Mysterious Milk Ejection Reflex

Understanding the Mysterious Milk Ejection Reflex

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Disclosure

I have **no financial relationships** with commercial interests that pertain to the content presented in this program

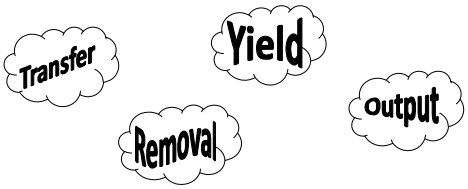
"ORIGIN OF THE MILKY WAY"

"Successful breastfeeding involves milk production, secretion and ejection controlled by a series of humoral and neural processes. *Among them, neuro-chemical events leading to milk letdown or milk ejection are the most fragile processes… studying [the] milk letdown reflex is critical to solving breastfeeding problems" – Yu-Feng Wang*

Oxytocin: the key to treating lactation-failure and associated diseas... (slideshare.net)

by Peter Paul Rubens Public Domain Mark 1.0

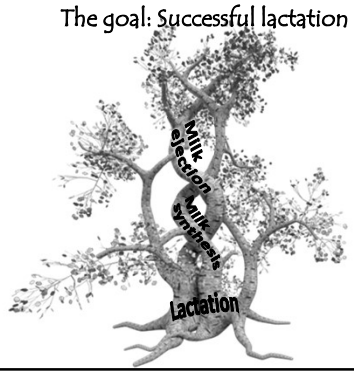
WHAT IS THE DIFFERENCE BETWEEN MILK PRODUCTION AND MILK YIELD?



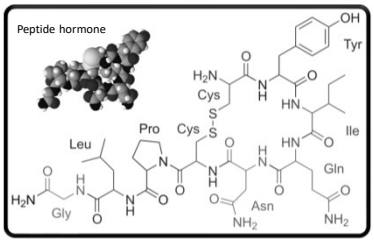
Creation vs Delivery

→ Parent's perception often based on yield ←

The goal: Successful lactation



OXYTOCIN: THE HORMONE OF LOVE, BONDING, & MILK EJECTION



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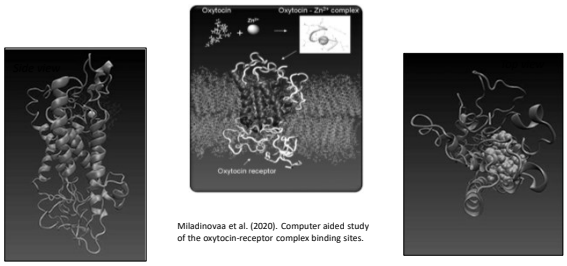
Oxytocin Receptor



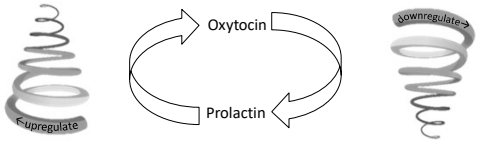
Miladinovaa et al. (2020). Computer aided study of the oxytocin-receptor complex binding sites.

Oxytocin: essential to Milk Production as well as Delivery

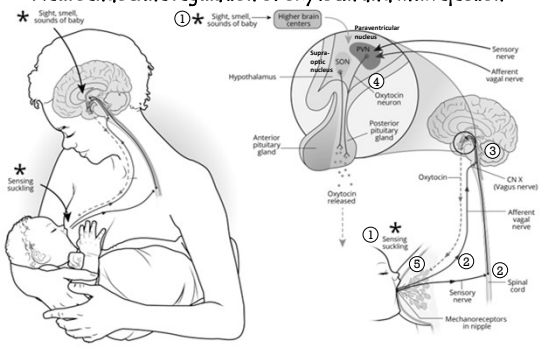
Oxytocin and Prolactin interact *symbiotically*

→ Oxytocin receptors on pituitary lactotrophs provide additional stimulation for prolactin release- *upregulation*

→ Effective milk removal stimulates strong production

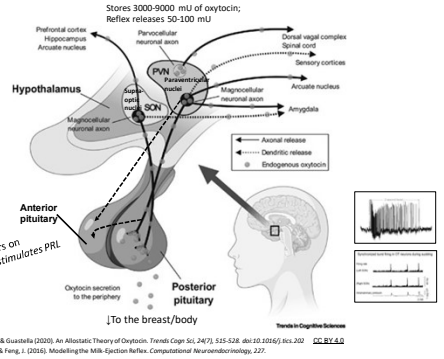


Neuroendocrine regulation of oxytocin and milk ejection



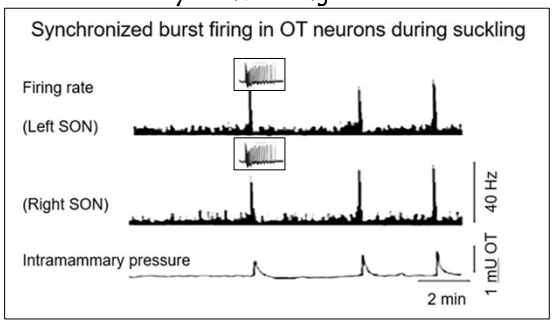
Pathways of Oxytocin release

Stores 3000-9000 mU of oxytocin;
Reflex releases 50-100 mU



Quintana & Guastella (2020). An Allostatic Theory of Oxytocin. *Trends Cogn Sci, 24(7), 515-528. doi:10.1016/j.tics.202* CC BY 4.0
Leng, G., & Feng, J. (2016). Modelling the Milk-Ejection Reflex. *Computational Neuroendocrinology, 227.*

Oxytocin Suckling Burst



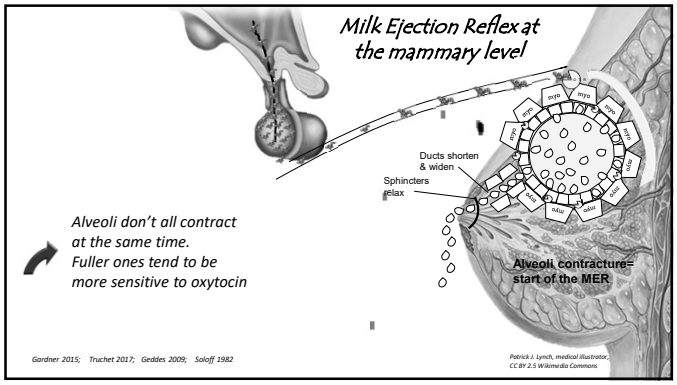
Baby plays a role, too

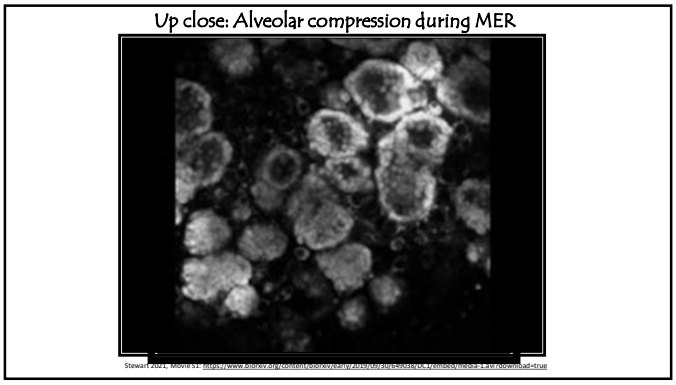
Sucking pressure
vs
Tactile sensation

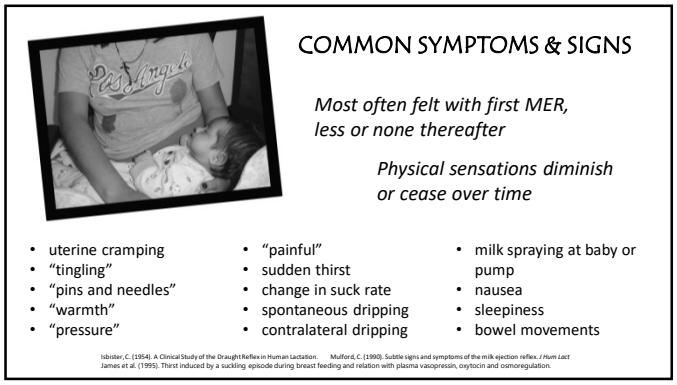
"Milk ejection bursts vary in amplitude from cell to cell and *according to the strength of the suckling…"* - Leng

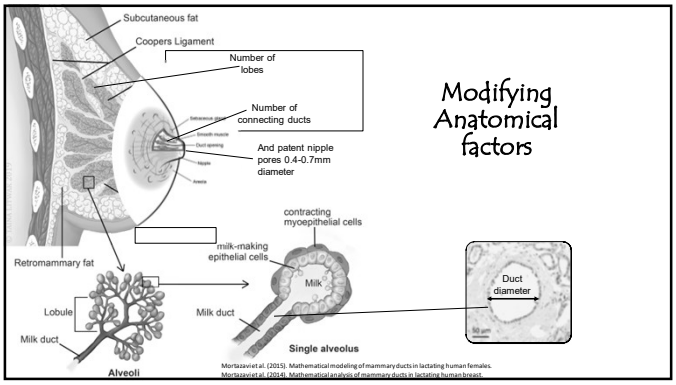
Luther et al. (1974). Suckling pressure in humans: relationship to oxytocin-reproducing reflex milk ejection.
Prieto et al. (1996). Sucking pressure and its relationship to milk transfer during breastfeeding in humans.
Leng, G., & Feng, J. (2016). Modelling the Milk-Ejection Reflex.

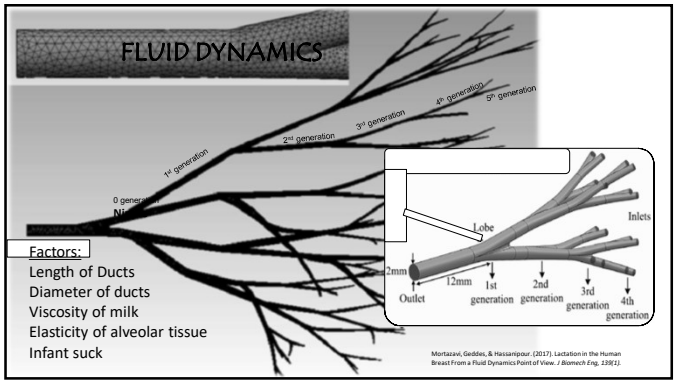
Mysterious Milk Ejection Reflex

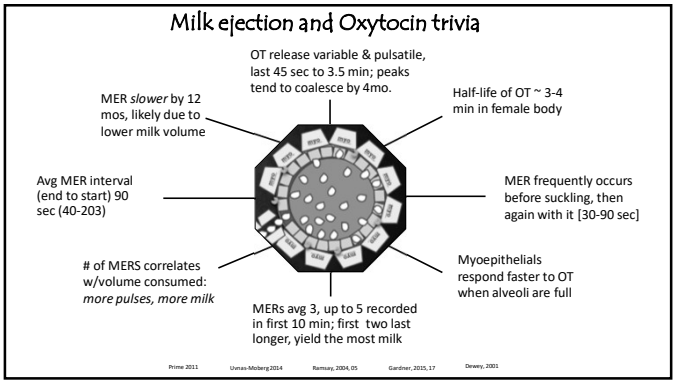










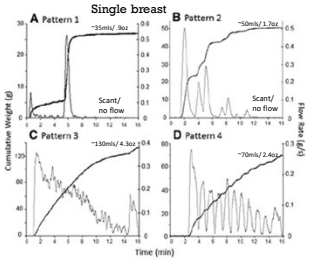


Mysterious Milk Ejection Reflex

Patterns vary between mothers/parents

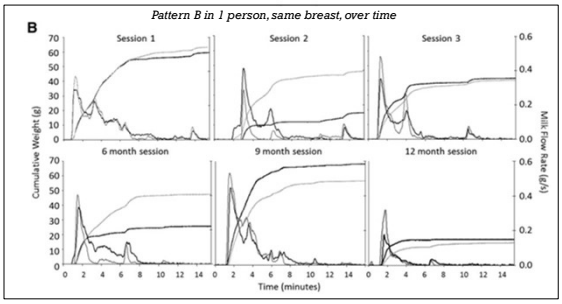
Gray line =
Flow rate in grams/second

Black line =
Cumulative milk in grams

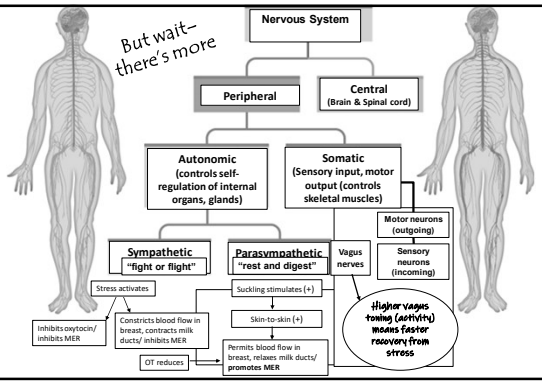


Prime et al. (2011). Comparison of the patterns of milk ejection during repeated breast expression sessions in women.

Patterns consistent *within* mothers/parents



Prime et al. (2011). Comparison of the patterns of milk ejection during repeated breast expression sessions in women.



Detailed Physiology of Milk Ejection– Lots of moving parts!

SUCKLING		EFFECT
Induces release of local peptides	⇨	Relaxes opening of milk ducts and blood vessels in skin overlying mammary glands
Induces release of OT into the circulation	⇨	*Contracts myoepithelial cells*
Induces activity in the NTS (nucleus tractus solitarius)	⇨	Decreases activity in the sympathetic nervous system
Releases OT from the PVN into the brain	⇨	Decreases activity in the sympathetic nervous system
Decreases fear and anxiety	⇨	Decreases activity in the sympathetic nervous system
All of the above	⇨ ⇨	Act in conjunction to increase skin temperature and cause MER

From Uvnas-Moberg, *Oxytocin: The Biological Guide to Motherhood.*

The unappreciated role of the Vagus/Vagal nerve (Cranial Nerve X)

"The Wandering Nerve"- longest in body

Operates outside of the spinal nerves

80-90% of fibers are afferent

Provides sensory information from the nipple along with somatosensory nerves; *many fibers also in chest*

The unappreciated role of the Vagus/Vagal nerve (Cranial Nerve X)

Large role in *parasympathetic* activity

Electrical stimulation, stroking of *ventral* side in rats caused immediate elevation of oxytocin

High vagal "tone" reflects increased resilience to stress, less anxiety, greater mental well-being

The Vagus Nerve: Why It's So Important + 8 Ways to Improve Vagal Tone - Nicola Monson

Mysterious Milk Ejection Reflex

MER Conditioning

**Happens over time

Positive vs Negative experience reinforcers

May be selective of setting: ie, baby vs pump

ROMANTIC ACTIVITY

Convery & Spatz (2009). Sexuality & breastfeeding: what do you know?

Campbell & Petersen. (1953). Milk let-down and the orgasm in the human female.

André Masson 1939)- La chute (Le viol ou l'amour de la vitesse)

THE MILK EJECTION EQUATION

Individual ductal system & nipple anatomy
+ Intact mammary nerves
+ Sufficient complement of myoepithelial cells
+ Quality of suckling or other stimulatory cues
→ Adequate oxytocin release
+ Fullness of alveoli
+ Balance of sympathetic/parasympathetic activity
→ ability of blood vessels and ducts relax and dilate
= Quality of milk ejection

+/-Conditioning

"Overactive Letdown Reflex"
What is it exactly?

What we know:

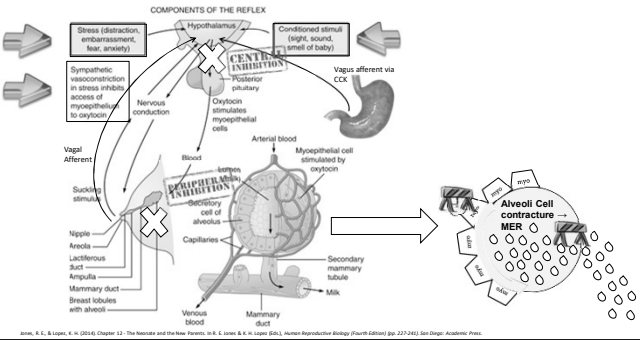
Full alveoli respond faster to oxytocin

Higher ductal pressure results in stronger flow

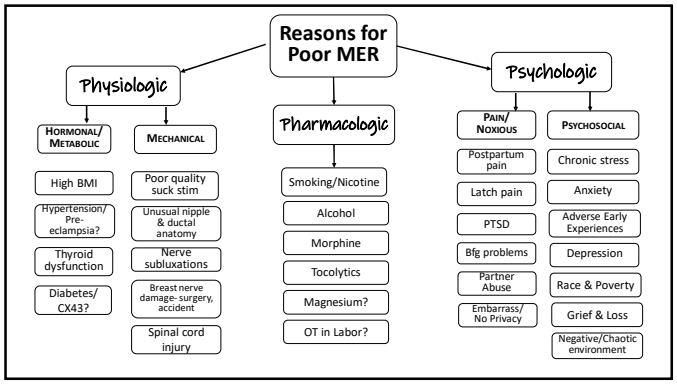
Larger duct diameter can deliver milk faster

WHEN THE MILK WON'T FLOW, WHAT ELSE SHOULD WE KNOW?

Two basic INHIBITORY problems



Mysterious Milk Ejection Reflex



How can psychological factors impair MER?

Less frequent oxytocin pulses

Frequent or chronic activation of the sympathetic nervous syst

Depression

High depressions scores associated with lower oxytocin levels before, during and after nursing (Uvnas-Moberg 2020; Stuebe 2013)

Depression and Disruptions in Oxytocin homeostasis *may have same root cause* (Stuebe 2012)

History of Adverse Childhood Experiences, Depression

→ Exposure to early life adversity associated with elevated depression levels @ 6 mos pp

→ Depression levels associated with reduced bfg duration

→ → Genetic make-up + early life experiences affects oxytocin function

Jonas et al. (2013). Genetic variation in oxytocin rs2740210 and early adversity associated with postpartum depression and breastfeeding duration.
Johnson, J. L., & Buisman-Pijlman, F. T. (2016). Adversity impacting on oxytocin and behaviour: timing matters. *Behav Pharmacol, 27*(6), 659-671.

Stress & Anxiety

Exposure to different types of stress during nursing was associated with significantly fewer oxytocin peaks

Uvnäs Moberg et al. (2020). Maternal plasma levels of oxytocin during breastfeeding-A systematic review. *PLoS One*
Ueda et al. (1994). Influence of psychological stress on suckling-induced pulsatile oxytocin release. *Obstet Gynecol*
Seng, J. S. (2010). Posttraumatic oxytocin dysregulation: is it a link among posttraumatic self disorders, posttraumatic stress disorder, and pelvic visceral dysregulation conditions in women? *J Trauma Dissociation*

Potential Mechanisms for Maternal Psychological Distress and Impaired Lactation

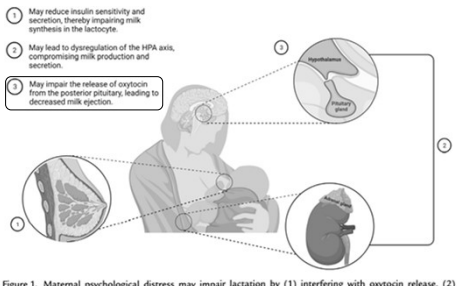


Figure 1. Maternal psychological distress may impair lactation by (1) interfering with oxytocin release, (2) reducing insulin sensitivity and secretion, or (3) causing dysregulation of the hypothalamic-pituitary-adrenocortical (HPA) axis. Figure created with BioRender.com.

Nagel et al. (2021). Maternal Psychological Distress and Lactation and Breastfeeding Outcomes: a Narrative Review. *Clinical Therapeutics.*

But wait!

Doesn't oxytocin actually *help* to counteract stress?

Mysterious Milk Ejection Reflex

But wait; doesn't oxytocin actually *help* to counteract stress?

Nagel et al. (2021). Maternal Psychological Distress and Lactation and Breastfeeding Outcomes: a Narrative Review. *Clinical Therapeutics.*
Stuebe, A. (2020). Does Breastfeeding Reduce Stress, or Does Stress Reduce Breastfeeding? *Breastfeed Med. doi:10.1089/bfm.2020.29168.ams*
Niwayama et al. (2017). Oxytocin Mediates a Calming Effect on Postpartum Mood in Primiparous Mothers. *Breastfeeding Medicine.*
Nagahashi, M. (2017). Oxytocin Mediates a Calming Effect on Postpartum Mood in Primiparous Mothers. *Breastfeeding Medicine.*

Impact of stress on Day 1

Table 2. Statistic Analysis

		Breast Milk		Total	P
		Ejected	Not Ejected		
Anxiety Level	No Anxiety	17 (77,30%)	2 (4,70%)	19 (29,20%)	0,000
	Anxiety	5 (22,70%)	41 (95,30%)	46 (70,80%)	

"Successful release of breast milk in the first 24 hrs"

**Anxiety/stress assessed with Hamilton Anxiety Rating tool*

Wahyuni & Aji. (2021). *Relationship Between Maternal Anxiety Level and Ejection of Breast Milk in the First 24 Hours of Postpartum Period.*

Pharmacologic

Alcohol & Nicotine

Central and/or peripheral via adrenaline

Lok 2018; Napierala 2018; Amir 2001

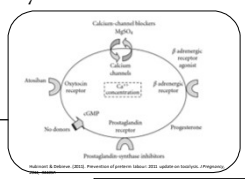
Haaastrup 2014; Cobo 1973

Doses >1g/kg inhibits MER, >2g/kg possibly completely- Cobo 1973

Photos by Marko Milivojevic & Shan Thomas/ Pixabay

Pregnancy & Labor-related

Tocolytics: *relax uterine smooth muscle*



Bjelakovic, et al. (2016). The Association of Prenatal Tocolysis and Breastfeeding Duration. *Breastfeeding Medicine.*

Lopez Gomez et al. (2018). Oxytocin Receptor Antagonist (Atosiban) in the Threat of Preterm Birth: Does It Have Any Effect on Breastfeeding in the Term Newborn? *Breastfeed Med.*

http://www.twin-pregnancy-and-beyond.com/preterm-labor-with-twins.html

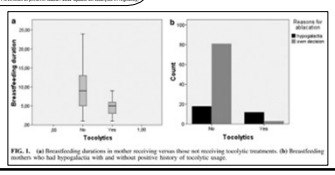
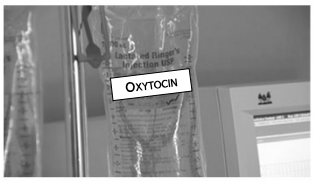


FIG. 1. (a) Breastfeeding durations in mother receiving versus those not receiving tocolytic treatments. (b) Breastfeeding mothers who had hypogalactia with and without positive history of tocolytic usage.

Oxytocin problems/MER

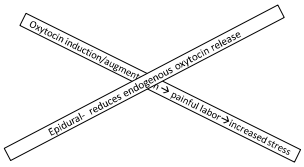


The more oxytocin infusion received during labor, the lower the natural oxytocin levels were during breastfeeding on day 2. *Jonas 2009*

→Temporarily interferes with the *Oxytocin System*, possibly via PH balance changes, feedback mechanisms *Uvnas-Moberg*

Mysterious Milk Ejection Reflex

Epidurals: Double the risk for oxytocin administration



Anything that disrupts homeostasis the first hours after birth- when imprinting is fragile and sensitive- risks disturbing the oxytocin system and the establishment of bfg

Wiklund, et al. (2009). Epidural analgesia: breast-feeding success and related factors. *Midwifery, 25(2), e31-38.*

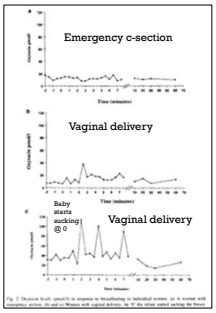
Pitocin injection for stage 3

Shortened duration of breastfeeding, more pain…

"Disrupts the finely balanced physiology of lactation"

~Infusion preferable to injection, which gives 8 hrs worth in one bolus~

Brown, A., & Jordan, S. (2014). Active Management of the Third Stage of Labor May Reduce Breastfeeding Duration Due to Pain and Physical Complications.



Nissen et al. (1996). Different patterns of oxytocin, prolactin but not cortisol release during breastfeeding in women delivered by caesarean section or by the vaginal route

Wang, Y. (2019). Time-associated effect of cesarean delivery on maternal behaviors and breastfeeding. *Clinical Surgery, 4.*

The problem of c-sections

Emergency c-section-
✓ Stress reaction activation

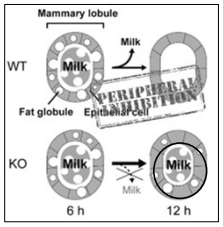
Elective/no prior labor- c-sections

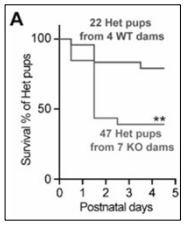
✓No OT bolus→ no fortification of the basal level→ no priming

✓NO rise in OT with skin-to-skin immediately after birth

Timing matters-
✓ *Better regulation after normal onset of labor (Wang)*

Pre-eclampsia & hypertension?





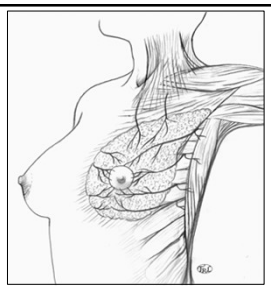
Comparable oxytocin levels and receptor expression to controls, but *contraction responses significantly lower,* possibly related to **elevated homocysteine levels**

Akahoshi et al. (2019). Preeclampsia-Like Features and Partial Lactation Failure in Mice Lacking Cystathionine gamma-Lyase-An Animal Model of Cystathioninuria.

Magnesium treatment: another layer

CLUE:
MgSO4 leads to *increased OT requirements* in order to maintain satisfactory uterine toning during c-section (Hasanein 2015)

Hasanein, R., & El-Shal, S. (2015). Does magnesium sulfate affect the oxytocin bolus requirement in pre-eclamptic patients undergoing cesarean section? *Ain-Shams Journal of Anaesthesiology, 8(1), 50.*



Any interruptions of the mammary nerve reflex arc by impingement, subluxation, surgical cuts or trauma have the potential to disrupt the milk ejection reflex

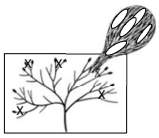
Lee 2019; Holmgren 2018

Mysterious Milk Ejection Reflex

Physiologic

HORMONAL

High BMI / diet-induced excessive weight



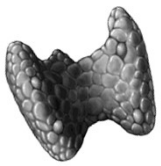
Fewer ducts, less branching, fewer myoepithelial cells
→ *Reversible w/ weight loss*

Kamikawa et al. (2009). Diet-induced obesity disrupts ductal development in the mammary glands of nonpregnant mice.

Chamberlin,et al. (2017). Obesity reversibly depletes the basal cell population and enhances mammary epithelial cell estrogen receptor alpha expression and progenitor activity.

Physiologic

HORMONAL



Thyroid function is important

Ahmed, R. (2018). Maternal hypothyroidism-milk ejections: What is the link. *ARC Journal of Nutrition and Growth*

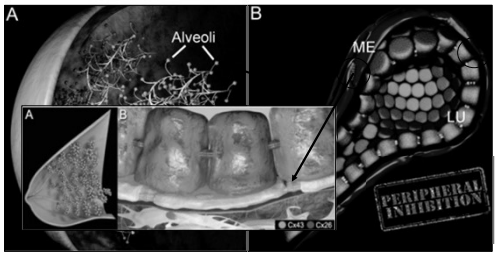
Hypothyroid rats showed had poorer lactation due to reduced circulating oxytocin postpartum and an *impaired milk ejection reflex*. (Hapon 2003)

Hyperthyroid rats showed good mammary growth & evidence of milk production but partial or complete lactation failure due to *poor oxytocin release & milk ejection* (Varas 2002)

Physiologic

HORMONAL

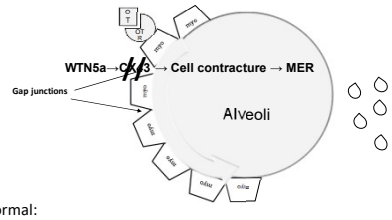
Connexin43 in the breast



Kidder & Winterhager. (2015). Physiological roles of connexins in labour and lactation. *Reproduction, 150(4), R129-136. doi:10.1530/rep-15-0134*

Stewart, Simek, & Laird. (2015). Insights into the role of connexins in mammary gland morphogenesis and function. *Reproduction*

What happened with CX43 mutant?



Normal:
Oxytocin production → oxytocin release → bind to oxytocin receptor
→ WTN5A regulation of CX43 → cell contracture → milk ejection

Plante et al. (2010). Milk secretion and ejection are impaired in the mammary gland of mice harboring a Cx43 mutant while expression and localization of tight and adherens junction proteins remain unchanged. *Biol Reprod*

CX43 animal research findings

CX43 necessary for milk ejection: "…we propose that WNT5A inhibits the response to oxytocin and prevents milk ejection through regulation of Cx43 function." Baxley, Jiang& Serra (2011)

Diabetes and thyroid hormones affect CX-43 in rat heart atria.
Mitasikova, et al (2009)

High glucose induces down-regulation of CX43…may contribute to breakdown of barrier tight junctions assoc w/diabetic retinopathy
Tien, Barrette, Chronopoulos & Roy. (2013)

Distribution of CX43 altered by risk factors such as high-fat diet
Bazzoun 2019

Mysterious Milk Ejection Reflex

CX43 animal research findings

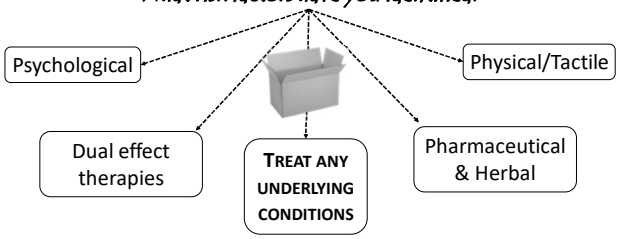
"CX43 deficiency would be expected to blunt the effect of oxytocin in inducing postnatal milk extrusion; such scenarios are not merely hypothetical, given that numerous human diseases and disabilities have been linked with mutations in connexin genes" - Kidder 2015

How can we help?

Folley, S. J. (1970). The milk-ejection reflex: a neuroendocrine theme in biology, myth and art. *Perspect Biol Med*

STRATEGIES TO IMPROVE MER

What risk factors have you identified?



Culture of success vs *Culture of struggle*

Keep the inhibition source in mind: Central, Peripheral or both?

The parent must feel safe!
Identify & tackle sources of stress

General Guidelines

for psychological-based inhibition

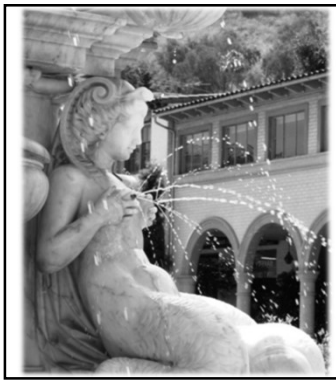
- ✓ Work towards creating an environment of safety, relaxation, and confidence
- ✓ Anti-stress techniques and practices
- ✓ Reinforce successes, positive thoughts

POSITIVE CONDITIONING OF THE LETDOWN REFLEX FOLLOWS THIS

Stuebe, A. (2020). Does Breastfeeding Reduce Stress, or Does Stress Reduce Breastfeeding?
Kendall-Tackett, K. (2019). Creating an Oxytocic Environment for New Mothers.

Reducing anxiety

Refocus on being present and away from "data" and other obsessions that add to anxiety



PHYSICAL TECHNIQUES

May directly trigger MER

May stimulate higher secretion for baseline

Mysterious Milk Ejection Reflex

Breast Compressions

Highest rates of MER coincide with greatest rises in mammary pressure-
(Alekseev 1994, 1998, 2000, 2016)

Warmth

Does not necessarily hasten MER *but*

- ✓Reduces sympathetic tone
- ✓Greater dilation of ducts
- ✓Facilitates more efficient MER:

More milk flows in less time

Kent, Geddes, Hepworth & Hartmann. (2011). Effect of warm breastshieldson breast milk pumping.
Yigit et al. (2012). Does Warming the Breasts Affect the Amount of Breastmilk Production?
Uvnas-Moberg 2014 *Oxytocin: Biological Guide to Motherhood*
Rosnani & Mediarti . (2019). *Warm Steam Therapy to Increase Breast Milk Production of Post-Partum Mothers.*

Photo by Rusty Clark- CC by 2.0

PERIPHERAL INHIBITION

Skin to skin: Decreases sympathetic activity Increases parasympathetic/calming

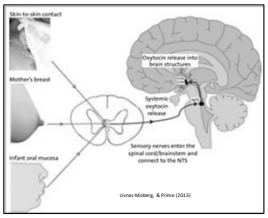
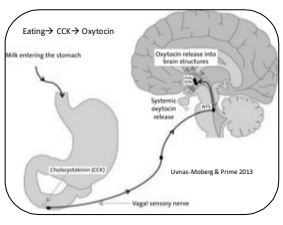


Photo by Cathy Genna

Matthiesen et al. (2001). Postpartum maternal oxytocin release by newborns: effects of infant hand massage and sucking.
Uvnas-Moberg, & Prime (2013). Oxytocin effects in mothers and infants during breastfeeding.

CENTRAL INHIBITION

Eat and drink while nursing



Feeding [oral sensory, CCK from small intestine] (Uvnäs-Moberg 2013, 2014; Stock 1988)

Chiropractic adjustment?

CENTRAL INHIBITION

Vallone, S. The Role of Subluxation and Chiropractic Care in Hypolactation. *J of Clin Chiro Ped* 2007

Mysterious Milk Ejection Reflex

CENTRAL INHIBITION

Untapped potential: Acupuncture, Acupressure, Reflexology

PERIPHERAL INHIBITION

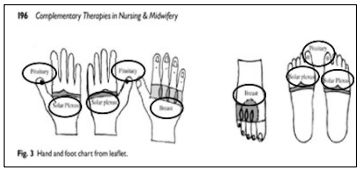
Photo by Antonika Chanel/Unsplash

Reflexology

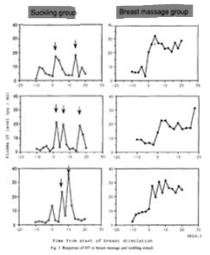
Philosophy
- Variation of TCM
- Promote relaxation, homeostasis

How it may work
- Reduce anxiety
- Stimulate OT

Indications
- High stress, fear
- Suspected retained placental tissue



Tipping & Mackereth. (2000). A concept analysis: the effect of reflexology on homeostasis to establish and maintain lactation. *Comple Therapies in Nursing and Midwifery,* Mohammadpour (2018). Investigating the Effect of Reflexology on the Breast Milk Volume of Preterm Infants' Mothers.



Response of OT to suckling and breast massage

Group	Basal level of OT (pg/ml)	Pulsatile release of OT (pulses/20 min)	ΔOT (pg/ml)
Suckling	1.90 ± 0.18	2.50 ± 0.19	2.19 ± 0.47
Breast massage	8.61 ± 0.84	0	11.06 ± 1.41

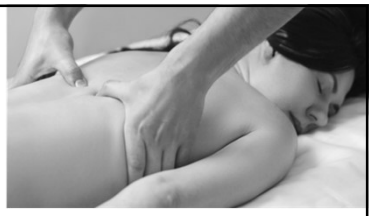
Values are means ± S.E. (n = 6)

Breast massage

Yokoyama et al. (1994). Releases of oxytocin and prolactin during breast massage and suckling in puerperal women. Machmudah 2019; Bowles 2011;

CENTRAL INHIBITION

BACK MASSAGE



Jogdeo & Bhore (2016). The Effect of Back Massage on Let Down Reflex among Mothers Who Had Undergone Cesarean Section. *International Journal of Science and Research (IJSR)*

Patel & Gedam. (2013). Effect Of Back Massage On Lactation Among Postnatal Mother. *Int'l Journal Of Medical And Research*

Maula, Widyawati & Suryono. (2019). Reducing Stress Level Cases of Hypogalactia Using Electric and Massage Stimulation Models. *E3S Web Conf*

Gustirini & Anggraini. (2020). Combination of breast care and oxytocin massage of breastfeeding mothers in infant weight gain. *Jurnal Kesehatan Prima*

PERIPHERAL INHIBITION

Any relaxing massage!

Relaxing with music

PERIPHERAL INHIBITION

CENTRAL INHIBITION

Düzgün & Özer. (2020). The effects of music ınterventıon on breast milk production in breastfeeding mothers: A systematic review and meta-analysis of randomized controlled trials. "sound evidence supporting its positive effects…"

Keith, Weaver & Vogel. (2012). The effect of music-based listening interventions on the volume, fat content, and caloric content of breast milk-produced by mothers of premature and critically ill infants. Fat increased- likely due to stronger MER

Eidelman, A. I. (2021). The Impact of Music on Breastfeeding Rates. *Breastfeed Med. "increase in oxytocin…may well result in a more robust letdown reflex"*

Sowndarya, Sanchana, Reshma, Sagayraj, B. M., & Sharma, N. (2021). Effect of Flute Music on Human Milk Production and Depression Among Lactating Mothers. *Depression down, production up*

Mysterious Milk Ejection Reflex

Feher 1989 RCT

Guided imagery, Hypnotherapy

- Mothers of preterm infants 5d pp
- 20 min relaxation & imagery audio before pumping for 1 wk
- Avg use once a day; Tx group 63% higher than controls
- Dose-response increase: mean 57ml <5x vs 112ml for ≥10x

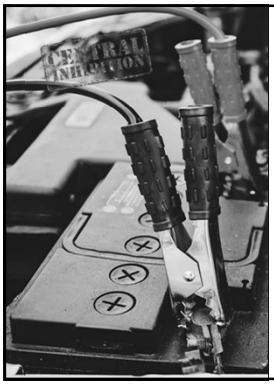
Mohd Shukri 2019 RCT- Malaysia

CENTRAL INHIBITION

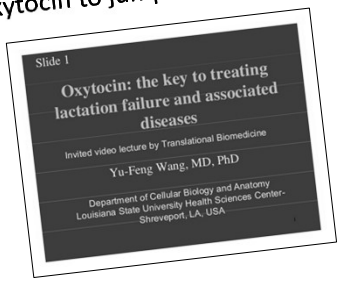
PERIPHERAL INHIBITION

- First time mothers listened to audio-guided imagery while nursing or expressing x 2-12 weeks
- Relaxation therapy: audio guided imagery protocol for bfg
- Listen while nursing or expressing for 2-12 weeks

For expressing/pumping: Harness the senses to enhance conditioning



What about exogenous oxytocin to jump start milk ?



History of oxytocin therapy for lactation

Study	Subjects	Form/Dosage	Results
Newton 1948, 1992	N=1 N=2	IM Pitocin .3cc vs saline, blinded	Pumped 10 min, injection, pump. (1) Pitocin yielded 8x more than saline.
Nickerson 1954	N=?	**.5 units IV or 2 units IM**	**"milk ejection occurs consistently"**
Newton 1958	19 bfg	**0.5ml OT in cotton, in nose**	**"produced a milk ejection reflex"**
Stewart 1961	N=165 bfg 228 no	Spray *each nostril* (2) prior As desired for engorge.	"successful assist" 72%
Huntingford 1961 RCT	N=50 bfg	Syntocinon spray, 1 nostril= 4-5 IU per dose; avg use 70 hours	No significant reduction in engorgement OT group infants less wt loss, better transfer day 7
Thornton 1961	N= 7 bfg 78 no bfg	OT nasal spray, 1 whiff *each nostril* (2)	"effect obtained excellent.. Increased milk flow that relieved pain" (engorgement)
Gonzalez 1958 36 cases, Mexico	N=36, various situations	**10 units IM x 3 10 units IM q6-8hrs, 6-8 doses**	**92% positive results, 8% doubtful**
Luhman 1963 Dbl blind RCT	N=226 bfg, in hosp	5cc/5 IU, 1 spray *each nostril* (2) prior = 10 IU?	*1st bfd @ 20 hrs.* Avg infant intake OT: 51g, Placebo 40g, significant;
Ruis 1981 RCT	N=12 1st 5d	3 units nasal spray before pumping 1st side, then 3 units before 2nd (pumped 4x/day) x 5days= 6 IU	8 primips- 3.5 fold increase 4 multips- 2-fold increase
Fewtrell 2006 RCT	N=51 premie, 1st 5 days pp	100ul (4 units) per dose before pumping	"did not significantly improve" milk volume
Xu 2006 RCT, China	N=150	"Nasal dropping" of OT "within 1-4 days after delivery"	Improved secretion

Maybe there's more to the story

Reasons for variable responses:

- ✓ Variations in anatomy → resultant airflow dynamic
- ✓ Vascularization
- ✓ Status of blood vessels
- ✓ Mode of spray application
- ✓ Galenic formulation (including presence of uptake enhancers, control release formulation)
- ✓ Amount (dosage!) and method of administration

Guastella et al. (2013). Recommendations for the standardisation of oxytocin nasal administration and guidelines for its reporting in human research. *Psychoneuroendocrinology, 38(5), 612-625.*

Mysterious Milk Ejection Reflex

Nasal Spray Sources

COMPOUNDING OXYTOCIN NASAL SPRAY:

Nasal Spray Bottle = 2 mL or 5 mL

Each 1 mL contains:

~4 IU/spray

Oxytocin: 40 USP units

Preservatives:

Chlorobutanol (0.05%), methyparaben, propylparaben

Buffers:

Citric acid, sodium phosphate, sodium chloride

Vehicles:

Glycerin, sorbitol, purified water

Dosage: 1 spray in one or both nostrils 2-3 minutes prior to nursing. No more than 2 days of usually will result in a positive outcome. –Frank Nice, BS, MS, MPA, DPA

Prescription or OTC- in some countries

Over the counter: is it the same?

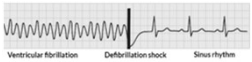
Patient handout: healthonline.washington.edu/sites/default/files/record_pdfs/09-Oxytocin_Nasal_Spray_8_09.pdf

Pro's and Con's

Yes — ? — No

- ✓Provides instant oxytocin to the system
- ✓Might be the only viable option if there is a physical/hormonal block to oxytocin release
- ✓Does not address underlying psychological or pain contributions to MER problem
- ✓No recent clinical trials for safety and efficacy
- ✓Body may respond less over time (tachyphylaxis)
- ✓Parent may become emotionally dependent on it

NEW INSIGHTS: INTRANASAL OXYTOCIN TO RESTORE NORMAL RHYTHM



Strategy: activate mitral cells in the olfactory bulb to activate oxytocin neurons

Only a small amount needed: ~1IU (spray each nostril 5 min prior to first 2 nursing sessions, x 7 days).

Could dilute a compounded version with water 1:4 – *study in process to refine this*

Liu . . . Wang, Y. F. (2019). Effects of Intranasal Oxytocin on Pup Deprivation-Evoked Aberrant Maternal Behavior and Hypogalactia in Rat Dams and the Underlying Mechanisms. *Front Neurosci, 13, 122.*

Wang, Tong, Wang, Ping;. (2019). *Dynamic activity of the oxytocin-secreting system following cesarean delivery and its modulation by intranasal oxytocin. Paper presented at the BIT's 7th International Congress of Obstetrics and Gynaicology 2019: Stream 4: Obstetric Medicine, Chengdu, China.*

Another paradigm: Treat Perinatal Mood and Anxiety Disorders (PMADs) for stress-related lactation dysfunction

Overcoming spinal cord injury challenges

Psychogenic & pharmacologic induction of the let-down reflex can facilitate breastfeeding by tetraplegic women- study of 3 cases *-Cowley 2005*

Creative compensations

Liu & Krassioukov (2014). Response to 'Breastfeeding by women with tetraplegia: some evidence for optimism'. *Spinal Cord*

Herbals/teas

PERIPHERAL INHIBITION — CENTRAL INHIBITION

RELAXING
Chamomile
Lemon balm
Vervain
Milky oat pods

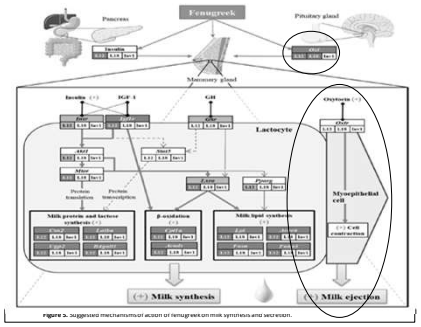
HOMEOPATHICS/REMEDIES
Lactuca virosa (wild lettuce)
Shizandra
Rescue Remedy
Lact humanum

OXYTOCICS
Fenugreek
Fennel
Blessed thistle
Anise
Dill
Red raspberry leaf (short term)
Black cohosh

Good Resources: *Kingsbury 2012; Marasco & West 2020; Patil 2017; Herbal Data Base by Luna Lactation*

Mysterious Milk Ejection Reflex

Fenugreek mechanism study



Green arrows denote positive activation, bold and thin arrows represent main and secondary fenugreek action pathways, respectively. Dotted lines represent hypothetical pathway of action. Dark and light green boxes represent significant or trend increase respectively of gene expression or plasma concentration overall for upper box and at each lactation period for lower boxes. White boxes depict the lack of modulation by fenugreek.

"fenugreek may increase milk ejection by activation of oxytocin secretion"

Sevrin et al. (2020). Fenugreek Stimulates the Expression of Genes Involved in Milk Synthesis and Milk Flow through Modulation of Insulin/GH/IGF-1 Axis and Oxytocin Secretion. *Genes (Basel)*

Electrical stimulation? Research needed

CENTRAL INHIBITION

Precedent 1: electrical stimulation of sciatic and vagal nerve increased plasma oxytocin levels in rats (Stock & Uvnas-Moberg, 1988)

Precedent 2: historical case studies (Routh 1879)

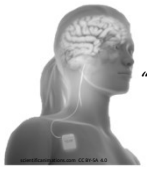
Routh, C. H. F. (1879). *Infant feeding and its influence on life, or, The causes and prevention of infant mortality*. William Wood & Co.

Reducing stress level cases of hypogalactia using electric and massage stimulation models

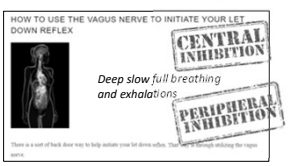
- ✓ Novel dual approach used massage and electrical stimulation on various acupuncture points for lactation
- ✓ Goal: reduce stress and thereby improve milk *production*
- ✓ *Focused on prolactin but likely worked strongly on oxytocin and milk ejection side*

Maula et al. (2019). Reducing Stress Level Cases of Hypogalactia Using Electric and Massage Stimulation Models.

Vagus nerve stimulation?



"Mothers with longer breastfeeding duration displayed… higher vagal control…indicating a calmer & regulated state." Lan 2022



Clancy et al. (2014). Non-invasive vagus nerve stimulation in healthy humans reduces sympathetic nerve activity.
Grazzi et al. (2016). Non-invasive Vagus Nerve Stimulation (nVNS) as mini-prophylaxis for menstrual related migraine

Non-Invasive Nerve Stimulation Boosts Learning of Foreign Language Sounds | UC San Francisco (ucsf.edu)
Lan, Q., Li, H., Wang, L., & Chang, S. (2022). Breastfeeding duration and vagal regulation of infants and mothers. *Early Hum Dev*

A lesson from traditional cultures