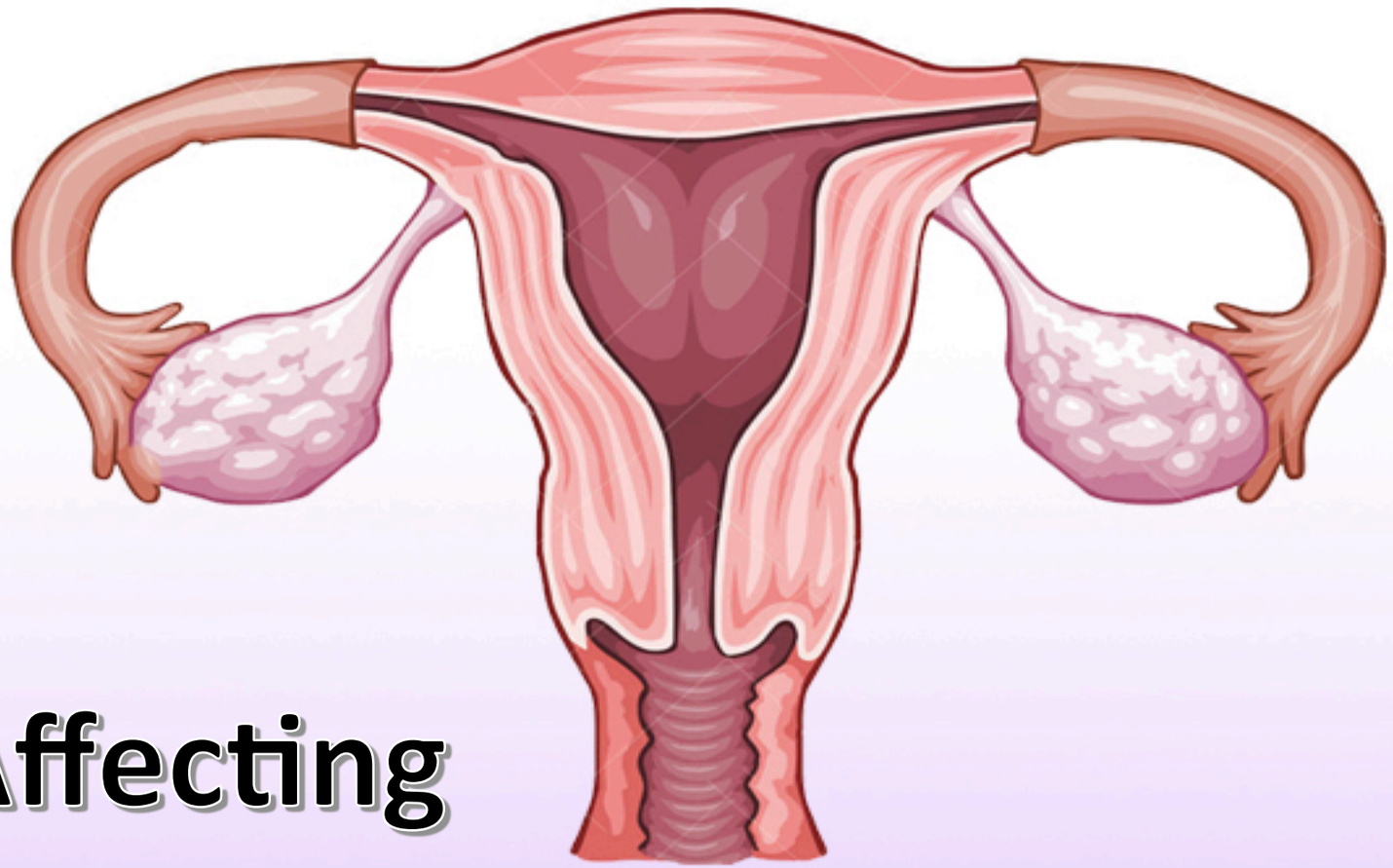
Physiology team



L8-Hormones Affecting Female Breasts

Sources:

- ✓ Male Slides
- ✓ Guyton And Hall (P1014)

Objectives

By the end of this lecture, you should be able to:

- Describe the hormones involved in the different phases of lactation:
  - **Mammogenesis**
  - **Lactogenesis**
  - **Galactopoeisis**

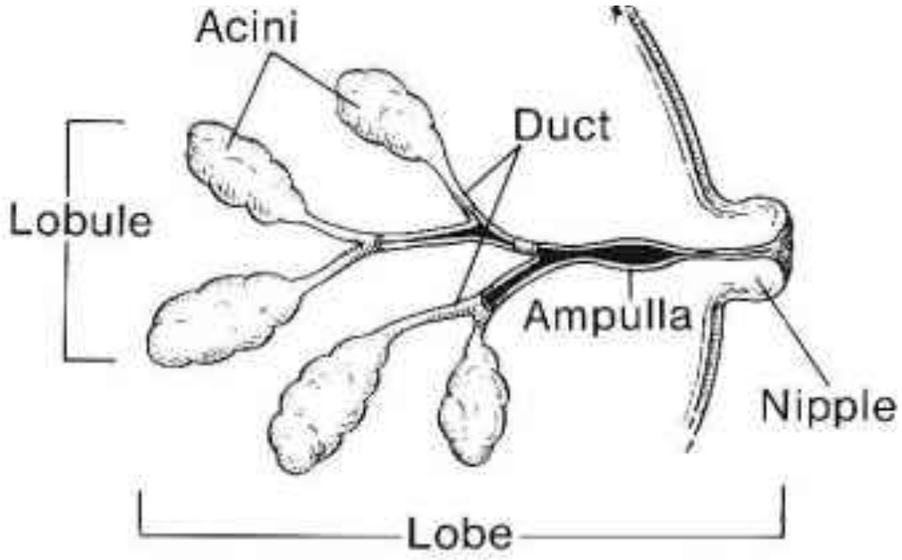
- Explain the physiological basis of suckling reflex and its role in lactation.

We advise you to study the Anatomy of the breast first

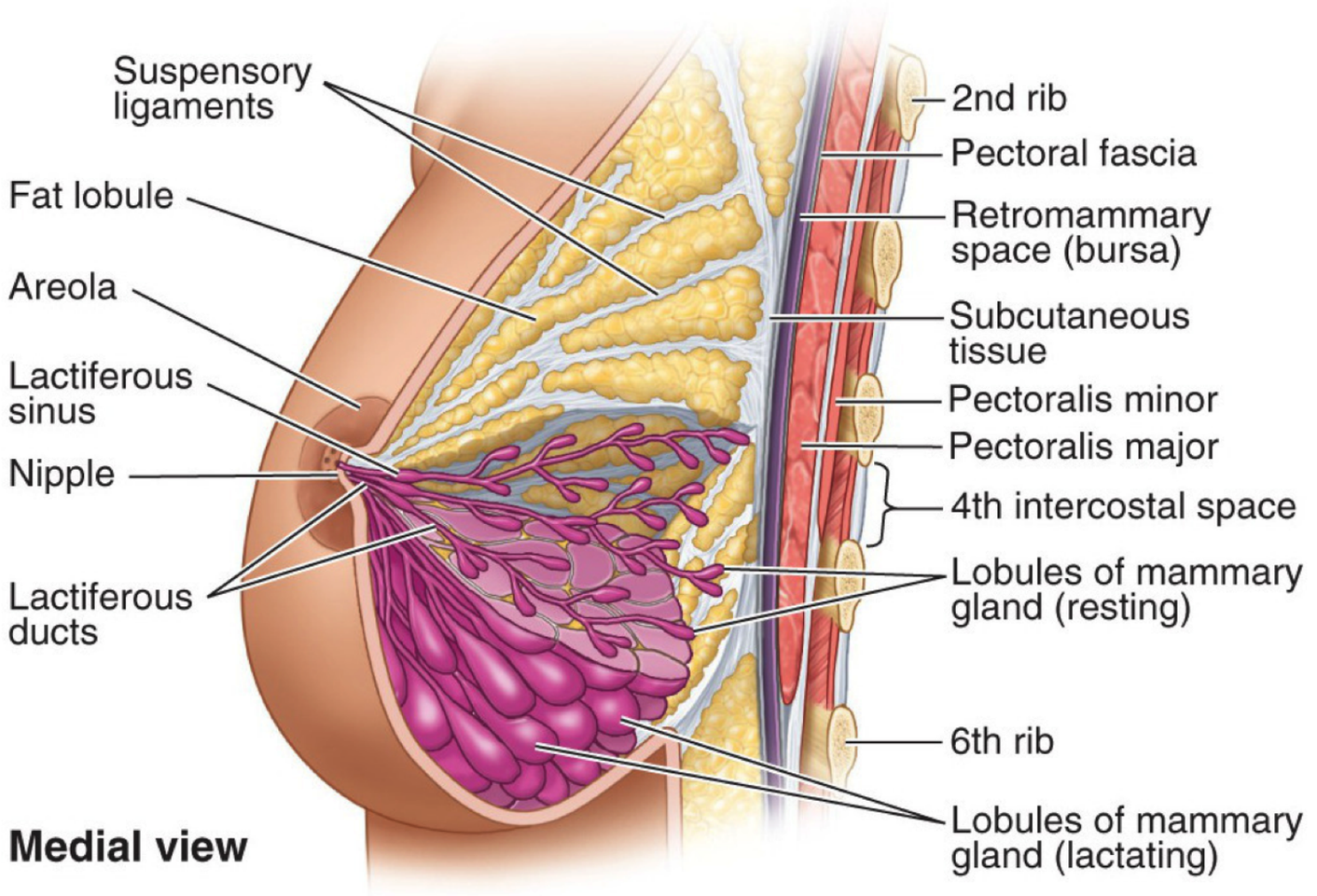
Structure Of The Mammary Gland

- **The Breasts begin to develop at puberty. This development is stimulated by the estrogens of the monthly female sexual cycle; estrogens stimulate growth of the breasts mammary gland and the deposition of fat to give the breasts mass. At the high-estrogen state of pregnancy far greater growth occur and only then the glandular tissue become completely developed for the production of milk.**
- **Each breast consists of 23 lobes of secretory tissue and every Lobe is composed of lobules and**

  Lobules are composed of alveoli. Each lobe has one lactiferous duct (End to it).
- **Lobes (and ducts) are arranged radially.**

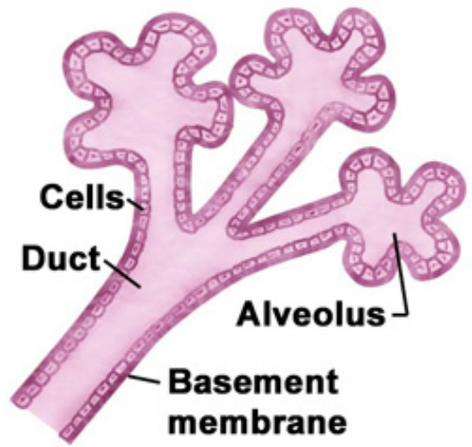


Duct structure (11)



Ductal System (Dr. AlOtaibi said its not important)

Alveolar tubule → Secondary tubule → Mammary duct → Ampulla → (lactiferous sinus) → Lactiferous duct



Physiology Of Lactation

- **Three main phases of lactation:**

1- Mammogenesis : Mammary growth).
2- Lactogenesis : initiation of milk secretion which has two stages.
3- Galactopoiesis or as referred to in some resources as Stage 3 of the Lactogenesis and in this phase maintenance of milk secretion happen.

Mammogenesis – Breast Development

Dr. Otaibi Said the functions of Hormones specially Estrogen are so important.

During Puberty :

- **Estrogen stimulates proliferation of Duct and Deposition of fats.**
- Progesterone stimulates development of lobules.

During pregnancy complete development of mammary glands occur:

- **Estrogens** Stimulate Growth of the Ductal System of the Breasts

All through pregnancy, the large quantities of estrogens secreted by the placenta **cause the ductal system of the breasts to grow and branch (with the help of GH)**. Simultaneously, the stroma of the breasts increases in quantity, **and large quantities of fat are laid down in the stroma.**

- **Breast size depends mainly upon fat deposition.**

- **Progesterone** Is Required for Full Development of the Lobule-Alveolar System

Final development of the breasts into milk-secreting organs also requires progesterone. Progesterone acts synergistically with estrogens, as well as with other hormones **causes additional growth of the breasts lobules, with budding of the alveoli and development of secretory characteristics in the cells of alveoli. So the progesterone secreted from the placenta causes 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. (that's why there's no milk secretion during pregnancy = due to the high levels of progesterone mainly and estrogen from the placenta)**

Mammogenesis – Breast Development

Prolactin :

This hormone is secreted by the mother's anterior pituitary gland and it's concentration in her blood rises steadily from the fifth week of pregnancy until birth of the baby (up to 10-20 times the normal non-pregnant level).
It stimulates mammary gland ductal growth and proliferation of alveolar epithelial cells which induce milk protein synthesis and **promotes milk secretion.**
As Estrogen and progesterone have an inhibitory effect on milk secretion Sudden drop their levels after delivery allows milk production.
Prolactin It is controlled mainly by **hypothalamic** hormone ***PIH (Dopamine).*** " the hypothalamus mainly stimulates production of all the other hormones but it mainly inhibits Prolactin production"

Human placental lactogen (human chorionic somatomammotropin- hCS)

The placenta secrets large quantities of hCS which has lactogenic properties.

- ✓ Facilitates Mammogenesis
- ✓ supports the prolactin during pregnancy (lactogenic properties)
- ✓ Delays milk production

Hormones involved in Mammary Growth:

1. Estrogens
2. Progesterone
3. Growth hormone
4. Human placental lactogens (hPL)
5. Prolactin (PL)
6. Glucocorticoids
7. Insulin

Lactogenesis:

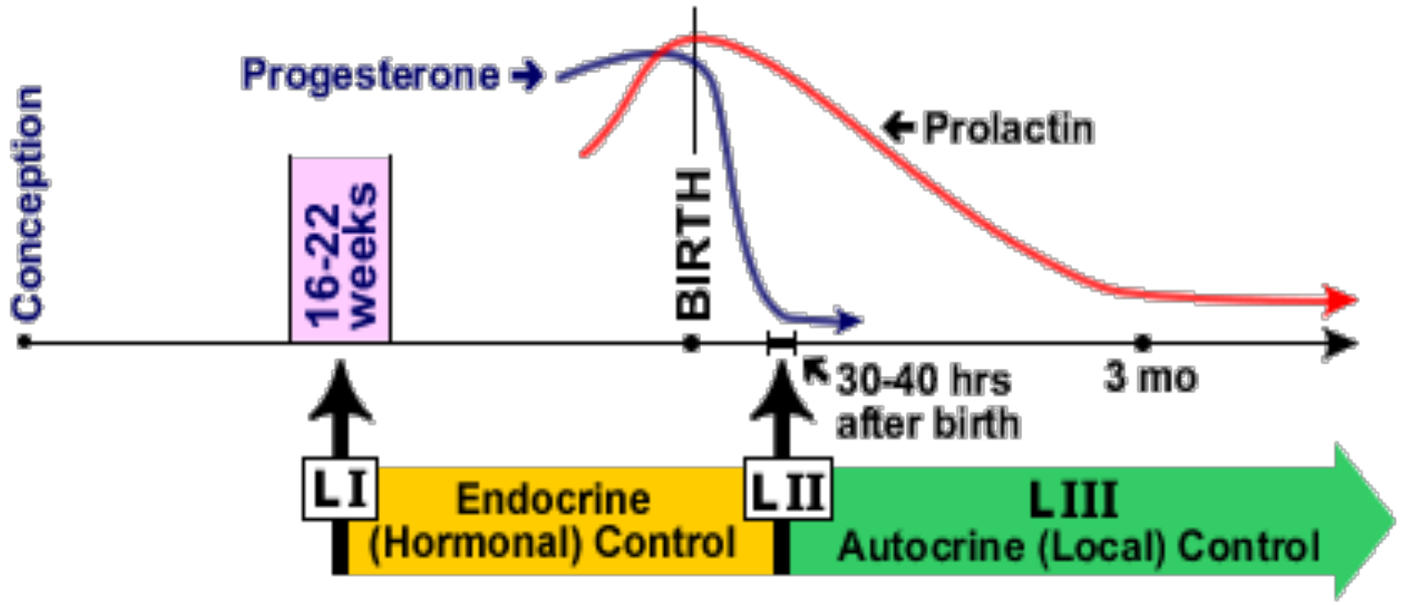
-Cellular changes by which mammary epithelial cell switches from a growing non-secretory tissue to a secreting non-growing tissue (initiation of milk secretion)

-Change is endocrine mediated

Involves 2 stages:

- Lactogenesis (stage) 1
- Lactogenesis (stage)2

- There are about (4-5 days) between these stages.



Mammogenesis **Lactogenesis** **Galactopoesis**

Lactogenesis : (endocrine mediated)

-	Lactogenesis (stage) 1: (Cytological and enzymatic differentiation of alveolar epithelial cells).	Lactogenesis (stage) 2: (Copious secretion of all milk components)
Duration	Starts in mid-pregnancy (5th month) and continue till labor (end after parturition)	Copious secretion starts 2-3 days postpartum and end at the (8^{th} – 9^{th}) day . After that the milk start to be secreted.
Characteristics	expression of many genes involved in the synthesis of milk components (increases in uptake transport systems for amino acids, glucose, and calcium required for milk synthesis pic on the next slid)	-Secretion of colostrum (the first milk that is secreted) followed by milk -Further increase in expression of milk protein genes - Glands absorb large quantities of metabolic substrates from the blood - Movement of cytoplasmic lipid droplets and casein into alveolar lumen -Transfer of immunoglobulins (mostly IgA) -Suckling stimulates further increase in expression of genes involved in milk secretion with expansion of alveolar epithelium -Lactation is maintained by removal of milk (as many as the baby suckle the milk is removed and the more milk will be produced again and prolonge the lactation period)
Endocrine regulation	**1- Progesterone:** promotes mammary growth, blocks epithelial secretion **2- Prolactin**: Maturation of Golgi , Secretory vesicles, epithelial secretion **3- Growth hormone** **4- Glucocorticoids** (Cortisol): development of rough endoplasmic reticulum (RER is mainly supported by Glucocorticoids) -Glucocorticoids increase from the 5^{th} month	1- high level of prolactin 2- withdrawal of progesterone 1- Prolactin level starts to increase from the 5^{th} week of pregnancy and continue to elevate , while the progesterone is present during pregnancy until the delivery of the baby and placenta ends, it will drop . 2- after the delivery of placenta , the breast takes about 2-3 days to start milk secretion “complete clearance of progesterone and estrogen from the blood” - Even though there’s no milk in day 1 postpartum the mother has to breastfeed her baby to keep the prolactin levels high & initiate the reflexes.

Secretory epithelial cells pathways :

1/ secretory pathway :

Vesicles Containing sugars, salts and proteins (produced by RER).

2/ Transcellular :

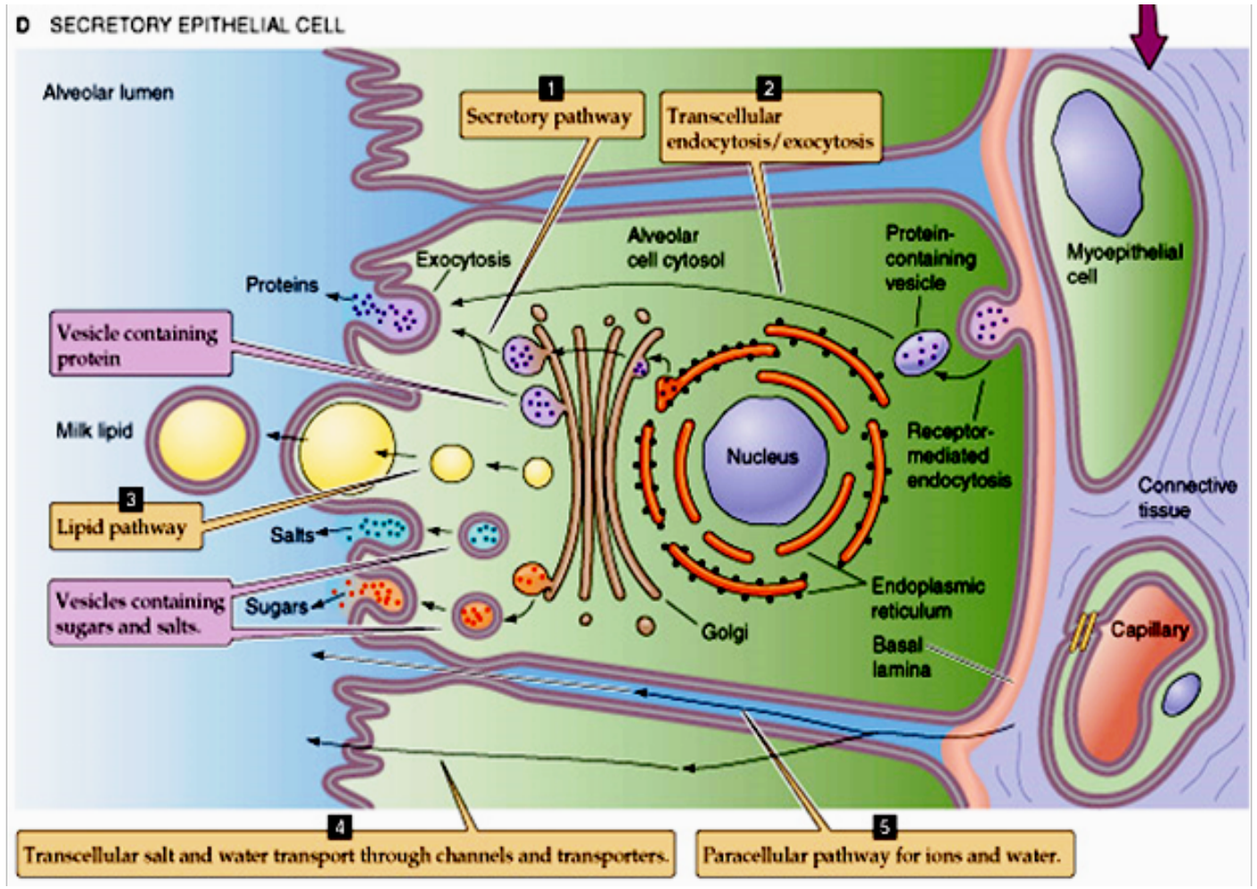
A. Endocytosis and exocytosis of proteins.

B. Water and slats transport through channels and transporters

3/ Paracellular :

Pathway for ions and water

4/ lipid pathway



Endocrine Control of Lactation :

1/ Milk Production Reflex:

Prolactin is a key lactogenic hormone, stimulating initial alveolar milk production (stimulation through the suckling reflex , as many as the baby suckle more milk will be produced)

2/ 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

Galactopoeisis : **Autocrine mediated.**

- Definition: Galactopoeisis is defined as the **maintenance** of lactation once lactation has been established.
- Duration : starts 9-15 days postpartum and continue until weaning م (it depends on the mother mainly , if she stop lactating after on year for example there will be no milk)

Galactopoeitic Hormones:

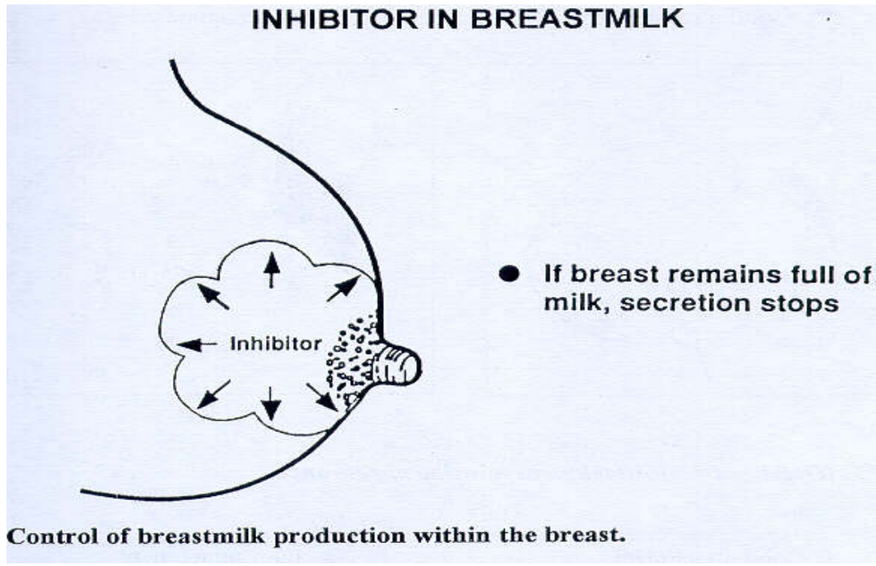
1. Prolactin: the most important galactopoeitic hormones involved in the maintenance of lactation.
2. Growth Hormone: supports increase in the synthesis of lactose, protein, and fat in the mammary gland
3. Glucocorticoids (for the acid and proteins in the milk)
4. Thyroid and parathyroid Hormones (PTH for calcium in milk)

   Fun fact: That's why women who breast feed their babies lose the baby wight faster than the ones who don't (because of the high levels of thyroid hormone).
5. Insulin (importanat for the glucose, the con. of glucose which will pass through the epithelial cells will be high)

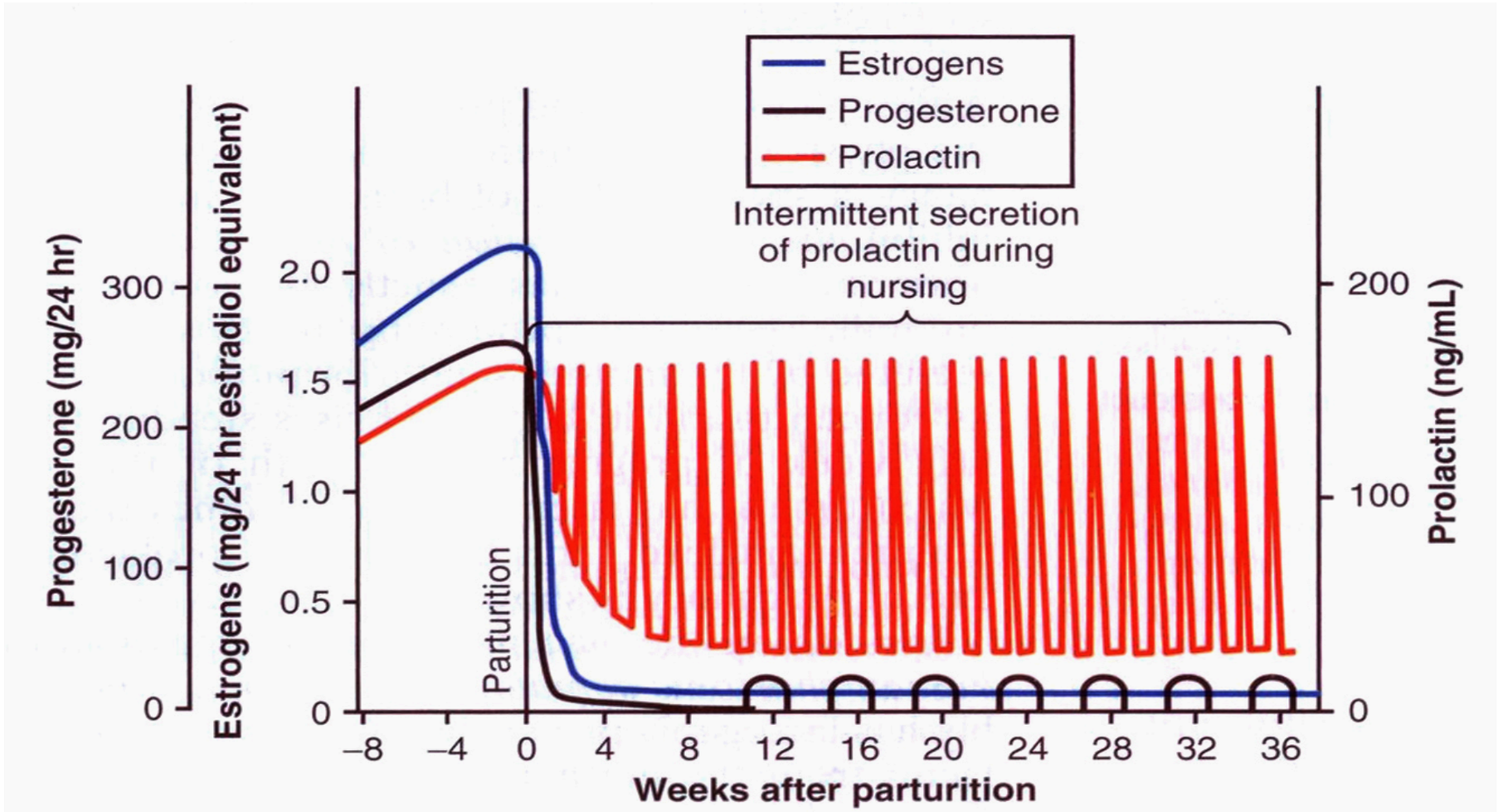
Autocrine Control of Lactation :

It is not just the level of maternal hormones, but the efficiency of **milk removal** that governs the volume product in each breast (milk removal means when the baby suckle the milk so it's removed from the breast, and new milk in going to be produced)

- A protein factor called **feedback inhibitor of lactation (FIL)** is secreted with other milk components into the alveolar lumen (FIL is normally present in the milk)
- **FIL** insensitive to prolactin → ↓ milk production
- When the mother doesn't feed her baby for days , this FIL will accumulate in the breast which will cause the negative feedback that inhibit the prolactin and milk production
- FIL is autocrine

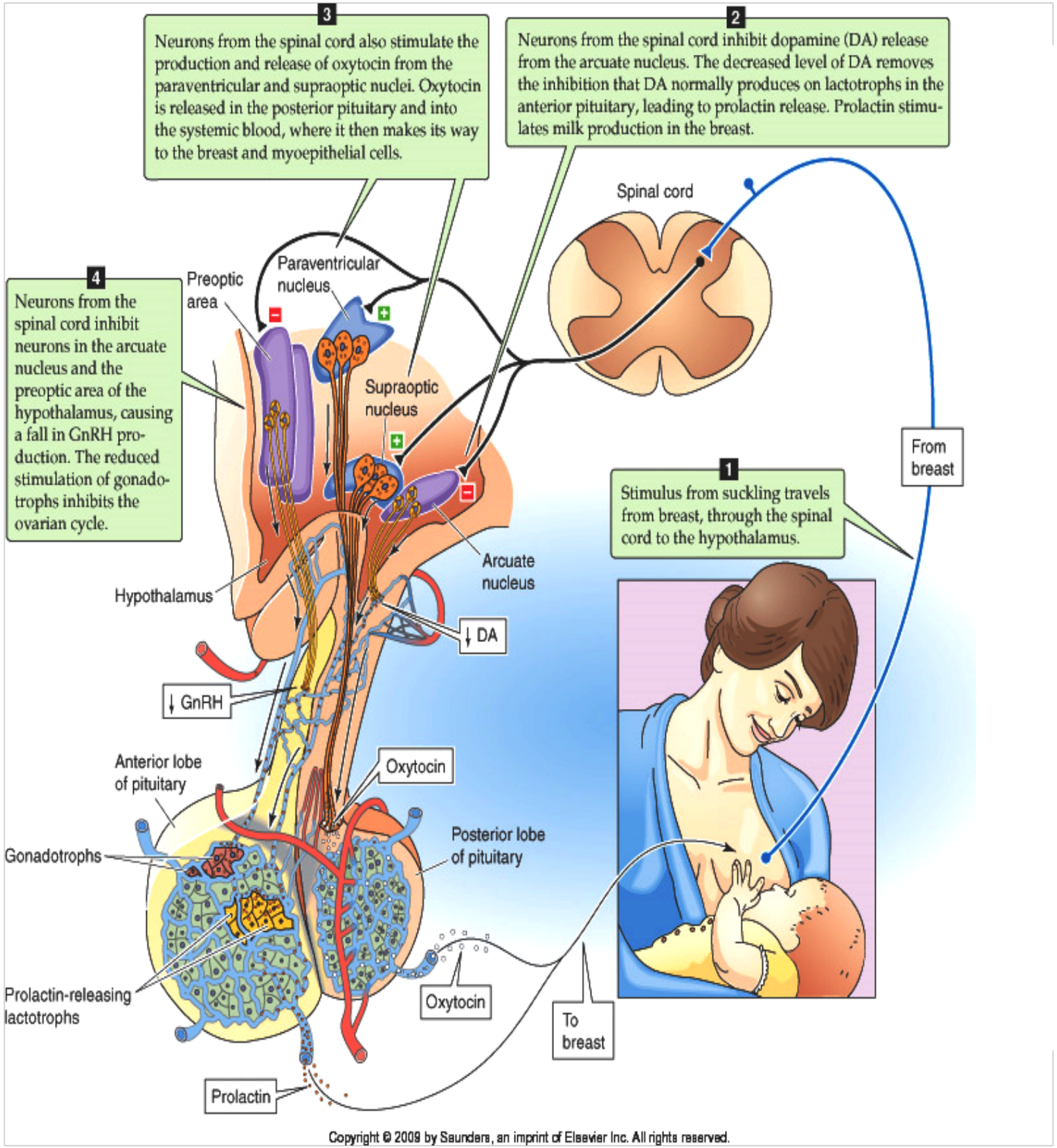


Control of breastmilk production within the breast.



- After giving birth (parturition) the levels of estrogen, progesterone & prolactin will go down.
- Prolactin will increase with each time the mother breastfeed her baby (preparing milk for the next time she feeds him).
- As long as the mother **continuously** breastfeed her baby= no ovulation = no period = no pregnancy.

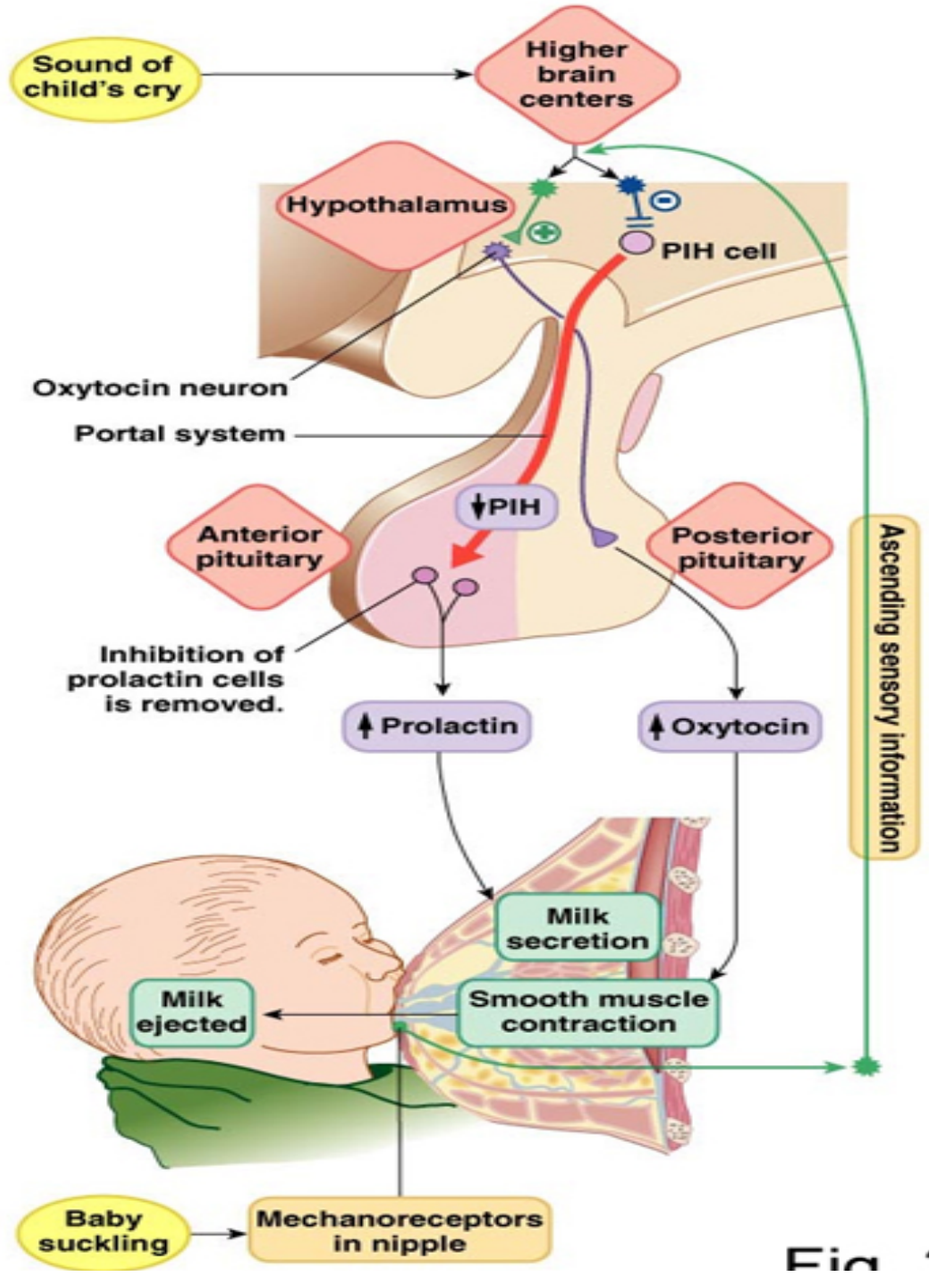
Suckling reflex (suckling inhibit the GnRH)



Neural reflex arc

Important slid

Neural reflex by the **mechanoreceptors** in the nipple



Milk production :

- 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. The first days after labor the milk production is low becouse of the cholesterol “estrogen and progesterone” presence in the blood

- Milk production by day 3 reaches 500 ml/day.

-Involution: This is when the breasts stop producing milk completely after weaning (under the influence of endocrin)

AAP Recommendations (American Academy of Pediatrics) :

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’

Some notes from the doctor :

- Prolactin acts on the alveolar epithelial cells to produce milk
- Oxytocine acts on the myoepithelial cells to contract and eject the milk toward the nipple
- Progesterone doesn’t have receptor on the alveolar epithelial cells Unlike the estrogen (that’s why they give the lactating women minipill as contraception)
- when the baby suckle , the mechanoreceptor reflex will stimuli the prolactin secretion , which will prepare the milk for next breast feeding

(يعني لمن البيبي بيكون يرضع راح يحفز افراز البرولاكتين عشان يجهز الحليب للرضعة الجديدة و بالتالي مع استمرار ارضاع الام لطفلها و بيستمر انتاج الحليب)

- most of the milk secretion is watery , that’s why the baby become hungry very quickly

Summery

5. Lactation

- Estrogens and progesterone stimulate the growth and development of the breasts throughout pregnancy.
- **Prolactin levels increase steadily during pregnancy** because estrogen stimulates prolactin secretion from the anterior pituitary.
- **Lactation does not occur during pregnancy because estrogen and progesterone block the action of prolactin on the breast.**
- After parturition, estrogen and progesterone levels decrease abruptly and lactation occurs.
- Lactation is maintained by suckling, which stimulates both oxytocin and prolactin secretion.
- **Ovulation is suppressed** as long as lactation continues because prolactin has the following effects:

  a. Inhibits hypothalamic GnRH secretion.
  b. Inhibits the action of GnRH on the anterior pituitary, and consequently inhibits LH and FSH secretion.
  c. Antagonizes the actions of LH and FSH on the ovaries.

Summery

- During puberty , Estrogen stimulate development of ducts of mammary gland and deposition of fat . While Progesterone stimulate Full development of lobule-alveolar system .

- Endocrine system has a major role in development "mamogenesis" and function "lactogenesis of mammary gland.

- Three categories of hormones which are :

- Reproductive – Endocrine – (strogen, progesterone, prolactin, oxytocin and hPL (
- Metabolic – Endocrine – (GH, corticosteroids, thyroxin, PTH and insulin (
- Mammary – Autocrine – (GH, prolactin, parathyroid hormone-related protein and leptin (

- Estrogen and Progesterone (from Placenta) inhibit secretion of milk by inhibiting Prolactin affect on breast.

)Dr. AlOtaibi says that they down regulate prolactin receptors but don't inhibit it secretion (

- Prolactin main function is milk secretion and it's controlled by hypothalamic hormone

PIH (Dopamine (which inhibit secreatin of prolactin

- Human placental lactogen (Placenta) "somatomammotropin " : facilitate mammogensis and Delay milk production.

Summery

Lactogenesis: Cellular changes by which mammary epithelial cell switches from a growing non secretory tissue to a secreting non-growing tissue (initiation of milk secretion)

❖ **Lactogenesis 1 :**

- It is the Cytological and enzymatic differentiation of alveolar epithelial cells
- Hormones at this stage (PPGG): **Progesterone – Prolactin – GH – Glucocorticoides**

❖ **Lactogenesis 2 :**

➢ Copious secretion of all milk Components due to withdrawal of progesterone + high level of prolactin

➢ Hormones (PO):

1. Prolactin "secaretory cells\milk production“
2. Oxytocin "myoepithelial cells\milk ejection“

❖ **Galactopoeisis:**

- is the maintenance of lactation once lactation has been established
- Hormones (PPGGIT): **Prolactin (most important) – Parathyroid - GH – Glucocorticoides - Insulin – Thyroid**
- Suckling reflux :- slide 13 (very important(

- 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**
- Exclusive breast feeding for the **first six months of life**

MCQs

1.All of the following will Stimulate milk production except :

A.Prolactin

B.Suckling

C.Oxytocin

D.Progesterone

2. regarding Prolactin hormone choose the incorrect statement :

A.it has action in breast development

B.it has action in milk production

3. Regarding lactogenesis , which one is correct :

A.Cortisol is involved in the 2nd stage .

B.High level of Prolactin in the 1ststage

C.Progesterone is high during 1st stage

D.Synthesis of milk component during 1st stage

4. Which ONE of the following is released by suckling the nipple?

A.Cortisol

B.Dopamine

C.Oxytocin

D.Gonadotropin Releasing Hormon

1-D 2-A 3-C 4-C

Physiology team

Gratitude

Our dear batch this lecture was the last physiology lecture for the entire block, year and most importantly in our basic science years. We were honored to be part of this batch and blessed to work with each member of this team, so excuse our flaws and mistakes. We wish that we as a team achieved the aim of teamwork and made this subject clear and easy. May understanding this subject help you to be better giving doctors.

In closing, we would like to express our gratitude for you, our members – and to 433 batch that helped to make this team.

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Reproductive Block