenic Hormones) Promoting initiation /onset of milk production by alveolar cells.

Prolactin (milk production)

Growth hormone

Glucocorticoid (Cortisol)

Oxytocin (milk let-down)

Insulin

Thyroid hormone (Thyroxine)

Hormonal regulation of lactogenesis

Female slides

1-Reproductive hormones (endocrine)

2-Metabolic hormones (**endocrine**)
Direct effect

3-Mammary hormones (**autocrine**)

Growth Hormone

1>>Its secretion is stimulated by progesterone 2>> Increases production of IGF-I by the liver and locally. 3>> Mediate cell survival and ductal growth

Corticosteroids

>> Increases during pregnancy (five fold)
>> Involved in breast development (permissive action on milk protein synthesis)

Thyroxine

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

Parathyroid Hormone

Insulin

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

Prolactin

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

Prolactin

Male slides

- ◆ Secreted from the anterior pituitary gland (**Lactotrophs**).
- ◆ Its level **ris**es steadily from the **5th week** of pregnancy **until birth** (10-20 times the nonpregnant level), (enhanced by Estrogen).
- ◆ It has mammogenic, lactogenic and galactopoietic effects.
- ◆ It stimulates expression of genes that encode several milk components (casein/lactalbumin, lactose and lipids).
- ◆ Sudden **drop** in **E&P** after delivery **allows** milk production.
- ◆ It is **inhibited** **tonically** in **males & Females** mainly by hypothalamic hormone (**Dopamine**). Also Called **Prolactin inhibiting Hormone**.
- ◆ Thyrotropin-releasing hormone (TRH) can **increase** PRL لكن! تأثير الدوبامين أقوى



Milk synthesis

Female slides

#Check pic4

Milk fat secretion via the milk fat globule.

Transcytosis of components of the interstitial space.

Exocytosis of milk protein, lactose, and other components of the aqueous phase in Golgi-derived secretory vesicles.

Direct movement of monovalent ions, water, and glucose across the apical membrane of the cells

The paracellular pathway for plasma components and leukocytes. Pathway V is open only during pregnancy, involution, and in inflammatory states such as mastitis.

Galactopoiesis

Definition: Galactopoiesis is defined as The maintenance of lactation once lactation has been established. Starts 9-15 days postpartum.

Galactopoietic Hormones: maintaining milk production after it has been established:

1-Prolactin (primary):

Lactogenic Hormone: Prolactin ثم prolactin ثم Prolactin



لو Female عندها Cortisol قليل، Growth Hormone قليل شويه، هلي معناه انه يحصل عندها Failure of Lactation ؟
لا ابدأ
لو جاء سؤال الـ Galactopoiesis وظيفة مين؟ Prolactin

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

2-Growth hormones (permissive) Oxytocin : Support increase in synthesis of lactose, protein, and fat in the mammary gland.

3-Glucocorticoids: galactopoietic in physiological doses.

4-Thyroid Hormones: galactopoietic.

5-Ovarian Hormones:

-**Estrogen** (very low dose is galactopoietic)

-**Progesterone** (alone has no effect on galactopoiesis because there is no progesterone receptors in the mammary glands during lactation)

5-Oxytocin*

-Cortisol+insulin+Thyroid And growth hormones (Permissive).

Autocrine control of Lactation

Male
slides

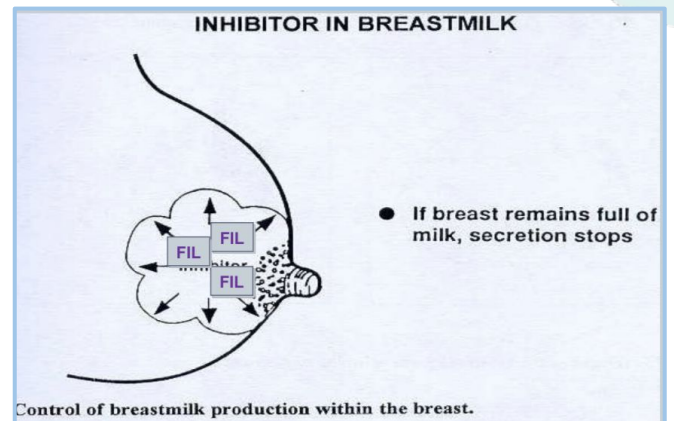
★ Influence of Local Factors Acting on the Breasts:

It is not just the level of maternal hormones, but the efficiency of milk removal that governs the volume product in each breast.

A protein factor called **feedback inhibitor of lactation (FIL)** is secreted with other milk components into the alveolar lumen.

FIL, insensitive to prolactin → ↓ **milk production**.

لو ما حصلش Flow, حيتوقف الـ Lactation



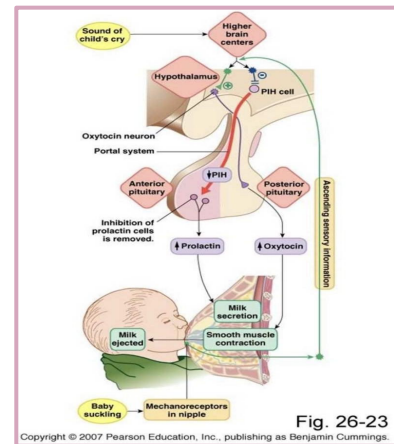
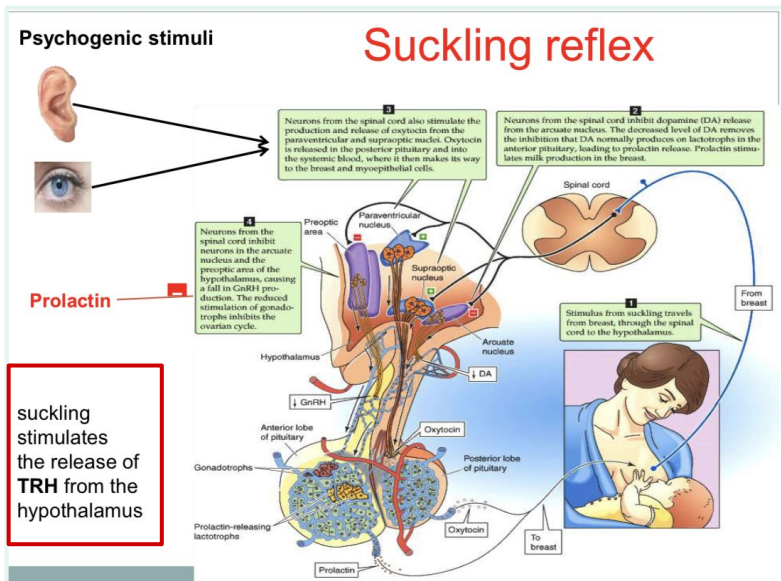
Milk production

- ❖ Milk production is a "use it or lose it" process.
- ❖ The more often and effectively the baby nurses, more milk will be produced.
- ❖ Lactation is maintained by continuous removal of milk.
- ❖ Milk production <100 ml/day in day 1 postpartum.
- ❖ Milk production by day 3 reaches **500 ml/day**.
- ❖ Milk composition changes dramatically (↓Na+2 & Cl-) due to closure of tight junctions that block paracellular pathway.
- ❖ **Involution**: when the breasts stop producing milk completely after **weaning**.

APP recommendation

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

Suckling / Galactokinetic Reflex



Why oxytocin synthesized in Hypothalamus?
(We know that ADH synthesized there bcz Osmoreceptors are there!) What about Oxytocin?
bcz Emotional centers are there!
What is the strongest emotions في التاريخ؟
المعروفة في التاريخ؟
الألمومة

-Oxytocin and psychogenic stimuli initiate milk ejection ("let-down"):

- Galactokinetic Hormones: (promoting contraction of myoepithelial cells, and thus milk ejection).
- Oxytocin** (OT)

-Milk Ejection Reflex:

Oxytocin contracts the myoepithelial cells, forcing milk from the alveoli into the ducts and sinuses where it is removed by the infant (galactokinetic effect).

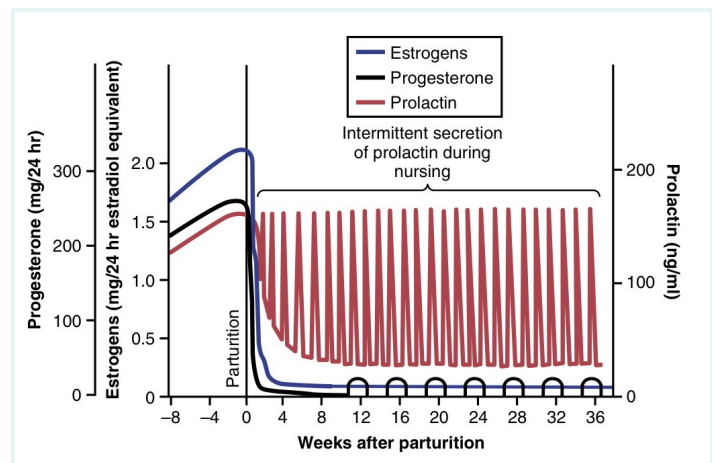
(There is also some psychogenic stimuli for oxytocin release like when seeing something that reminds her of her child or when she hears something that makes her remember this causes some lactation to occur).

Male slides

Suckling is the most powerful physiological stimulus for PRL and oxytocin release.

Nipple and areola very sensitive (extensive Nerve supply) so the suckling reflex elect impulses → لذلك يظهر بالقراف كيف أن البرولاكتين متذبذب مع كل مرة

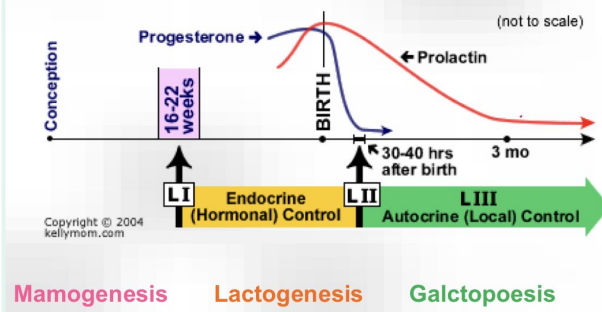
Estrogen and progesterone levels rises in the weeks before labour to give its mammogenetic effect on the breasts and when labour happens they drop, and prolactin is increased in pulsatile manner with the help of suckling to prevent down regulation to occur, thus maintaining the prolactin surges.



Pulsatile Release of PRL: To prevent Down Regulation

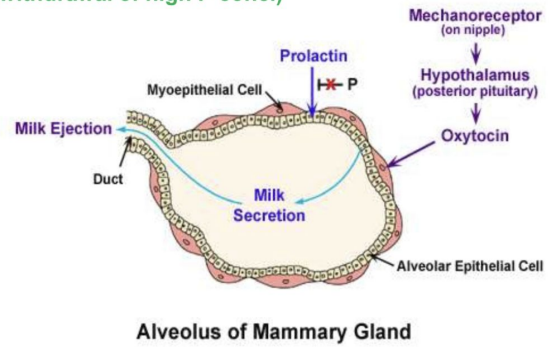
Pictures/ Graphs

Stages of lactogenesis



1

After delivery of placenta (withdrawal of high P conc.)

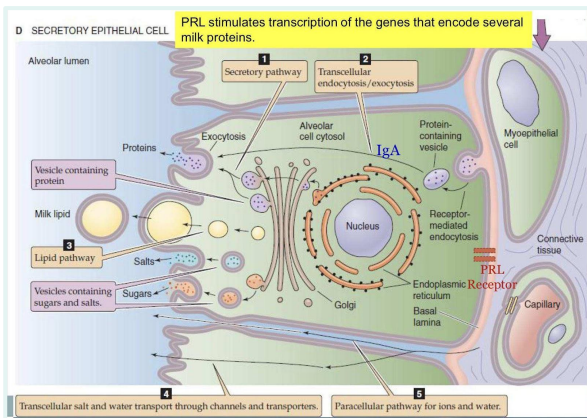


2

Notes:

Prolactin acts on the alveolar cells to produce milk (main action), Oxytocin is released by stimulation of mechanoreceptors on the nipple, this stimulation sends impulses from the hypothalamus to the posterior pituitary to release oxytocin. Oxytocin acts on the myoepithelial cells to eject milk. Progesterone inhibits milk production.

The alveolar cell secretes the components of milk through five pathways



3

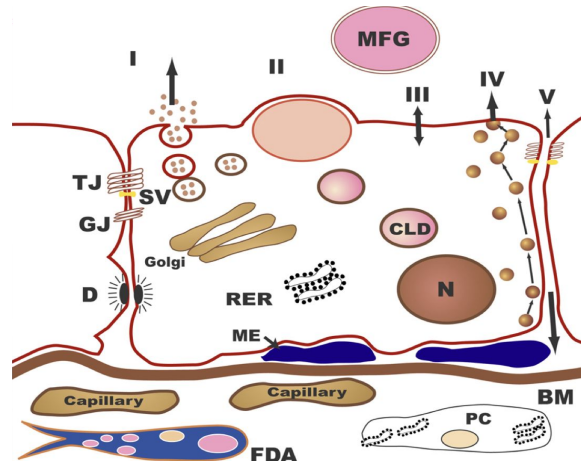
Mechanisms of secretion:

The secretory pathway: Proteins are synthesized in the endoplasmic reticulum and stored in Golgi apparatus and released from there when they're needed for milk production, proteins are released in vesicles which fuse with the cell membrane and exocytosed to the lumen to be added to the milk.

The Transcellular mechanism: cell will take the protein from the blood by endocytosis, form a vesicle, this vesicle will travel inside the cell until it reaches the apical membrane of the cell and it will be released into the milk by exocytosis.

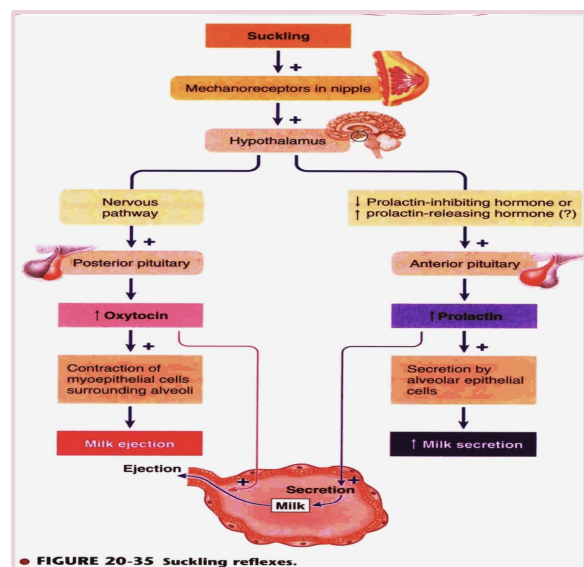
Lipid pathway: lipids are synthesized in the cell and will form a globule that is transported to the lumen by exocytosis.

Glucose is also released by exocytosis. Ions and water have two mechanisms, paracellular and transcellular, salt and water are released initially paracellularly but then the mechanism changes due to an increase in the number of tight junctions. The tight junctions don't allow the passage of salt.



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.

4



Why is milk produced only after delivery, not before?

Levels of luteinizing hormone and follicle-stimulating hormone are too low during pregnancy to support milk production

High levels of progesterone and estrogen during pregnancy suppress milk production

The alveolar cells of the breast do not reach maturity until after delivery

High levels of oxytocin are required for milk production to begin, and oxytocin is not secreted until baby stimulates the nipple

A 30-year-old woman is breast-feeding her infant. During suckling, which of the following hormonal responses is expected?

Increased secretion of antidiuretic hormone (ADH) from the supraoptic nuclei

Increased secretion of ADH from the paraventricular nuclei

Increased secretion of oxytocin from the paraventricular nuclei

Increased plasma levels of both oxytocin and ADH

Why is it important to feed newborn infants every few hours?

The hepatic capacity to store and synthesize glycogen and glucose is not adequate to maintain the plasma glucose concentration in a normal range for more than a few hours after feeding

If adequate fluid is not ingested frequently, the plasma protein concentration will rise to greater than normal levels within a few hours

The function of the gastrointestinal system is poorly developed and can be improved by keeping food in the stomach at all times

The hepatic capacity to form plasma proteins is minimal and requires the constant availability of amino acids from food to avoid hypoproteinemic edema

Want Explanation  ? [Your Finger HERE!](#)

Leaders

Rafan Alhazzani

Fahad Almughaiseeb



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