Physiology Team 439

MED439
KING SAUD UNIVERSITY

Revised & Approved
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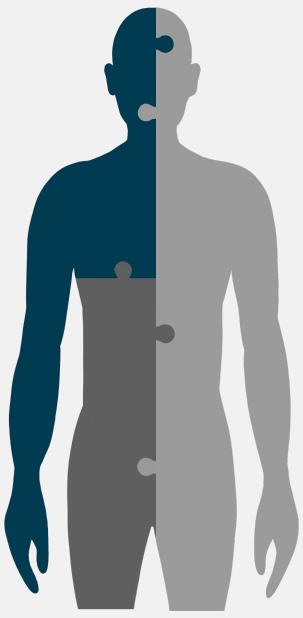


Hormones Affecting Female Breast

Objectives:

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

Color index:

- Important.
- Girls slide only.
- Boys slide only.
- Dr's note.
- Extra information.

Editing File

Structure of the human breast

Ductal System

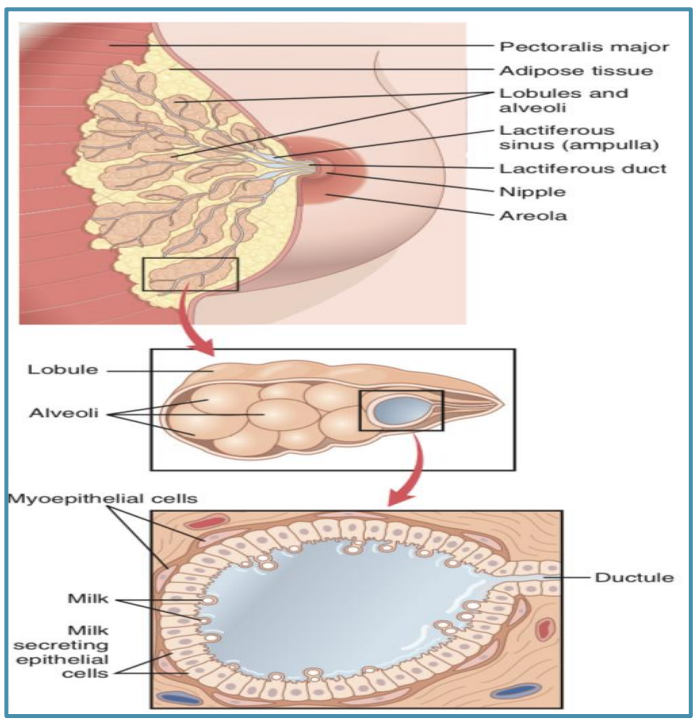
- Alveolar tubule
- Secondary tubule
- Mammary duct
- Ampulla (lactiferous sinus)
- Lactiferous duct

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.

❑ 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.
5. The fundamental secretory unit of the breast is the alveolus.



Note:
- Normally in a normal state the female breast isn't secretory in function nor it produces milk in a normal state there are some steps that are involved to make it functional.
- The size of the breast isn't related to the milk production. What affects milk production is the suckling by the baby.

Where Does the Milk Come From?

❖ Uterine milk theory:

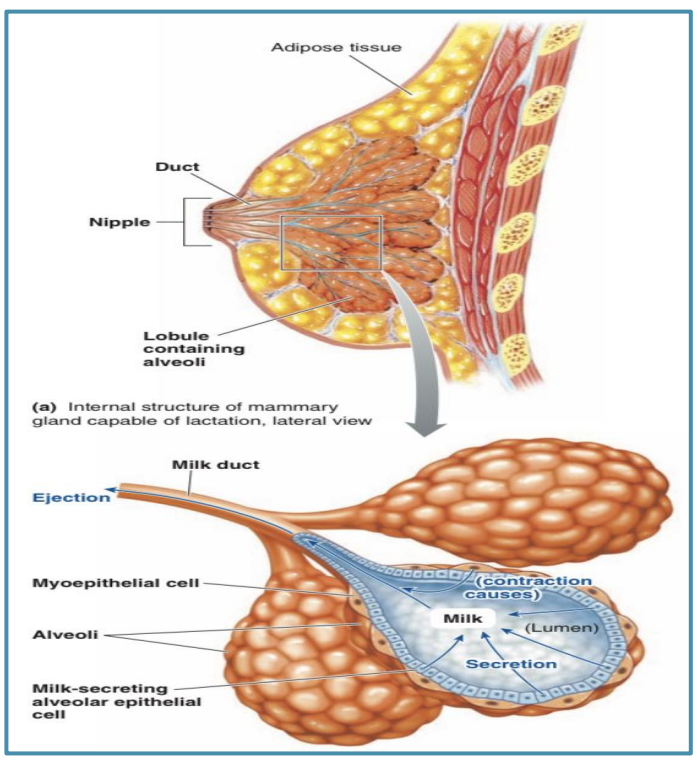
Vessel connecting the uterus to the breast (diversion of menstrual blood to the breast).

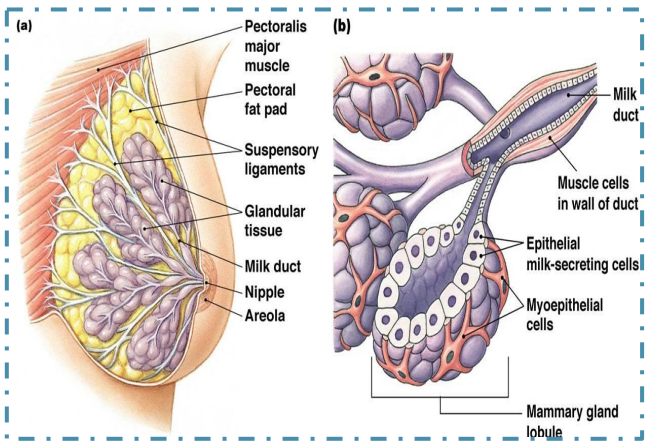
❖ Chyle theory:

Milk is derived directly from chyle (milky fluid of emulsified fat absorbed from the intestinal tract into lymphatic system).

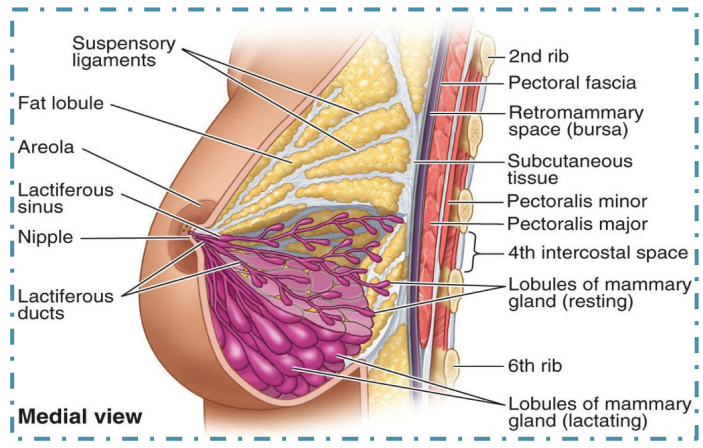
❖ Synthesis theory:

Milk is formed from substrates carried to the gland in the blood.





Notes
- The structural unit (the alveolus) is lined by alveolar cells, which synthesize and produce milk.
- Alveolar cells can't function on their own, they need a network of capillaries around them, which will deliver all nutrients needed to produce milk to the alveolus.
- Once the milk is synthesized it needs to be ejected to the ducts, and that's the function of myoepithelial cells.



Stages of Mammary Gland Development

1 **Mammogenesis**
Growth and development of mammary gland to a functional state.

2 **Lactogenesis**
Initiation of milk secretion.
(It involves two phases)

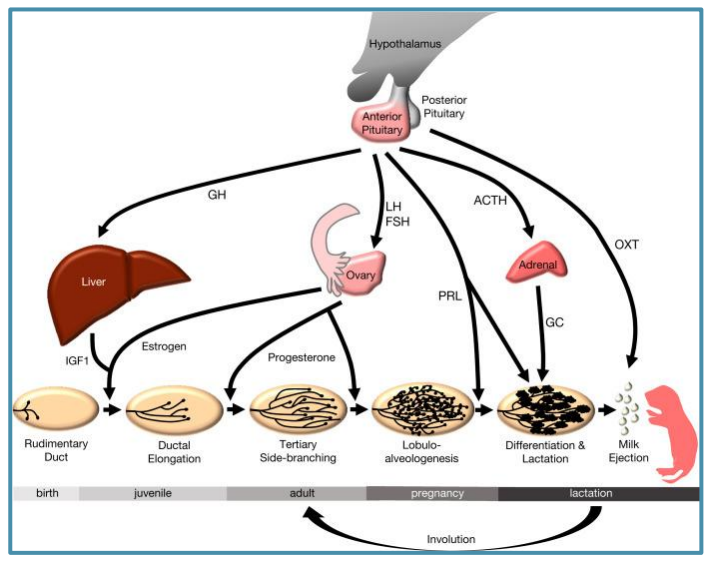
3 **Galactopoiesis**
Maintenance of milk secretion in the postpartum period.

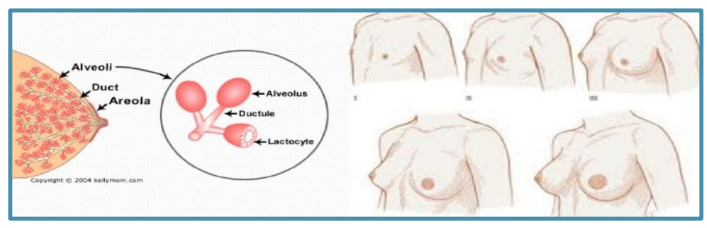
4 **Involution**
Cessation of milk production.

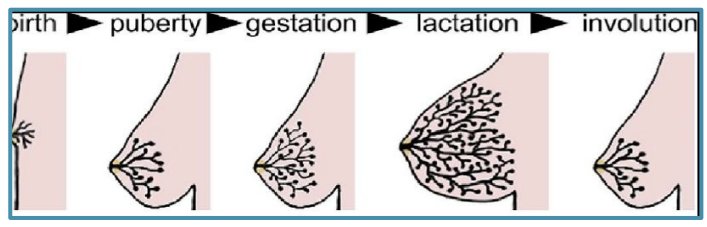
Breast Development (Mammogenesis)

The postnatal development of female mammary tissue occurs in several steps:

- ❖ 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.
  - Estrogen stimulate proliferation of ducts 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 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.







Note:
At breast development the two most important hormones are estrogen and progesterone they complement each other functions in this stage that's why they are increased during puberty to increase the female breast to prepare it for lactation.

Three Categories of Hormones*

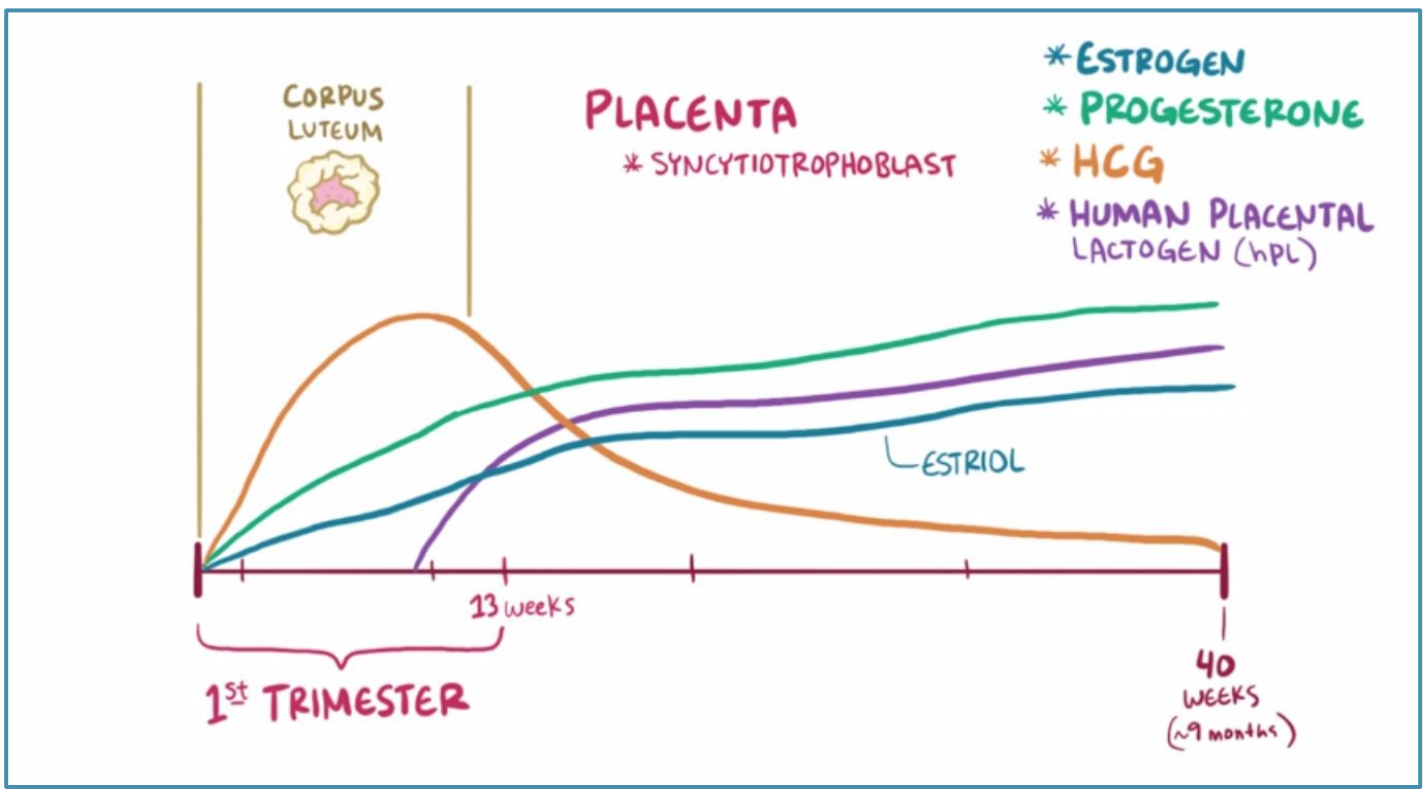
Reproductive hormones (endocrine)	Metabolic hormones (endocrine)	Mammary hormones (autocrine)
Estrogen,progesterone ,prolactin, oxytocin and hPL (prolactin-like effect).	GH1,corticosteroids (cortisol) ,thyroxine,PTH and insulin.	GH, prolactin, parathyroid hormone-related protein (PTHrP) and leptin.

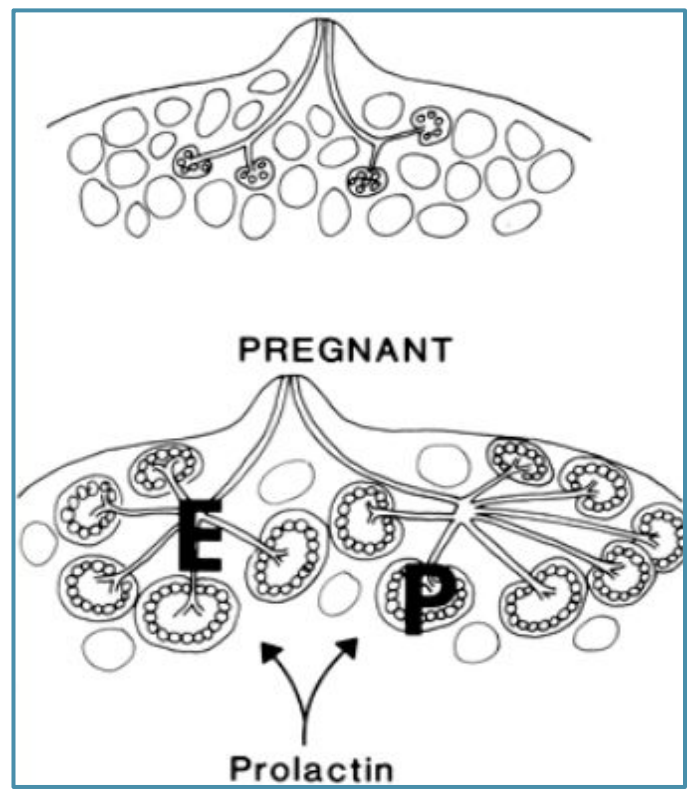
The endocrine system plays a major role in synchronizing development (mammogenesis) and function (lactogenesis) of mammary gland with reproduction.

Mammogenic hormones: promoting the proliferation of ductal and alveolar cells (ductal & alveolar morphogenesis).

Reproductive Hormones (Direct Effect)*

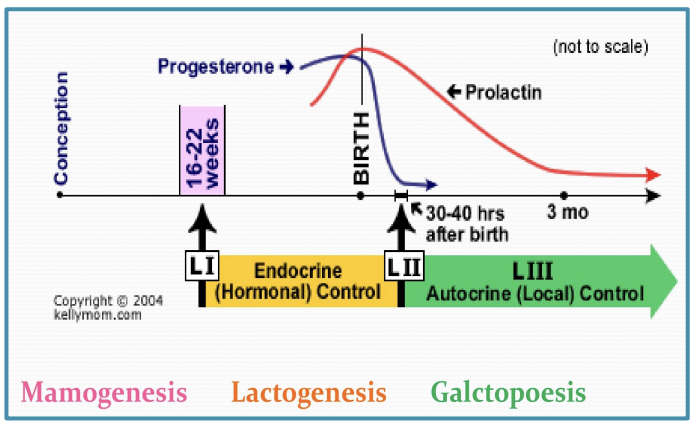
Estrogen (placenta)	❖ Growth & branching of ductal system (with GH) ❖ Fat deposition in the stroma.
Progesterone (placenta)	❖ Growth of lobule-alveolar system (budding of alveoli and secretory changes in epithelial cells). ❖ Although estrogen and progesterone are essential for physical development of the breasts, they inhibit actual secretion of milk during pregnancy by interacting with prolactin receptors.
Prolactin (anterior pituitary)	❖ Secreted from anterior pituitary gland (Lactotrophs). ❖ Its level steadily rises from the 5th week of pregnancy until birth, enhanced by estrogen (10-20 times nonpregnant level). ❖ Its main function is milk production. Acts on alveolar cells ❖ 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 estrogen & progesterone after delivery allows milk production. ❖ That's why ladies suffer from engorgement first 3 days after delivery and they need to breastfeed the baby or eject the milk by a pump to relieve the pressure ❖ It is inhibited mainly by hypothalamic hormone, PIH (Dopamine) inhibitory centrally. ❖ Thyrotropin-releasing hormone (TRH) can increase PRL. ❖ Why is prolactin tonically inhibited ? Because it isn't needed throughout a lifetime, it is only used in exceptional periods that's when an inhibition of dopamine occurs. ❖ Prolactin (high levels) exerts a negative feedback on GnRH that causes the female to have lactic amenorrhea that can last form 3-6 months maybe even longer. So in the 6 months after pregnancy it can be reliable as a contraceptive method after that we have to use medications.
Human placental lactogen (placenta)	❖ Facilitate mammogenesis ❖ Delay milk production





Lactogenesis

❖ Cellular changes by which mammary alveolar epithelial cells are converted from a non secretory state (genetic upregulation) to a secretory state (initiation of milk secretion).



Lactogenic Hormones

❖ Promoting initiation /onset of milk production by alveolar cells.

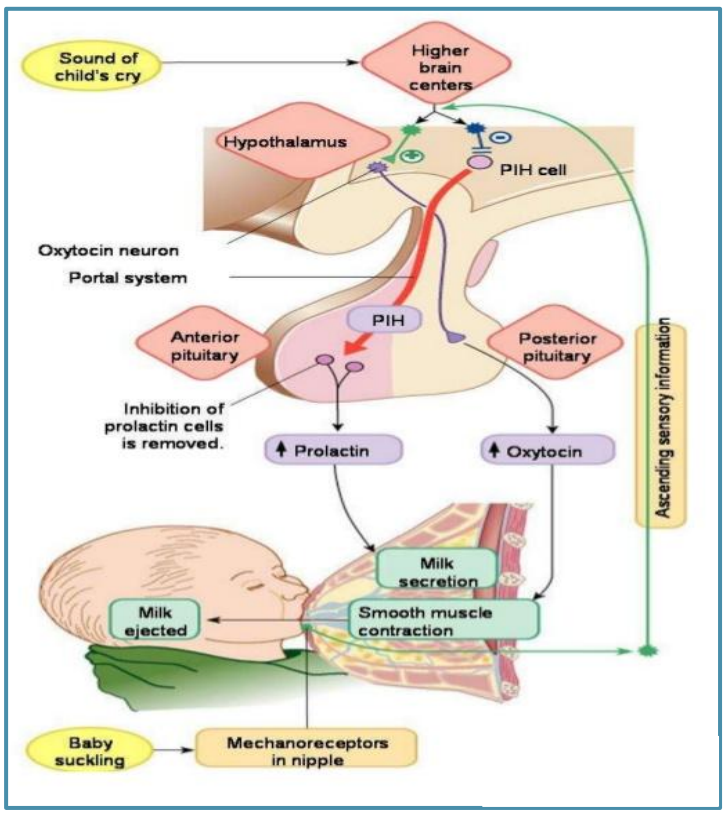
Lactogenesis involves 2 stages:

Lactogenesis 1

❖ Cytologic (histological) and enzymatic differentiation of alveolar epithelial cells.
❖ Starts in mid pregnancy 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.
❖ Hormones involved:*

1. Progesterone (suppresses milk secretion)
2. Prolactin
3. Placental lactogen (hCS)
4. Growth hormone
5. Glucocorticoids (Cortisol)

❖ Further differentiation is inhibited by high levels of progesterone from the placenta.
❖ Production and secretion of milk components in this stage are restricted to a limited number of alveolar epithelial cells with incompletely developed secretory mechanisms.



Notes
Lactogenesis 1:
During this stage prolactin is the most important hormone during this stage but progesterone is still exerting a minimal inhibitory effect on prolactin so we can say a stage between mammogenesis and lactogenesis.

Lactogenesis 2

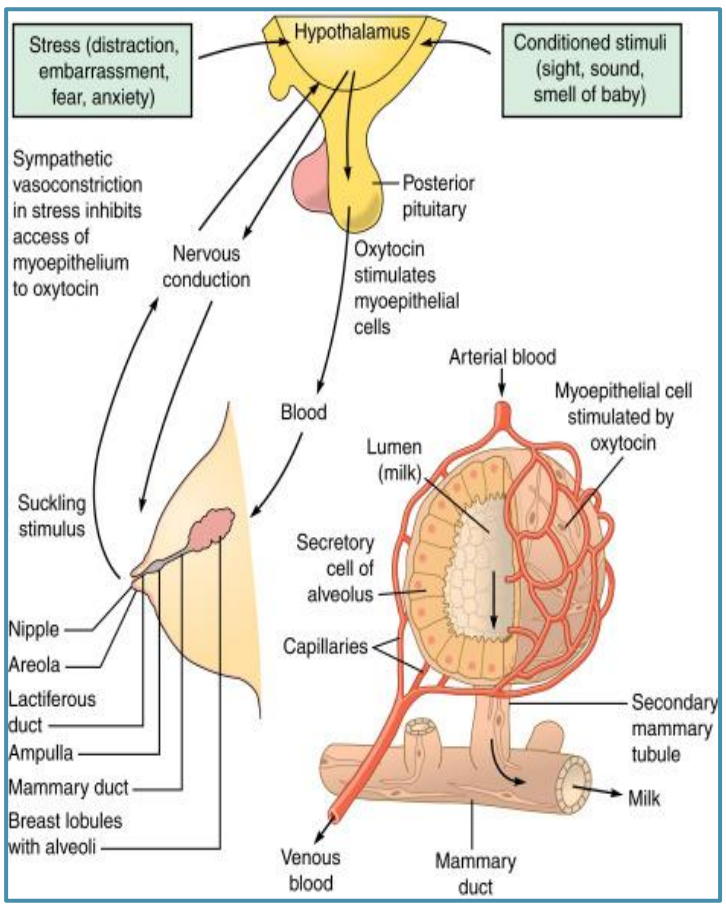
❖ Copious secretion of all milk components, starts 2-3 days postpartum.
❖ At parturition, withdrawal of progesterone + high level of prolactin leads to:

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 (IgA). To give some immunity to the baby
5. Secretion of colostrum followed by milk. بعض الامهات كانوا يرمونه يحسبونه مو زين لان لونه اصفر
6. Suckling stimulates further increase in expression of genes involved in milk secretion with expansion of alveolar epithelium.
7. Lactation is maintained by removal of milk due to switch from endocrine to autocrine control of milk production. حتى لو البيبي مايقدر يرضع لانه بالعناية مثلا لازم الام تشفط

❖ Hormones involved:*

1. Prolactin (milk production)
2. Oxytocin (milk let-down)
3. Growth hormone
4. Glucocorticoid (Cortisol)
5. Thyroid hormone
6. Insulin

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



Notes
- Separation of placenta will cut the source of progesterone and estrogen
- Colostrum is full of Immunoglobulins, it's released in the first 3 days, very important for immunity of the baby
- They recommend putting the baby on the breast within 30 minutes after delivery initiate the lactation

Hormonal Regulation of Lactogenesis

Metabolic Hormones (Direct Effect)	
GH	❖ Its secretion is stimulated by progesterone. ❖ Increases production of IGF-1 by the liver and locally. ❖ Mediate ductal cell survival and ductal growth.
Corticosteroids	❖ Increases during pregnancy (five fold). ❖ Involved in breast development (permissive action on milk protein synthesis).
Thyroxin	❖ Essential for milk production. ❖ Thyroxine & TSH level decreases during lactation. ❖ TRH increases leading to stimulation of PRL (TRH can be administered nasally to treat inadequate lactation).
Insulin	❖ Low during lactation. Insulin is an anabolic hormone, it promotes the transport of nutrients from the blood into the cells واحنا نحتاجهم بالدم لإنتاج الحليب، قلة الانسولين جيدة في هذي الفترة ❖ Shunt of nutrients from storage depots to milk synthesis.

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

Milk Synthesis

The alveolar cell secretes the components of milk through five pathways.

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

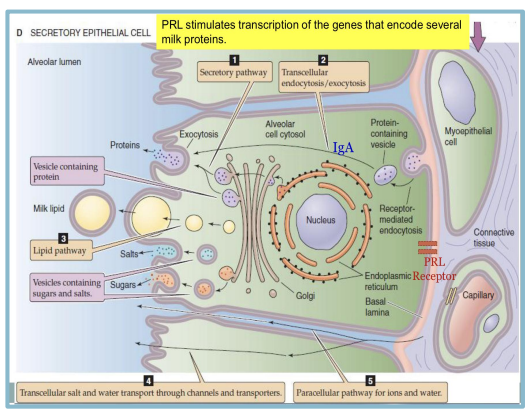
I. Exocytosis of milk protein, lactose, and other components of the aqueous phase in Golgi-derived secretory vesicles.

II. Milk fat secretion via the milk fat globule.

III. Direct movement of monovalent 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.

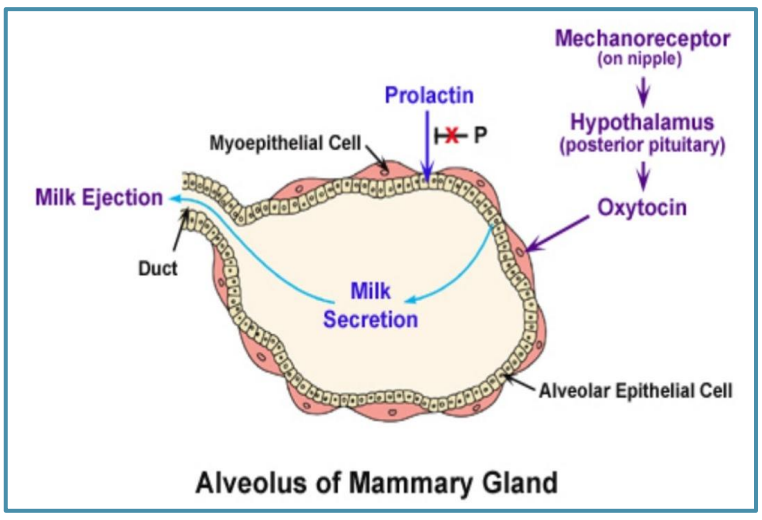


Mechanisms of Secretion:

- 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 وهذا يميز حليب الام أن مافيه ملح مقارنة بالصناعي

Galactopoiesis

- The maintenance of lactation once lactation has been established, starts 9-15 days postpartum.



Alveolus of Mammary Gland

Galactopoietic Hormones*

Maintaining milk production after it has been established

- PRL (primary)
- Cortisol, Insulin, thyroid hormone and growth hormone (permissive)
- Oxytocin
- Ovarian hormones

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.

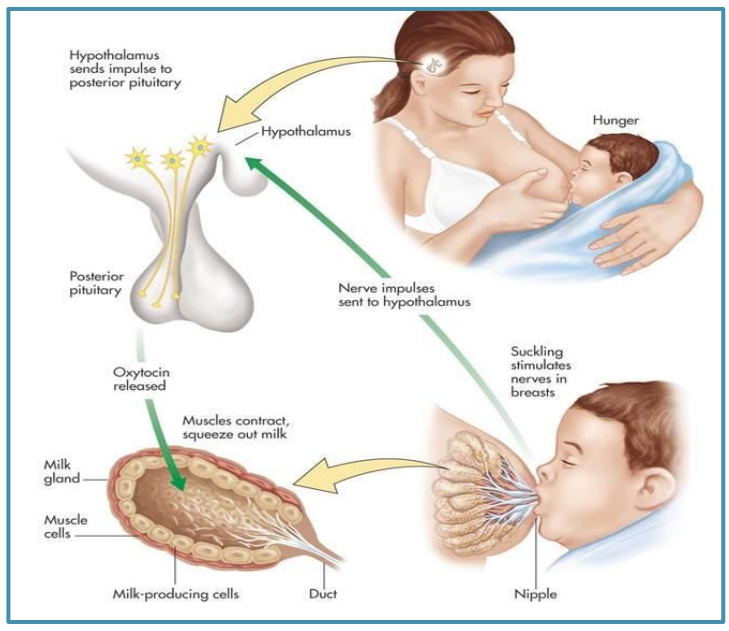
Galactopoietic Hormones

Prolactin	Milking-induced surge is a direct link between the act of nursing (or milk removal) and the galactopoietic hormones involved in maintaining lactation.
Growth Hormone	Support increase in synthesis of lactose, protein, and fat in the mammary gland.
Glucocorticoids	Galactopoietic in physiological doses.
Thyroid Hormones	Galactopoietic.
Ovarian Hormones	❖ **Estrogen** in very low doses is galactopoietic. It interferes with lactation in high doses, that's why OC pills containing estrogen are contraindicated ❖ **Progesterone** alone has no effect on galactopoiesis because there are no progesterone receptors in the mammary gland during lactation.

Oxytocin and Psychic Stimuli Initiate Milk Ejection ("let-down")*

1. 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 (galacto-kinetic effect).



2. Galacto-kinetic Hormone

- Promoting contraction of myoepithelial cells, and thus milk ejection).
  - Oxytocin
  - Vasopressin (similar chemical structure, differ by two amino acids. Even oxytocin has ADH effects)

Notes
Oxytocin uses calcium signaling because calcium is the contractile ion; all the effects of oxytocin is contractile including contraction of uterus during sexual intercourse (suction of sperm) also during labor expulsion of the baby. Furthermore contraction of the myoepithelial cells so hard that the baby doesnt even need to do anything.

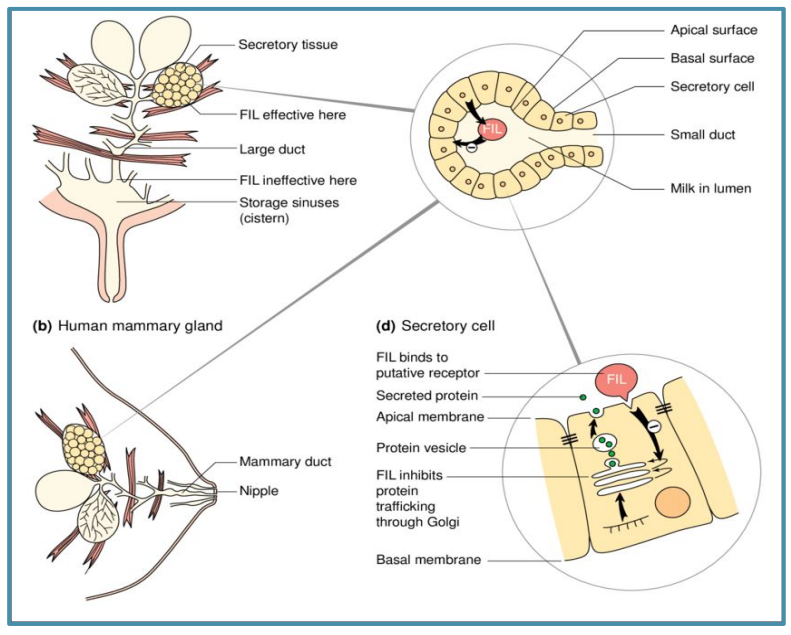
Autocrine Control of Lactation*

❑ 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 decreases milk production.



Notes

There is an inhibitory factor that is released with every milk production that is called feedback inhibition of lactin. If the milk is trapped inside the women's breast there will be no more prolactin production because of the FIL thus no milk production so the baby has to suck out the milk to continue production

❑ 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. To make the production easier and to prevent milk production to become hard to initiate.

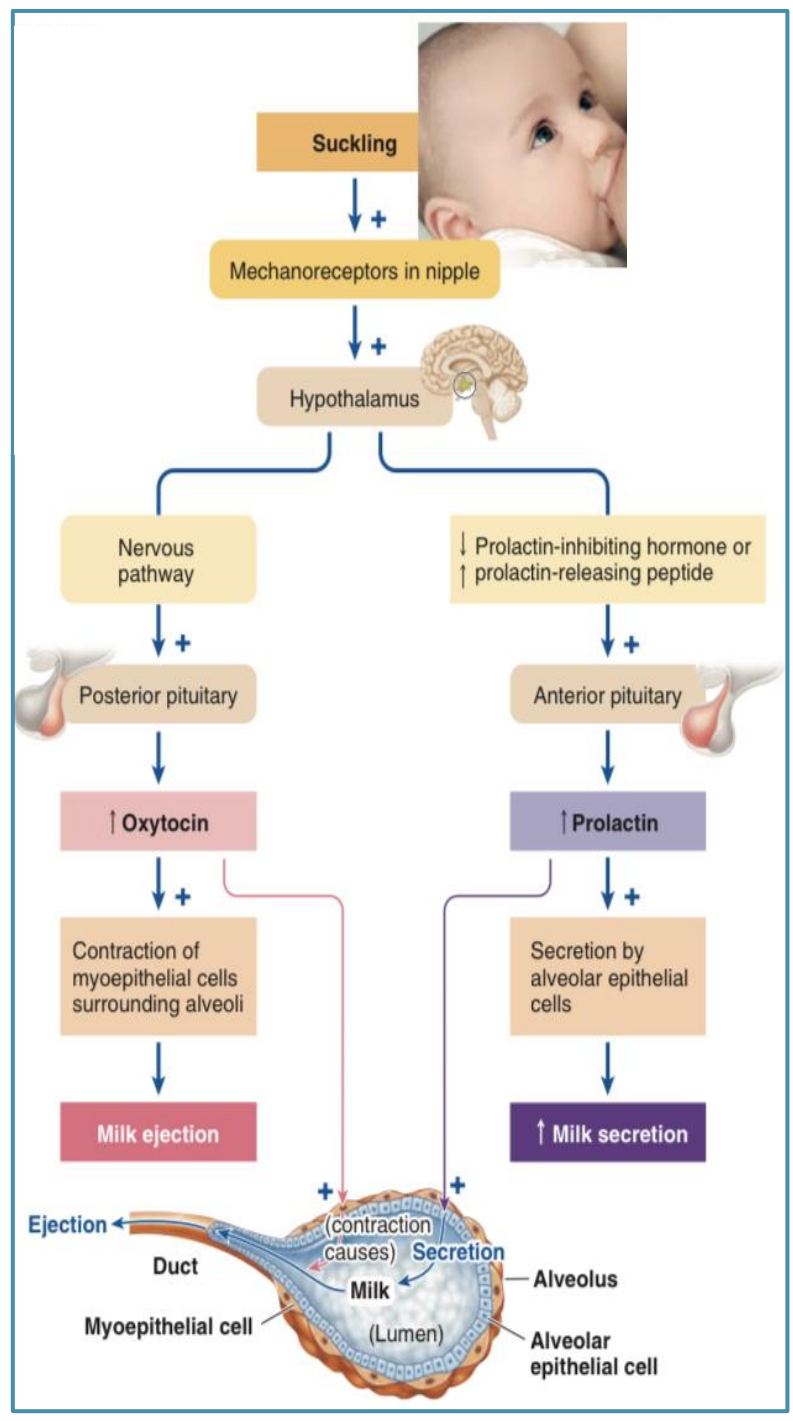
Lactation is maintained by continuous removal of milk.

Milk production <100 ml/day in day 1 postpartum.

Milk production by day 3 reaches 500 ml/day.

Involution: when the breasts stop producing milk completely after weaning(الفطام).

Milk composition changes dramatically (↓Na+2 & Cl-) due to closure of tight junctions that block paracellular pathway.

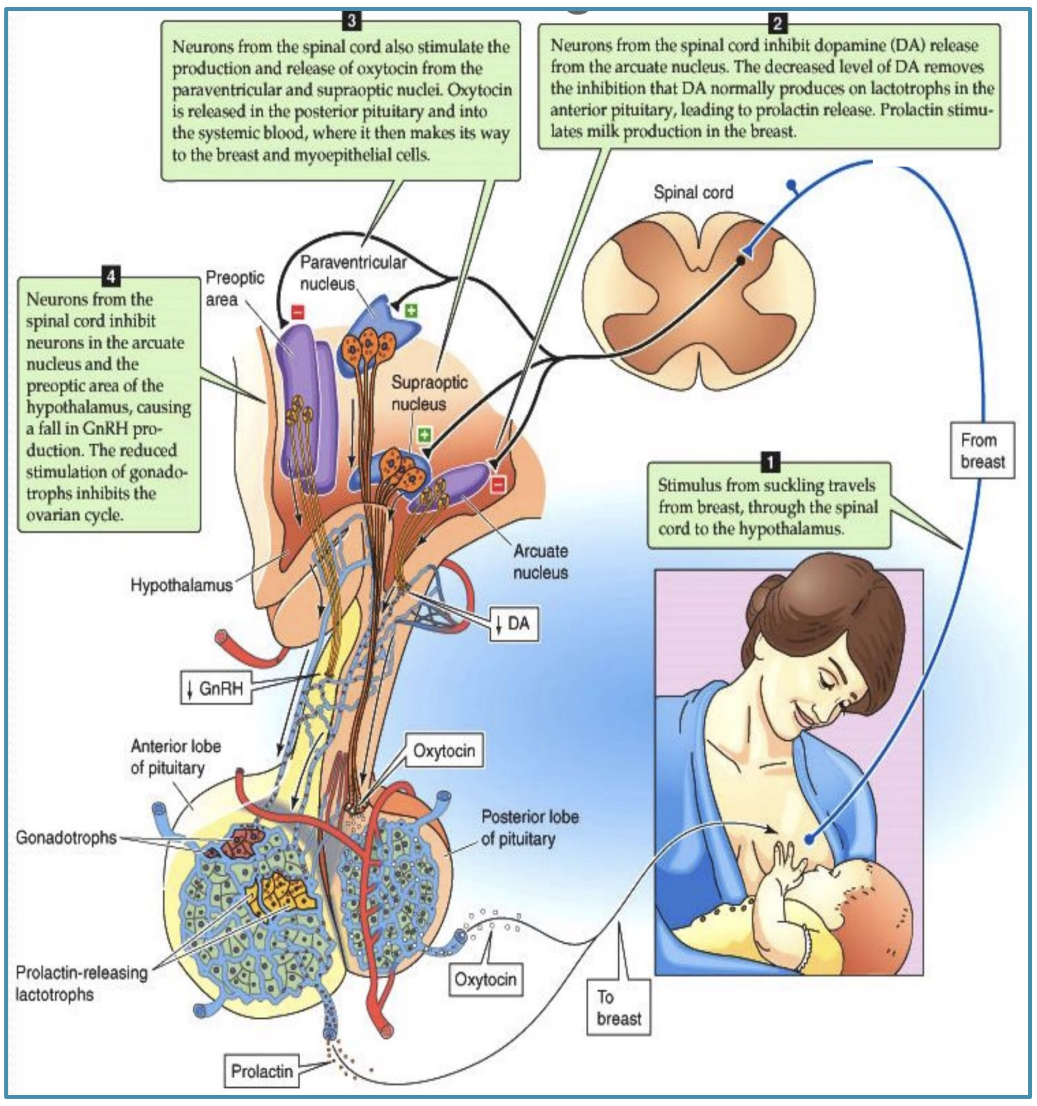


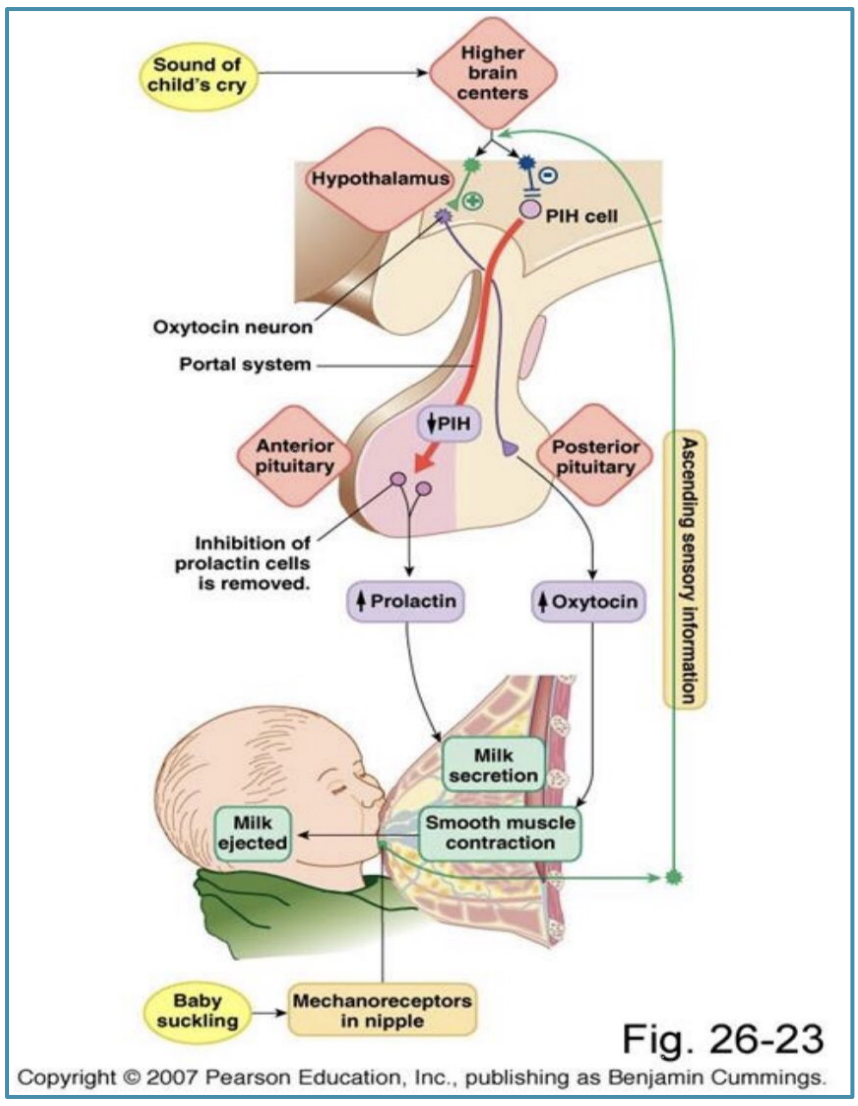
❑ AAP Recommendations

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 Reflex IMP for MCQ

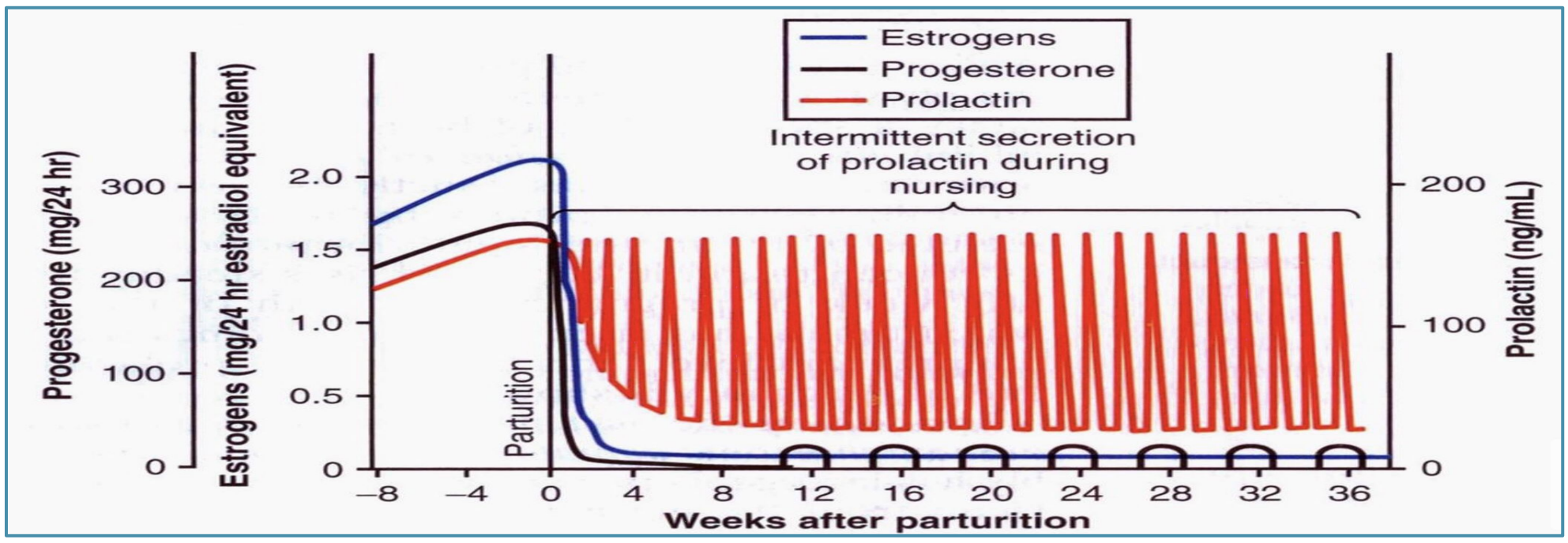




Suckling stimulates the release of TRH from the hypothalamus.

The other breast will also be stimulated.

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.



Suckling is the most powerful physiological stimulus for PRL release.

This graph shows the peaks in prolactin release in response to suckling.

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.

A Special Thanks to Team 438

MCQ & SAQ:

Q1: The lobes in the human bread are arranged:

A. Radially
B. Diagonally
C. Vertically
D. Horizontally

Q2: Which one of the following hormones will be low during lactation ?

A. Insulin
B. GH
C. Thyroxine
D. Corticosteroid

Q3: One of the following is not included in the ductal system:

A. Secondary tubule
B. Tertiary tubule
C. Alveolar tubule
D. Ampulla

Q4: Which of the following hormones is essential for forcing the milk (ejection) ?

A. prolactin
B. Thyroid
C. Oxytocin
D. GH

Q5: Progesterone is mainly responsible for which of the following effects on the breasts?

A. Deposition of fat
B. Proliferation of ducts
C. Stimulate development of lobules
D. Deposition of stroma

Q6: Which one of the following grades do you think you'll get during this block ?

A. A+
B. أ+
C. A & B
D. B & A

answer key:
1: A
2: A
3: B
4: C
5: C
6: A

1- Where does the milk come from according to the synthesis theory?

2- List the 4 stages of mammary gland development respectively

3- Define Lactogenesis

4- List the galactopoietic hormones

A1: Milk is formed from substrates carried to the gland in the blood.

A2: Mammogenesis, Lactogenesis, Galactopoiesis, Involution.

A3 : Cellular changes by which mammary alveolar epithelial cells are converted from a non secretory state to a secretory state (initiation of milk secretion)

A4: PRL, Cortisol, Insulin, thyroid hormone and growth hormone (permissive) ,Oxytocin and Ovarian hormones

🎉🎊 Congratulations 🎊🎉

We Have Reached The End of Our Journey In The Physiology Team

A Special Thanks To All The Academic & Team Leaders Who Contributed In The Success Of Our Team.

- Abdullah Alsubaihi
- Bassam Alasmari
- Rania Almutiri
- Faisal Alotaibi
- Shayma Alghanoum
- Yusuf Alkahtani

Previous Team Leaders:

Haya Alanazi, Abdulrahman Alswat, Teif Almutairi, Abdulaziz Alkraida, Abdulaziz Alsuhaim, Sarah AlQahtani, Sadem Alzayed, Ghada Aljedaie, Homoud Algadheb, Raghad Albarrak, Samar Almohammedi, Yara Alasmari, Aljoud Algazlan, Albandari Ahmed,Sarah Alharbi, Fahd Alajmi, Abdulaziz Alsuhaim

Last But Not Least Our Amazing Members, We Couldn't Have Done It Without You. Thank You For All The Time And Effort You Put Into The Team. We Wish You All The Best.

- Mishal Althunayan
- Basel Fakeeha
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- Abdulaziz Alsuhaim
- Mohammad Alkatheri
- Morshed Alharbi
- Ahmad Al Khayat
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- Raed alntaifi
- Homoud alghadeb
- Mishal alhamed
- Musab alamri
- Fayez AlTabbaa
- Mohammed alsalman
- Renad Alhomaidi
- Aseel alshehri
- Noura abdulaziz
- Yasmin Al Qarni
- Alaa Alsulmi
- Farah Albakr
- Muneerah alsadhan
- Sarah alobaid
- Farrah alsaid
- Noura almsaud
- Hessah alalyan
- Rema alhdleg
- Raghad alsweed
- Raghad asiari
- Ghadah alouthman
- Asma alamri
- Rania Almutiri
- Yara alasmari
- Asma alamri
- Basel Fakeeha.
- Fatimah Saad.
- Hessah Alalyan.
- Majed Alaskar.
- Mayasem Alhazmi.
- Sadeem Al Zayed.
- Fahad Alajmi.
- Hessah Alalyan.
- Reem Aldosari
- Shuaa Khdary.
- Saud Alrsheed.
- Abdulaziz Alrabiah.
- Abdulaziz Alderaywsh.
- Abdulaziz Alamri.
- Abdulaziz Alomar.
- Abdullah Alburikan.
- Abdullah Binjadou.
- Abdullah Alanzan.
- Abdullah Alhumimidi.
- Abdulrahman Almegbel .
- Abdulrahman Barashid.
- Abdulrhman Alsuhaibany.
- Abeer Awwad
- Ahmad Alkhayatt.
- Aljoharah Albnyan.
- Aljoud Algazlan.
- Almaha Alshathri.
- Arwa Al-Qahtani.
- Bader Alrayes.
- Bassam Alasmari.
- Bushra Alotaibi
- Faisal Jazzar.
- Feras Alqaidi.
- Ghaida Alassiry.
- Ghaida Alshehri.
- Hamad Almousa.
- Haya Alanazi.
- Hind Almotywea.
- Ibraheem Altamimi.
- Ibrahim Alnamlah.
- Joud Alarifi.
- Khalid Altowaijeri.
- Khalid Almutlaq.
- Leen AlMadhyani.
- May Barakah.
- Mohamed Alquhidan.
- Mohammed Alkathiri.
- Murshed Alharby.
- Nada Bin Obied.
- Norah Alsalem.
- Norah Aldakhil
- Nouf Alsubaie.
- Noura Alshathri.
- Nurah Alqahtani.
- Omar Alhalabi.
- Rayan Jabaan.
- Reem Alqahtani.
- Sarah AlQuwayz.
- Saud Alhasani.
- Shaden Alobaid.
- Shahd Almezel.
- Shatha Aldossary.
- Shayma Alghanoum.
- Tarfah Alkaltham.
- Yara Alomar.
- Yara Alzahrani.
- Yazeed Alqahtani.
- ziyad Alhosan.
- ماجد العسكر
- مشعل الثنيان
- عبد العزيز الربيعة
- باسل فقيها
- محمد بياري
- محمد السلمان
- عبد الرحمن الدويش
- مرشد الحربي
- منيب الخطيب
- نايف الشهري
- فيصل العمري
- عبد العزيز الغليقة
- عبد العزيز السحيم
- حصة العليان
- شذى الظهير
- سمو الزير
- نورة الشثري
- سارة القحطاني
- ريناد الحميدي
- ياسمين القرني
- يارا الزهراني
- لمى الأحمدي
- آلاء السلمي
- سارة العيدروس
- بدور المبارك
- فرح البكر
- سارة العبيد
- محمد العكرش
- صالح القرني
- خالد القبلان

Leaders:

Abeer Awwad
Mohamed Alquhidan

A Special Thanks To Our loyal Reproductive Block Members.
🌹 ماقصرتوا بيض الله وجيهكم، رب يجعلها في ميزان حسناتكم 🌹

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- **Abdulaziz Alomairy**
- Abdullah Alburikan
- Albandari Alanazi
- Aljoharah Albnyan
- Asma Alamri
- Bader alrayes
- Budoor Almubarak
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