

Intrapartum administration of synthetic oxytocin and downstream effects on breastfeeding: elucidating physiologic pathways

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Research Article

Intrapartum Administration of Synthetic Oxytocin and Downstream Effects on Breastfeeding: Elucidating Physiologic Pathways

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Abstract

The importance of breastfeeding as a public health priority has increased as new research reinforces the health benefits to both mother and nursing, even continuing years after weaning. However, many women do not nurse as long as they intend. Birth practices, such as labor medications and the routine separation of mother and baby are two of the several intrapartum influences on breastfeeding outcomes. This paper seeks to elucidate the physiologic mechanisms affecting breastfeeding outcomes of the commonly administered intrapartum drug, synthetic oxytocin.

A modified ascending, link tracing methodology was used to identify studies

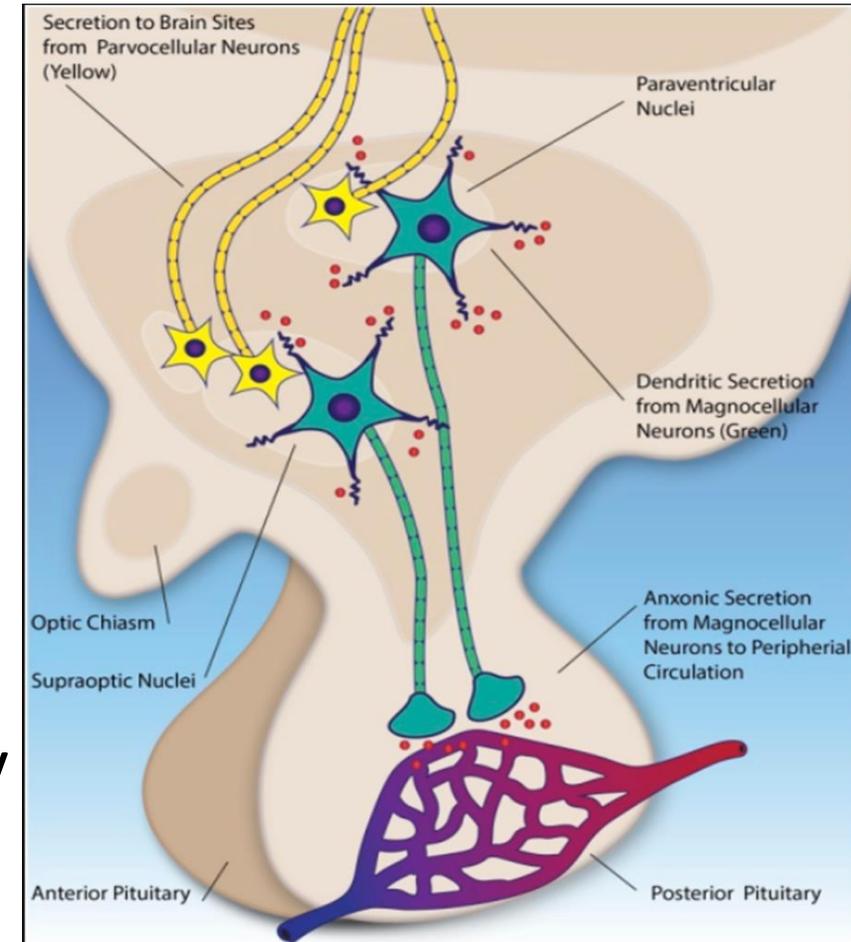


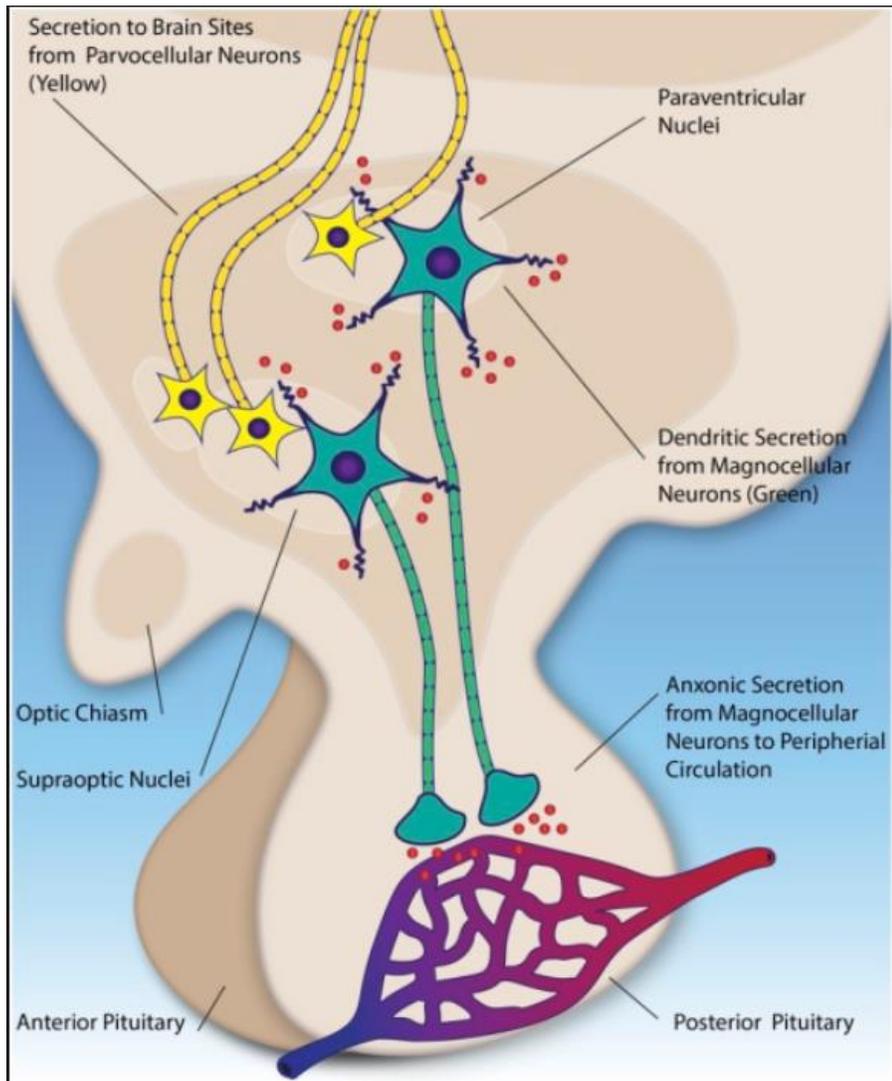
Oxytocin (OT) is from the Greek meaning “swift birth”

has several functions beyond the obvious one: the mediation of uterine contractions.

Oxytocin receptors (OTRs) are found on the smooth muscle cells in the uterus and the breast, where they work to contract the uterine muscles during labor and birth and the myoepithelial cells in the breast to eject milk.

Oxytocin is predominantly produced in the hypothalamus, stored and secreted in a periodic bolus fashion or pulses from the posterior pituitary and then into the blood stream.





When OT is secreted into the blood it also pulses further into the brain.

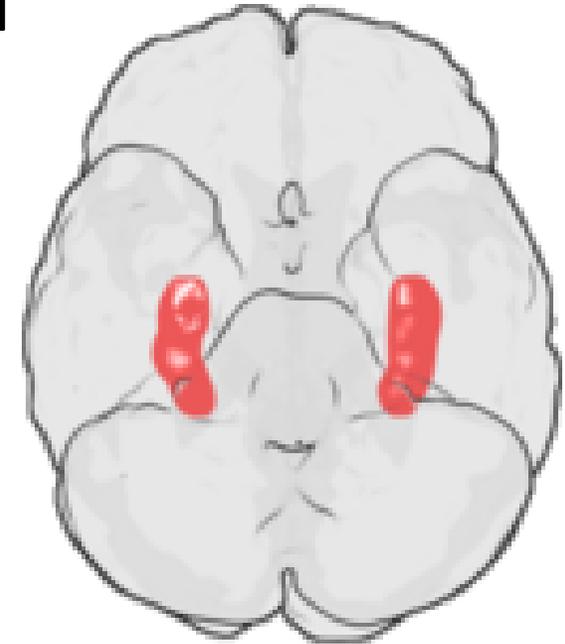
The **central nervous system**, including the spinal cord and the brain, have **OTRs**; the hippocampal clusters of OTRs in the brain are thought to be integral in facilitating social learning, memory consolidation and bonding.



The **hippocampus** is a part of the brain located inside the temporal lobe (humans have two hippocampi, one in each side of the brain).

It forms a part of the limbic system and plays a part in social memory and navigation.

The name derives from its curved shape, which supposedly resembles that of a **seahorse** (Greek: *hippocampus*).

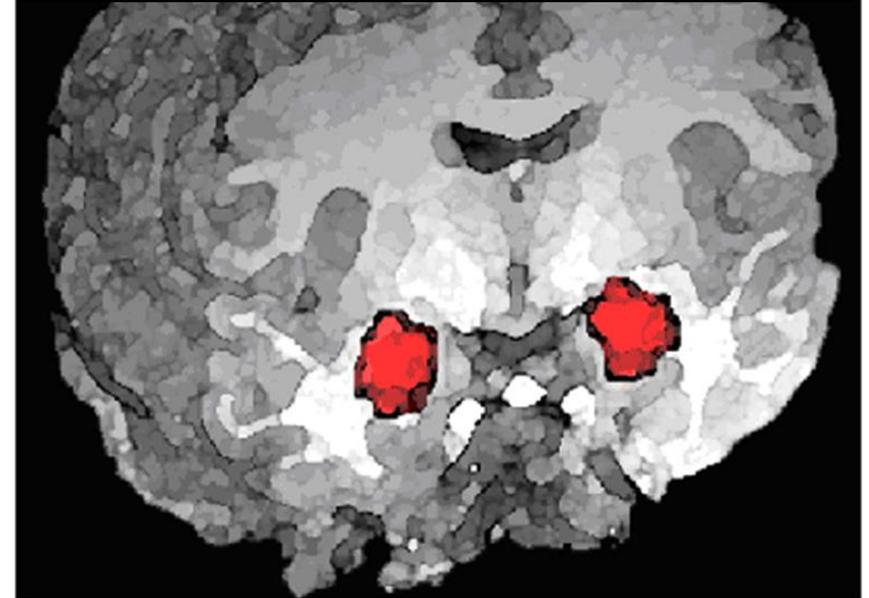


During pregnancy and lactation there are changes in the hippocampus.....

Social memory and the ability to navigate (**finding short cuts, multi-tasking**) seem to be especially positively affected.

Also, response to **fear**

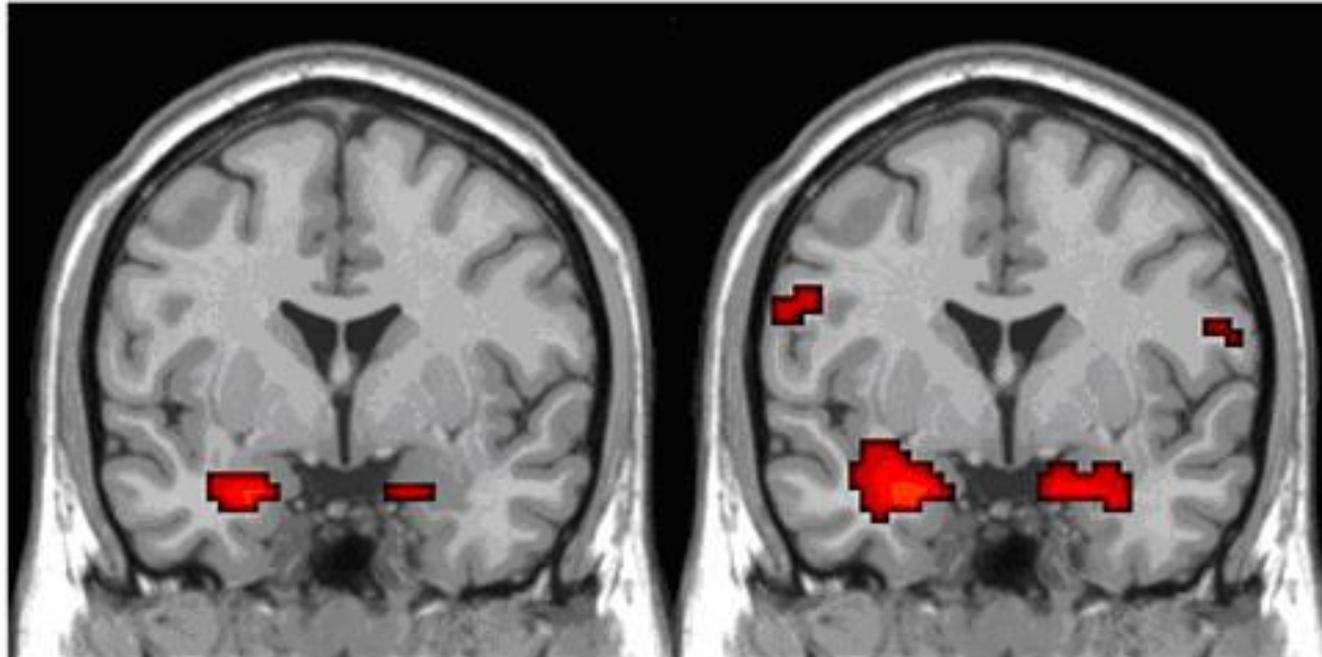
Frightened without oxytocin



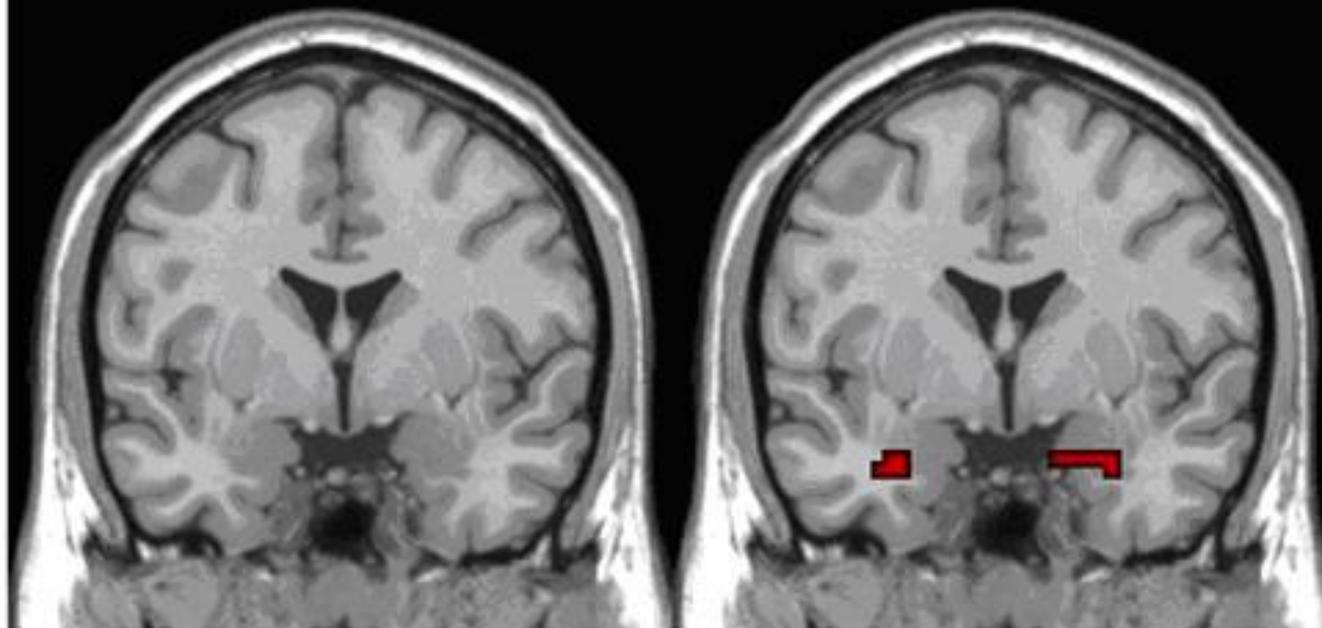
faces

scenes

Placebo



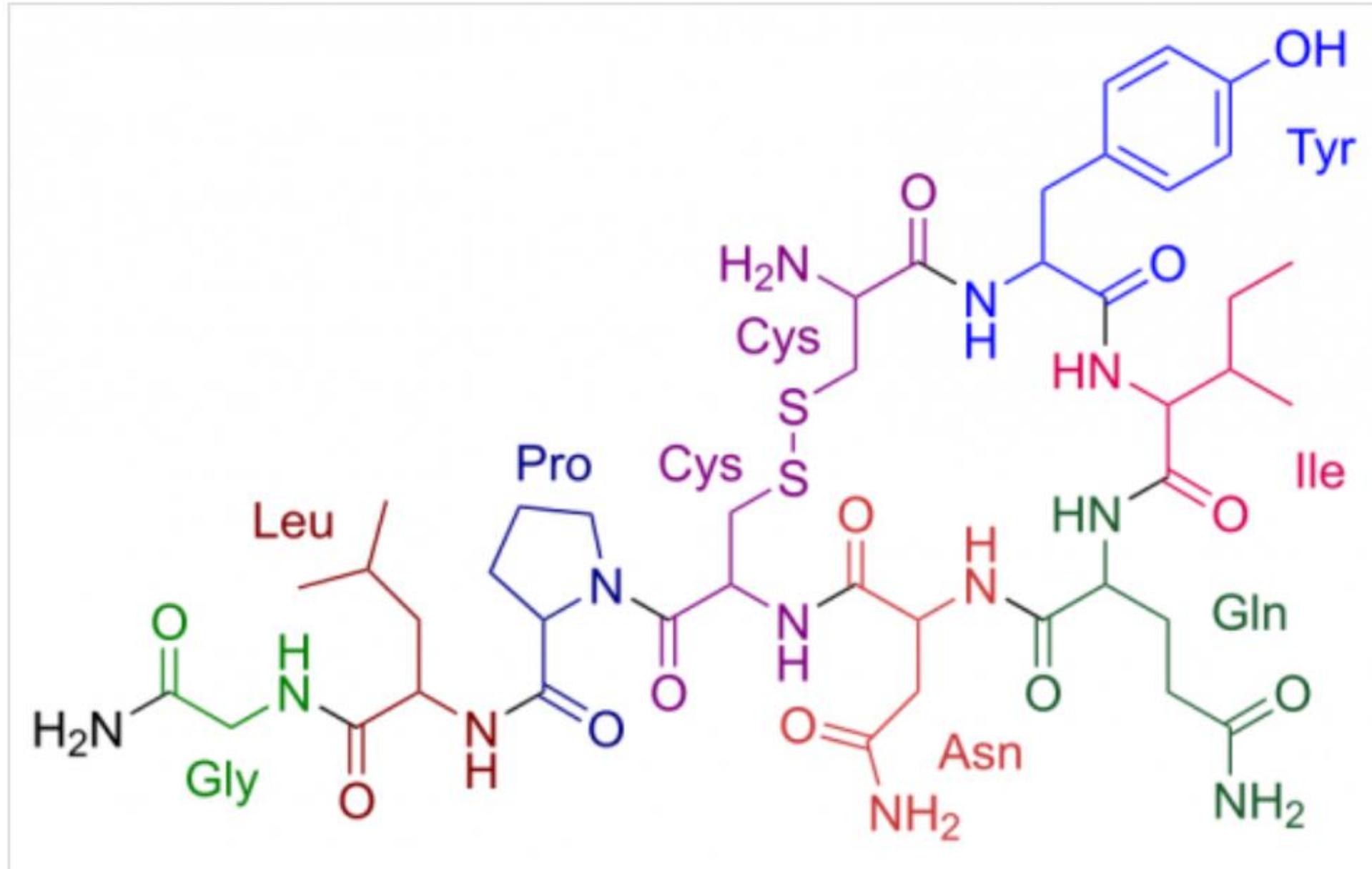
Oxytocin



Men and lactating women react to stress differently



This is OT ... This is also SynOT



SynOT (Pitocin or Syntocinon)

is a manufactured product **identical** to endogenous oxytocin (OT).
was synthesized by Vincent du Vigneaud, who won the Nobel Prize in chemistry in 1955 in part for this work.
Sandoz Pharmaceuticals made the commercial product available.

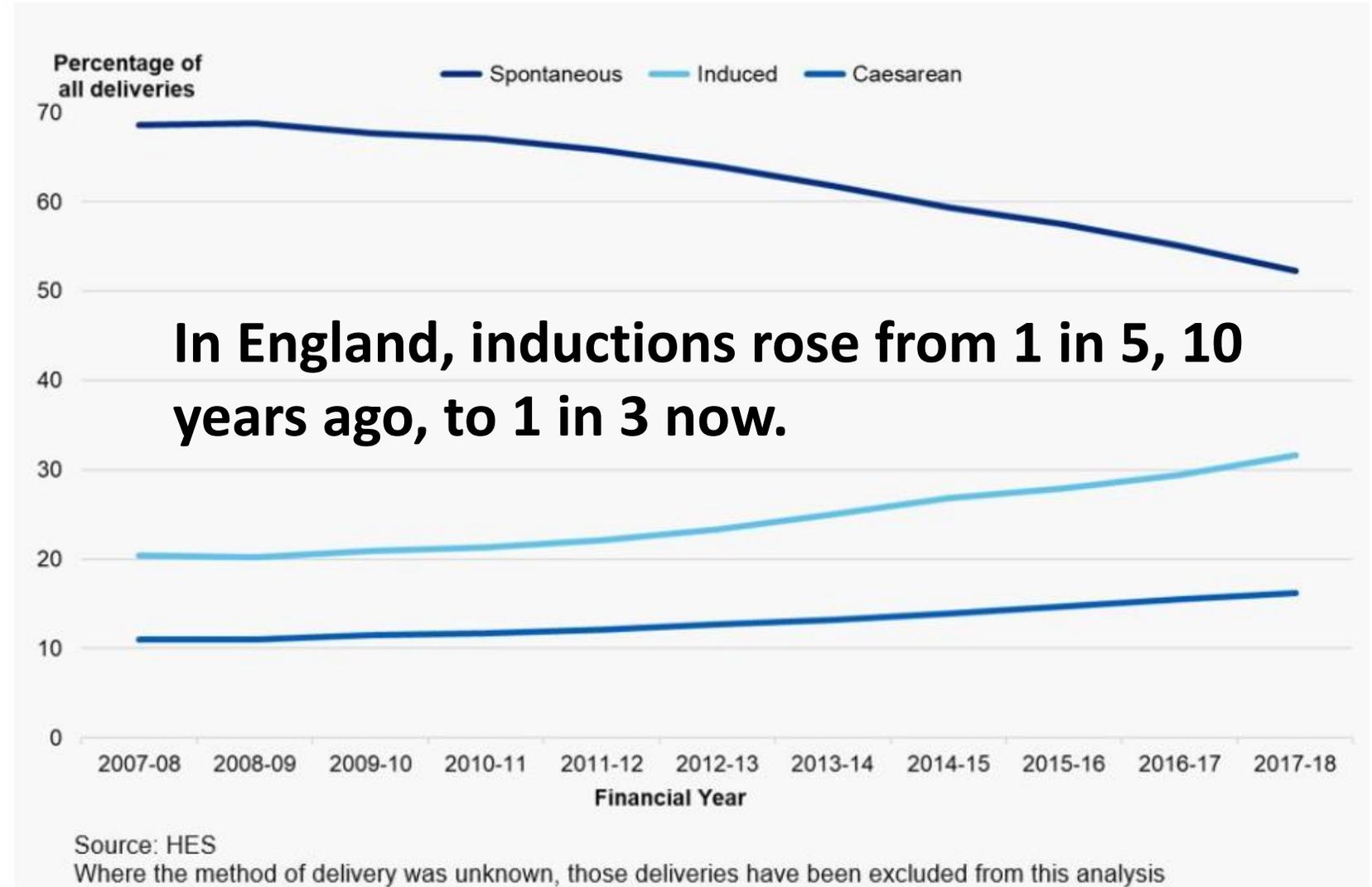


Research studies using synOT were published in the following years and the drug became integrated into clinical practice as an induction and augmentation agent in labor (via continuous IV infusion), to reduce blood loss after birth (via IM injection), and to stimulate milk ejection (as a nasal spray).



Over time, synOT has come to be understood not just as a drug to be administered in cases of obstetric crisis, but also as an elective management tool, useful in conforming women's bodies to a pre-determined time line.¹²

- The proportion of deliveries where labour was induced has increased from 20.4 per cent in 2007-08 to 32.6 per cent in 2017-18



Labor induction rates in the United States

have been increasing since the early 1990s to 23.8% nationally.

However in a study of 19 U.S. hospitals, the induction rate was reported to be **42.9% for first time mothers and 31.8% for multiparas.**

The rate of synOT used for **augmentation is estimated to be between 50 and 60%** with highest use in conjunction of an epidural for pain management.

In addition, women in the United States are to be administered an **IM injection of synOT after** the baby is born if they do not have an IV in place, suggesting that there is a **near universal exposure** to synOT for birthing women in the United States.



WHO recommendations for **Induction of labour**



Context	Recommendation	Quality of evidence	Strength
When induction of labour may be appropriate	1. Induction of labour is recommended for women who are known with certainty to have reached 41 weeks (>40 weeks + 7 days) of gestation.	Low	Weak
	2. Induction of labour is not recommended in women with an uncomplicated pregnancy at gestational age less than 41 weeks.	Low	Weak
	3. If gestational diabetes is the only abnormality, induction of labour before 41 weeks of gestation is not recommended.	Very low	Weak
	4. Induction of labour at term is not recommended for suspected fetal macrosomia.	Low	Weak
	5. Induction of labour is recommended for women with prelabour rupture of membranes at term.	High	Strong
	6. For induction of labour in women with an uncomplicated twin pregnancy at or near term, no recommendation was made as there was insufficient evidence to issue a recommendation.	–	–
Methods of induction of labour	7. If prostaglandins are not available, intravenous oxytocin alone should be used for induction of labour. Amniotomy alone is not recommended for induction of labour.	Moderate	Weak

WHO recommendations for augmentation of labour

Summary list of WHO recommendations for augmentation of labour

This table contains specific recommendations as formulated and approved by participants at the WHO technical consultation on augmentation of labour.

Context	Recommendation	Quality of evidence	Strength of recommendation
Diagnosis of delay in the first stage of labour	1. Active phase partograph with a four-hour action line is recommended for monitoring the progress of labour.	Very low	Strong
	2. Digital vaginal examination at intervals of four hours is recommended for routine assessment and identification of delay in active labour.	Very low	Weak
Prevention of delay in the first stage of labour	3. A package of care for active management of labour for prevention of delay in labour is not recommended.	Low	Weak
	4. The use of early amniotomy with early oxytocin augmentation for prevention of delay in labour is not recommended.	Very low	Weak
	5. The use of oxytocin for prevention of delay in labour in women receiving epidural analgesia is not recommended.	Low	Weak

Safety of synOT

The Institute for Safe Medication Practices (ISMP) has listed **IV oxytocin (synOT) as one of the 12 medications most implicated in harmful errors in acute care hospitals.**

‘According to a survey of liability cases, **approximately 50% of paid liability claims affecting maternity services involve alleged misuse of oxytocin.**’

In addition, synOT has received a **“Black Box” or “Boxed” warning** (the strongest caution the United States Food and Drug Administration (FDA) can give) which reads **‘Not for Elective Labor Induction: not indicated for elective labor induction since inadequate data to evaluate benefit vs. risk; elective induction defined as labor initiation without medical indications.’**



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In a prior study, we saw the correlation between dose of synOT administered and neonate self attaching and suckling while skin-to-skin in the first hour.

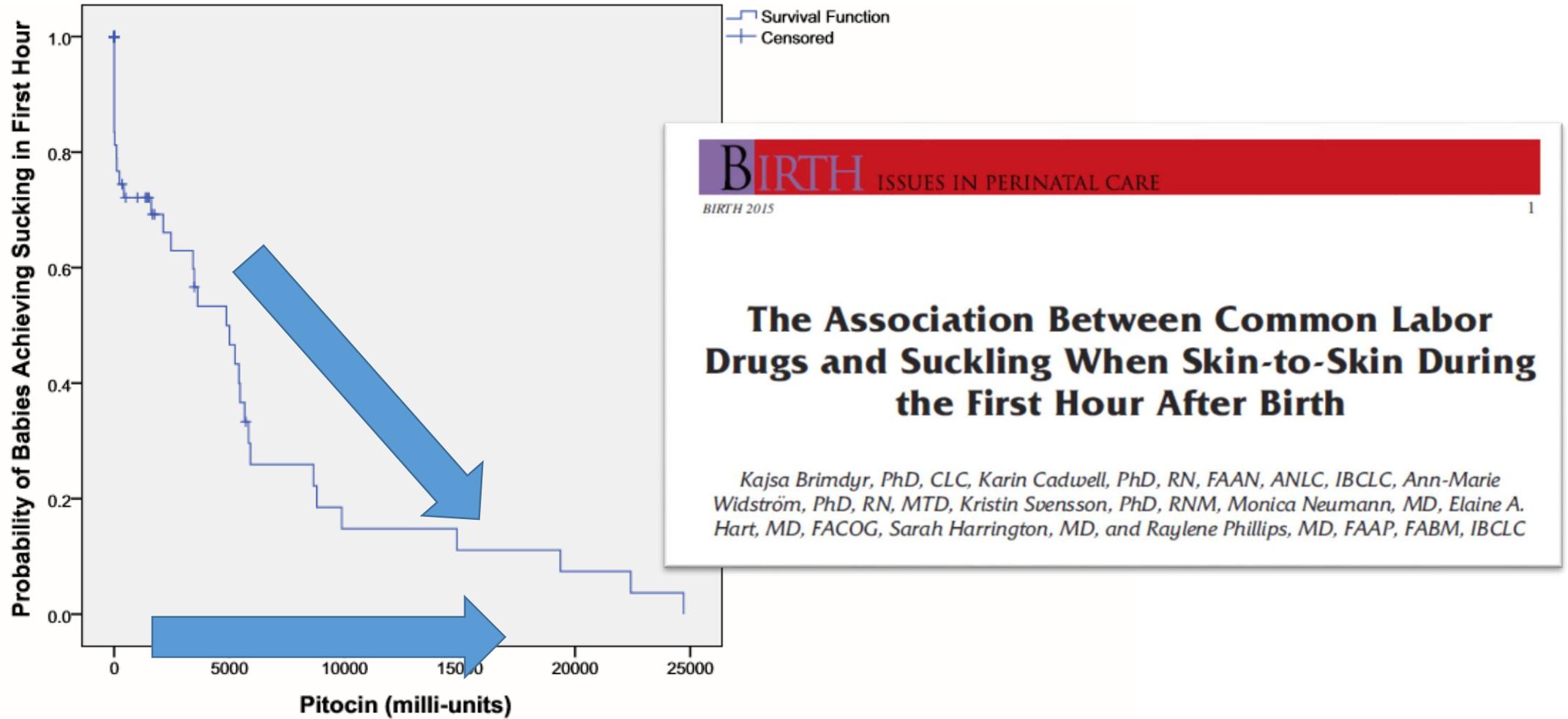
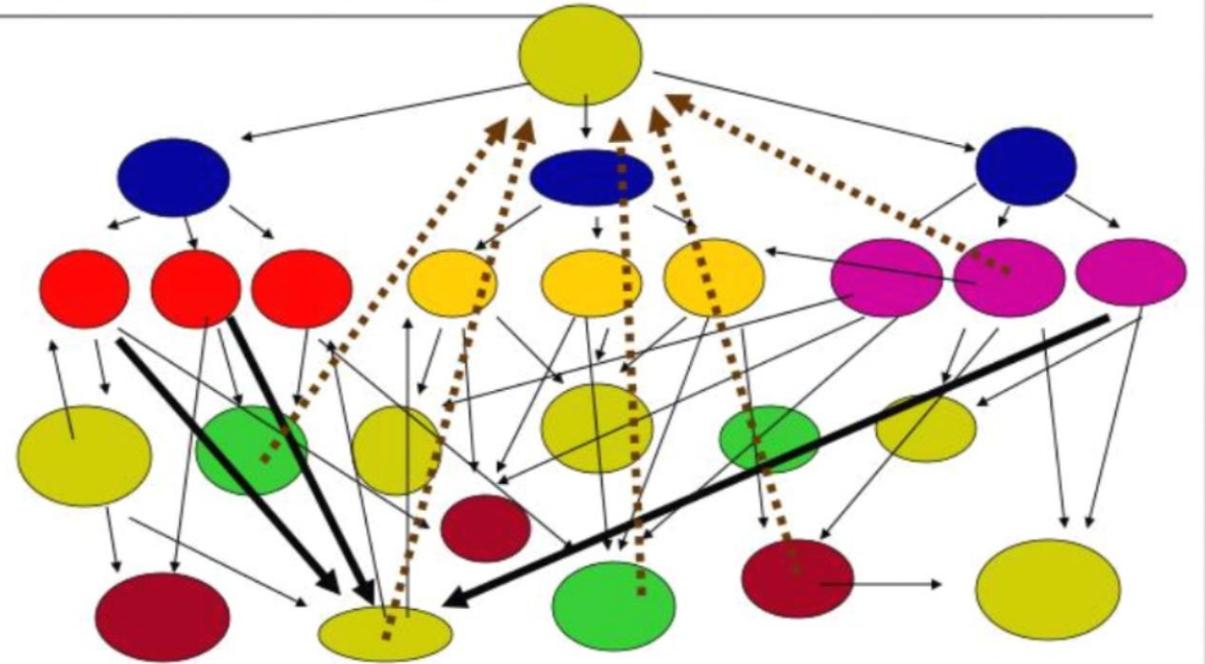


Fig. 6. Kaplan–Meier curve comparing the amount of synOT to the progression of suckling by the baby during the first hour, LLUMC, 2012. Note: The majority of these dyads also had exposure to fentanyl.

And we wondered about the possible physiologic mechanisms that could influence this phenomenon as well as any other downstream effects

We use the **link tracing method** (also called snowball sampling), a research method usually used in Sociologic or Public Health research in order to identify hard to find populations

Snowball Sampling



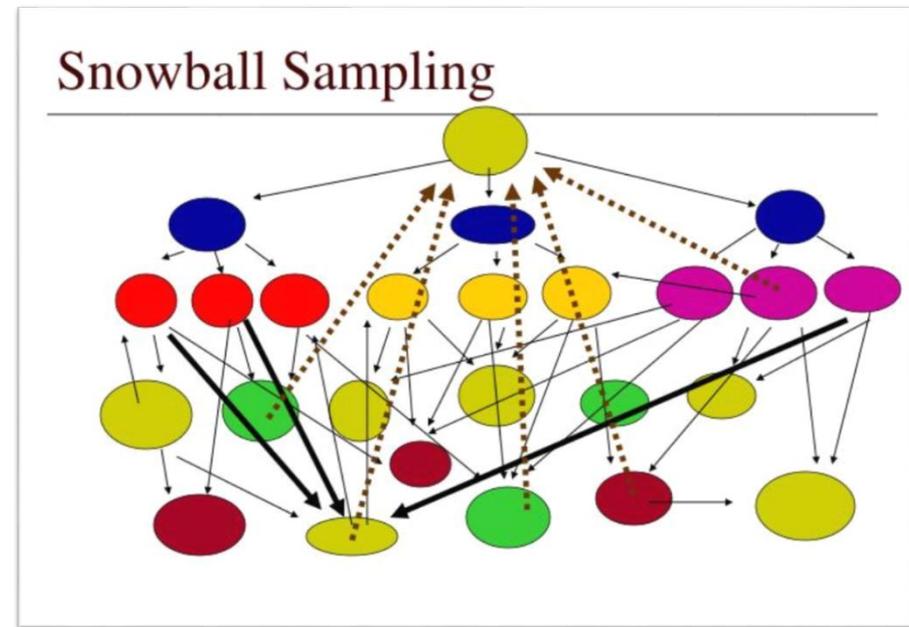
Beginning with one citation used in the prior study,

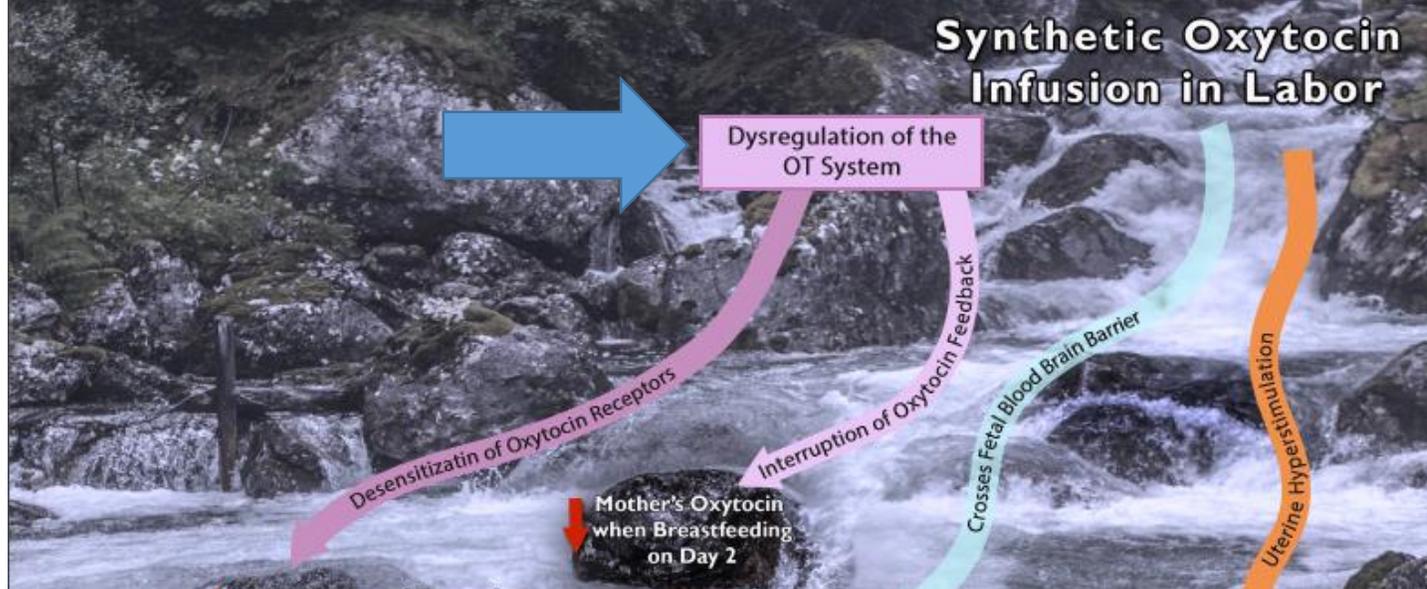
relevant studies were linked by locating any cited references that could refer to physiologic pathways that might be affected by synOT or the physiologic relationship of synOT to breastfeeding.

The references cited in the new article were accessed to continue the link tracing.

The PubMed feature “similar articles” for each article was also used to access the maximum possible number of articles.

This referral linking process was continued until reaching saturation, when no new physiologic pathways with downstream breastfeeding implications were identified.





We found 3 physiologic explanations related to breastfeeding outcomes:

1. synOT causes dysregulation of the mother's OT system
2. synOT crosses the infant's blood brain barrier
3. synOT can cause uterine hyperstimulation



Dysregulation of the mother's OT system

can be understood to be similar to the physiologic process of insulin dysregulation.

The administration of exogenous OT, synOT, may inhibit the action of the maternal endogenous OT in the immediate postpartum through desensitization of OT receptors, first via negative feedback mechanisms that inhibits the release of the mother's own OT

and subsequently a greater production of endogenous circulating OT, possibly due to receptor site damage or the resetting of the OT system upwards to a higher level.



Jonas and colleagues demonstrated that as soon as the second day postpartum, untoward effects of synOT infusion during labor could be measured in new mothers during a breastfeeding.

Jonas K, Johansson LM, Nissen E, Ejdebäck M, Ransjö-Arvidson AB, Uvnäs-Moberg K. Effects of intrapartum oxytocin administration and epidural analgesia on the concentration of plasma oxytocin and prolactin, in response to suckling during the second day postpartum. *Breastfeed Med Off J Acad Breastfeed Med.* 2009 Jun;4(2):71–82.

The results were inversely dose dependent - **the mothers who had received the highest doses of synOT released the lowest amount of their own, endogenous, OT.**

It is suspected that a negative feedback mechanism had been activated that inhibited the release of mothers' own OT at this early time postpartum.



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The desensitization of OT receptors in labor by synOT may be responsible for **longer-term effects as well.**

When studied at two and three months postpartum, **the amount of synOT the mother had received in labor was positively correlated with her own plasma OT levels.** Gu V, Feeley N, Gold I, Hayton B, Robins S, Mackinnon A, et al. Intrapartum Synthetic Oxytocin and Its Effects on Maternal Well-Being at 2 Months Postpartum. Birth. 2016 Mar;43(1):28–35.

This may be due to a physiologic phenomenon similar to insulin resistance in diabetes or that the ‘exposure to synOT “resets” the natural oxytocin system to a higher level to better respond to the body’s needs.

Breastfeeding outcomes were **negatively affected. The mothers with the highest amounts of OT transferred the least amount of milk!**



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Very high or very low levels of peripheral OT have been shown to be associated with symptoms of post-traumatic stress syndrome, depression and anxiety.

The finding that women who had been administered intrapartum synOT compared to mothers who had not been exposed had a more than 30% increased relative risk of depressive and anxiety disorders in the first year postpartum is concerning.

Kroll-Desrosiers AR, Nephew BC, Babb JA, Guilarte-Walker Y, Moore Simas TA, Deligiannidis KM. Association of peripartum synthetic oxytocin administration and depressive and anxiety disorders within the first postpartum year: K ROLL-DESROSIERS ET AL . *Depress Anxiety*. 2017 Feb;34(2):137–46.

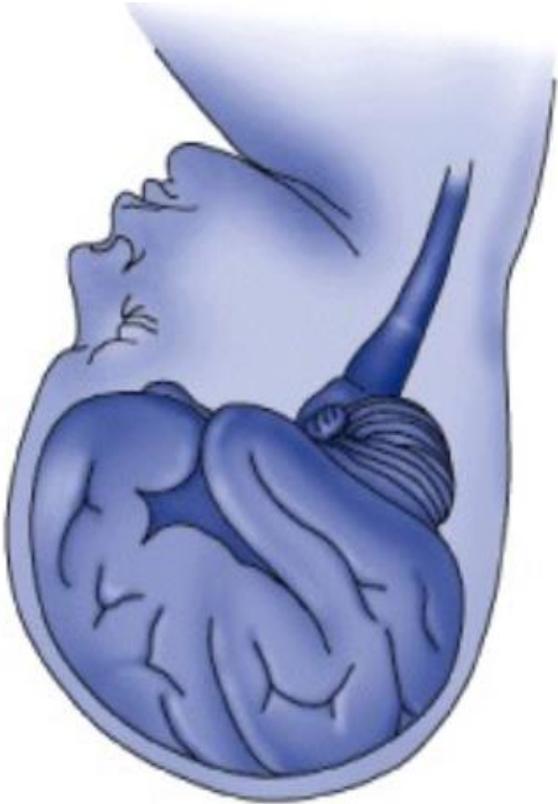
Gu and colleagues found similar results already at 2 months postpartum. The mothers in the Gu study also had an increased risk of symptoms of somatization in the mothers who had been exposed to synOT.



Synthetic Oxytocin Infusion in Labor



SynOT Crossing the Fetal Blood Brain Barrier



synOT administered to the laboring woman is thought to **cross the placenta and the not-completely-mature fetal blood-brain barrier during labor** and **desensitize the infant's central nervous system OTRs negatively affecting the function of the infant's nervous system OTRs.**

Studies of the expression of newborn neurobehavioral **pre-feeding cues and reflexes demonstrate the sensitivity to synOT** of the exposure of the baby during labor.



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Bell and colleagues found the babies who had been **exposed to synOT** were 11.5 times more likely to perform in the **lowest to medium levels of pre-feeding organization** compared to the babies of mothers who were not exposed. The babies of mothers who were not exposed were more likely to perform at the high level.

Bell AF, White-Traut R, Rankin K. Fetal exposure to synthetic oxytocin and the relationship with prefeeding cues within one hour postbirth. *Early Hum Dev.* 2013 Mar;89(3):137–43.

Other researchers studying newborn's primitive neonatal reflexes (PNRs) identified the **inhibition of several of the reflexes** including **all of those associated with breastfeeding (the rhythmic reflexes – suck, jaw jerk and swallowing)** as **significantly lower in the exposed group**. The results were not dose dependent.



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Newborns who were skin-to-skin with their mothers in the first hour after birth had a different experience of whether or not they suckled in the first hour according to the common meds the mothers had been administered.

Now we have analyzed the videotapes of the behavior of studied babies in relation to each of Widström's 9 Stages. This study is currently in peer review.

Six of the nine stages focus on the activities of the newborn during the first hour – propelling towards the ultimate goal of survival, suckling. The birth cry (stage 1) inflates the babies' lungs with the initial survival activity of breathing.



Activity (stage 3), crawling (stage 4) and familiarization (stage 7) are the locomotive/location aspects of the behavior driving towards suckling (stage 8).

What then is the purpose of the resting (stage 5) which occurs, not in order as the others, but interspersed throughout the first hour?



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After eliminating the confounder of epidural medications, the **synOT exposed babies had 10% fewer minutes of rest.**

Newborns exposed to neither synOT nor fentanyl epidural rested for a mean of 17:17.32 and a median (25th – 75th quartile) of 15:53.90 during the first hour after birth.

Newborns exposed to synOT (but not fentanyl epidural) rested for a shorter mean of 10:42.41 and a median of 11:22.85 during the first hour after birth.

Analysis of the means with the Mann-Whitney Test gives, **a significant difference (p=.031).**



Researchers have now described **a significant correlation between initial encoding and the subsequent period of awake rest.**

Awake rest is **an opportunity for the baby to consolidate the important learning of the first hour**, and the memories acquired through smelling, tasting and feeling the mother on the way to suckling, and continue this in memory consolidation stage 9, sleep, which has already been established by considerable research.



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Memory consolidation is thought to depend upon “a temporally evolving process that involves interactions between the hippocampus and neocortex.

While **the hippocampus is critical for the initial creation of an episodic memory trace**, it is hypothesized that long-term storage results from the restructuring of information across hippocampal-neocortical networks over time, resulting in a distributed memory representation.”

This consolidation ‘is thought to be mediated by ‘replay’” as baby nurses multiple times.



The more activity in the hippocampus and cortical regions of the brain at resting time, the stronger the memory when tested later.

With this recent addition of rest to sleep as a state where learning (through consolidating and strengthening memories) is solidified, **we hypothesized that the function of rest in the first hour is to consolidate the memories of the mother's face, her smell, touch, and sound.**

We wondered about the effect of synOT administration to the mother in labor on the infants rest while skin to skin in the first hour since there are clusters of OTRs in hippocampus, the site of memory consolidation.



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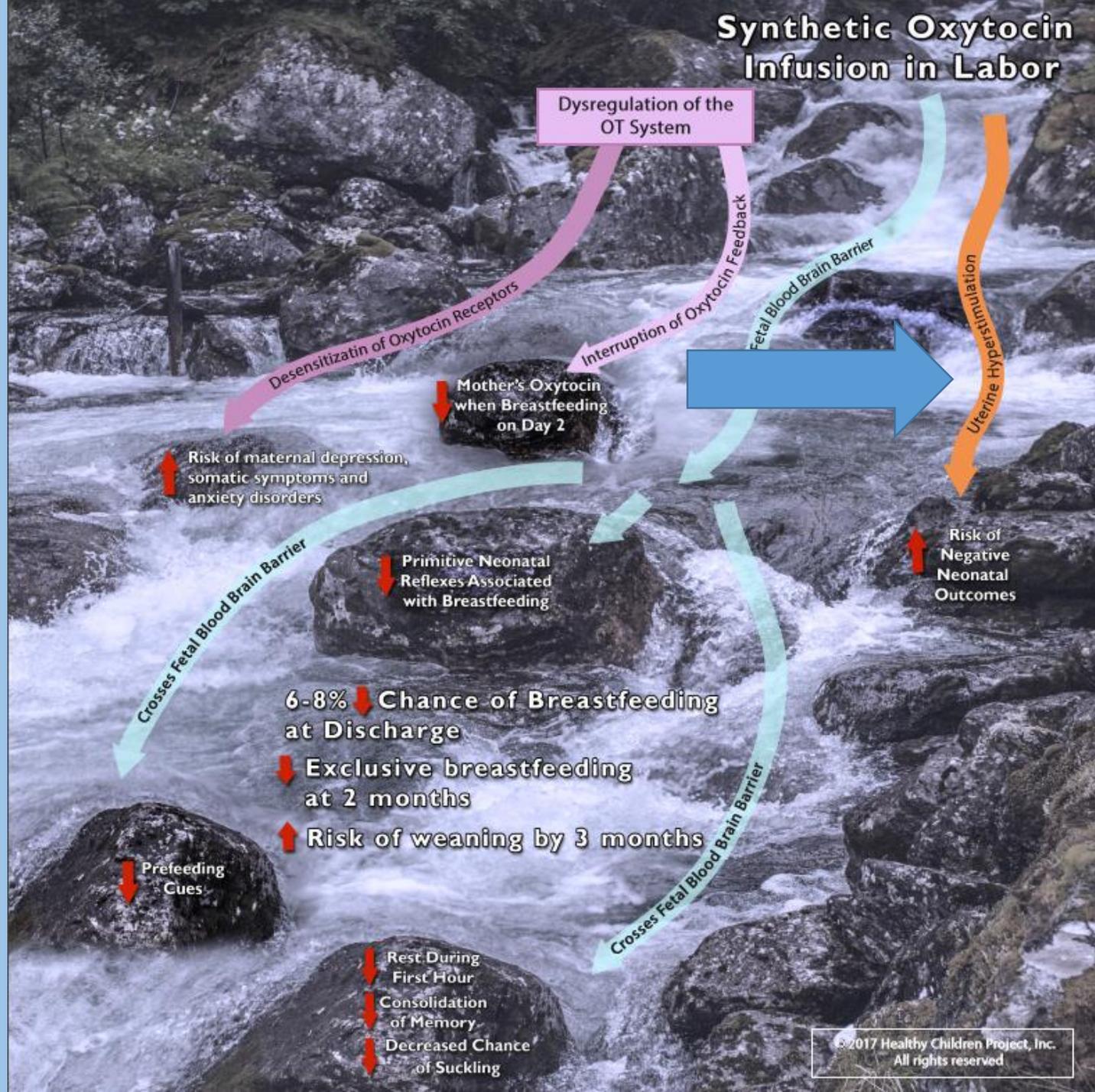
The **decreased duration of rest is significant** since the “quantity of neural reactivation during post-learning rest positivity predicts performance.”

The hippocampus with its clusters of OTRs is the part of the brain associated with **solidifying memories** as well as **social behavior and bonding**.

It is not surprising then, that the **babies who were exposed to synOT had a significantly diminished chance of suckling in the first hour compared to babies who were not exposed.** ($p = .027$)



Synthetic Oxytocin Infusion in Labor



Uterine Hyperstimulation

The uterine myometrium contains OTRs which increase as pregnancy advances. The uterus is responsive to oxytocin throughout pregnancy and, because synOT is biochemically identical to endogenous OT, when OTRs are occupied by either synOT or OT, myometrial contractions result.

Receptor sensitivity to oxytocin rapidly increases when a woman is in spontaneous labor.

Because OT is normally released in a pulsatile fashion, the smooth cells of the myometrium in the uterus are allowed to recover between pulses.



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However, **receptor desensitization as well as a decrease in the percentage of receptor cells can result when women are exposed to longer times of synOT infusions or higher amounts of synOT.**

Hyperstimulation, defined as more than 5 contractions in 10 minutes for 2 consecutive 10 minute periods, **was documented in 30.2% of labors induced with synOT.**



The more contractions experienced by the laboring mother and her fetus in 30 minutes, the greater the negative effect on the newborn infant.

The odds of neonatal morbidity are maintained even when augmentation and induction were assessed separately in a large population study.



The reduced intervillous exchange of oxygen and carbon dioxide associated with **uterine hyperstimulation may result in fetal hypoxia or acidosis.**

It's not clear, however, if the negative consequences seen in the infant are primarily due to acidosis or hypoxia.

Fetal and neonatal acidemia has been associated with multiorgan dysfunction, hypotoxic ischemia with encephalopathy, seizures, cerebral palsy, long-term neurological deficits and neonatal death.



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Uterine hyperstimulation and resulting acidosis may be measured as umbilical cord artery pH of 7.0 or less, although even a more neutral pH of ≤ 7.60 may place newborns at risk for adverse outcomes.

Newborns with an umbilical cord pH measured to be closer to the mean are more likely to **experience an APGAR less than 7 at 5 minutes**, the need for assisted ventilation and NICU admission – each with the possibility that the newborn will be separated from his mother.



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Elander and Lindberg's research paved the way for understanding the effects on the baby of the separation from mother shortly after birth for medical reasons and subsequent breastfeeding outcomes.

Elander G, Lindberg T. Short mother-infant separation during first week of life influences the duration of breastfeeding. Acta Paediatr Scand. 1984 Mar;73(2):237-40

Separated term newborns were compared with non-separated newborns at three months of age with the finding that that **the frequency of exclusive breastfeeding in the separated group was 37%.**

The frequency of exclusive breastfeeding in the non-separated group was 72%.



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Even brief separation of mother and baby for resuscitation, brief respiratory support or a low APGAR score may deprive the dyad of the experience of immediate, continuous and uninterrupted skin-to-skin in the first hour.

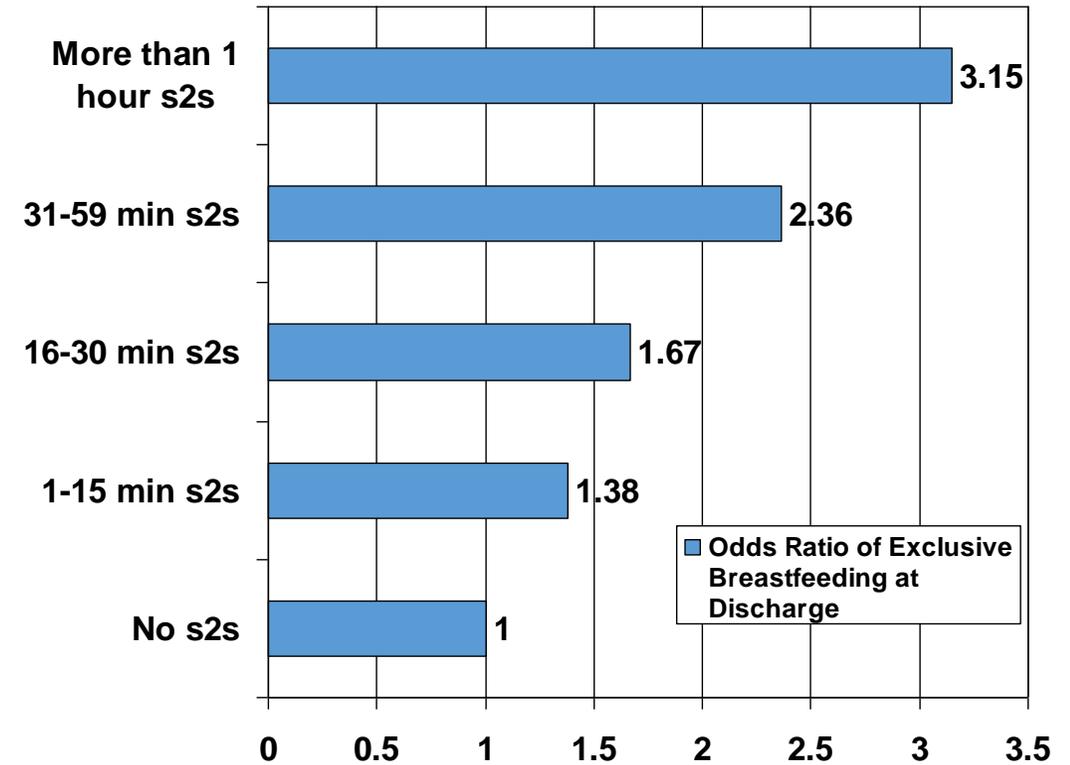


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A California study examined early separation of the mother and baby versus skin-to-skin contact for the first 1-3 hours after birth in relation to exclusive breastfeeding at hospital discharge.

With a sizable population of more than twenty-one thousand dyads, the robust findings indicate a **dose-response relationship between early skin-to-skin contact and breastfeeding exclusivity at hospital discharge.**



Bramson L, Lee JW, Moore E, Montgomery S, Neish C, Bahjri K, et al. Effect of early skin-to-skin mother--infant contact during the first hours following birth on exclusive breastfeeding during the maternity hospital stay. *J Hum Lact* 2010 May;26(2):130-7



If the

- **ejection** of the mother's milk,
- the baby's pre-feeding **cues**,
- the baby's primitive neonatal **reflexes** associated with feeding,
- the amount of **rest** (and memory consolidation) and
- whether or not the baby **suckles** in the first hour

are altered in babies exposed to synOT, it follows that **breastfeeding outcomes** should be affected as well.



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It shouldn't be a surprise, then, that a large study of almost 50,000 women showed that **the chance of breastfeeding at discharge from the hospital (day 2) was diminished by 6-8% if the mother had been administered intrapartum synOT.**

At two months postpartum, the mothers who **were most likely to be exclusively breastfeeding had received the lowest amounts of synOT or who had not been exposed at all.**

Jordan S, Emery S, Watkins A, Evans JD, Storey M, Morgan G. Associations of drugs routinely given in labour with breastfeeding at 48 hours: analysis of the Cardiff Births Survey. BJOG Int J Obstet Gynaecol. 2009 Nov;116(12):1622-1629; discussion 1630-1632



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The finding of **increased neonatal morbidity** with the use of synOT for both induction and augmentation is troubling. Although not every study examined in a recent systematic review of literature linking the administration of synOT and breastfeeding outcomes described negative effects of this common obstetrical practice, **no study found a favorable breastfeeding outcome.**

Erickson EN, Emeis CL. Breastfeeding Outcomes After Oxytocin Use During Childbirth: An Integrative Review. J Midwifery Womens Health. 2017 Jul;62(4):397–417



There is still much to learn about the effects of intrapartum administration of synOT. **Concerns continue to emerge.**

For example, it has been documented that in other mammals that **synOT infusions epigenetically alter the OTR gene**. Does this phenomenon happen in humans as well?

Is there a higher amount of OT in the first feedings of colostrum after administration of synOT? Could that effect the **immunological development** of the infant gut and contribute to other epigenetic changes?



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Is there a relationship between complications of labor, labor drugs, (including synOT) and the development of autism spectrum disorder (ASD)? Smallwood and colleagues found in their study that **children with autism were 2.32 times more likely to have been exposed to synOT than children without ASD $p=.004$** while another study found no relationship between labor induction and ASD diagnoses.

A 2017 meta-analysis that collated data from 37,634 autistic children and 12,081,416 non-autistic children enrolled in 17 studies, concluded that induction of labor was one of the prenatal, perinatal, and postnatal factors related to autism.

The authors remind us that the finding of autism may be a result of multiple rather than single factors.



As with the question of possible epigenetic effects, the physiologic pathway for autism is unclear.

It's also important to remember that **not all exposed babies and mothers are affected by synOT**; the hormone OT may play a part in directing other hormones.

Other factors, (stress, smoking, gestational age) may predispose mothers and/or their babies to be more vulnerable.



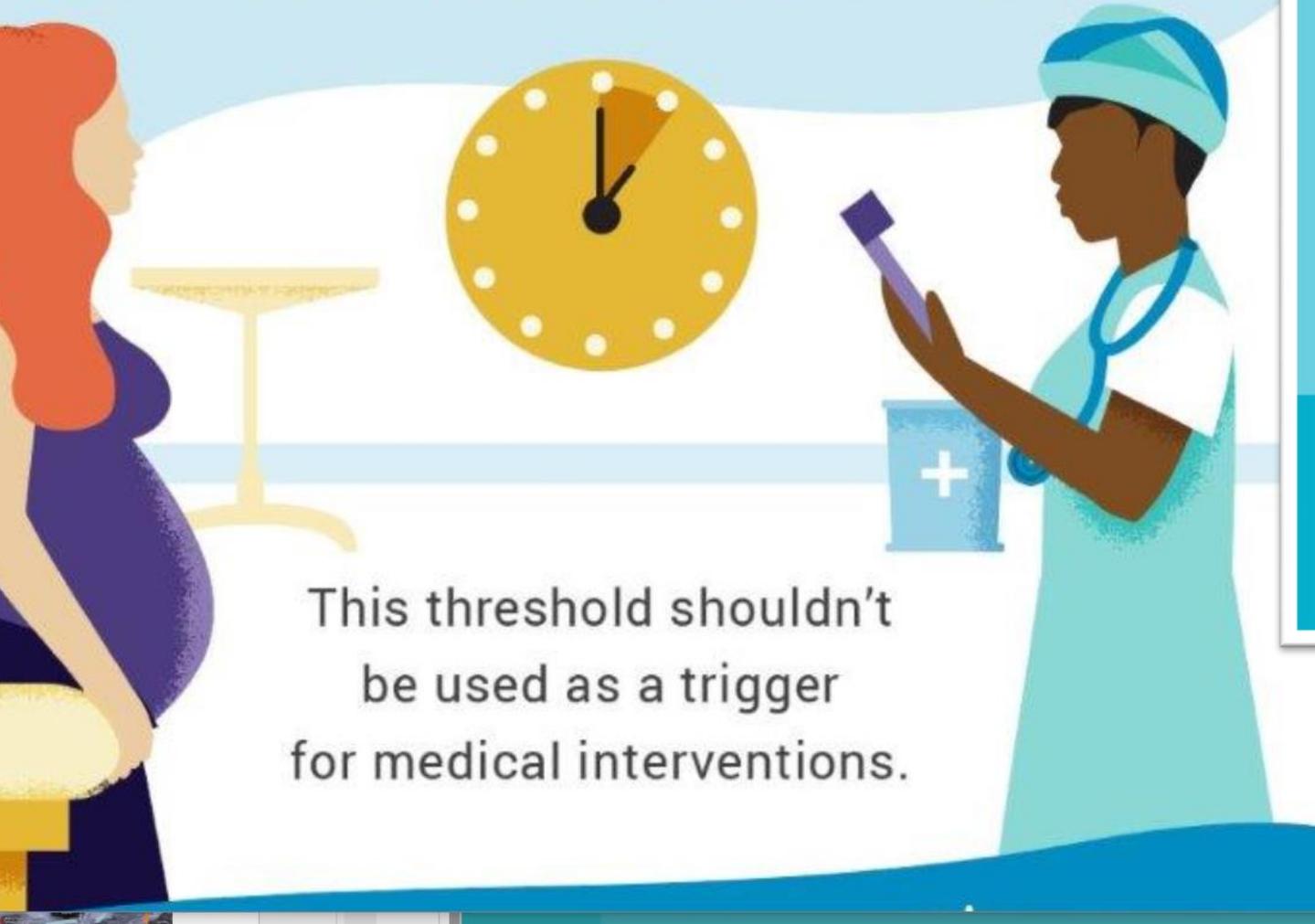
Ragusa and colleagues espouse the **pre-cautionary principle** when considering the use of synOT which “still **lacks reasonable assurance** that it is non-harmful for perinatal and immunological development.”

A large population Australian study found that “the risk of adverse outcomes was increased even among low risk women.”

In the light of these findings, **moderating intrapartum interventions, particularly the use of synOT, should be included in the list of preventive measures that can lead to an improvement in breastfeeding outcomes.**



LABOUR PROGRESSION AT 1 CM/HR DURING THE ACTIVE FIRST STAGE MAY BE UNREALISTIC FOR SOME



This threshold shouldn't
be used as a trigger
for medical interventions.

WHO recommendations
Intrapartum care for
a positive childbirth experience



 World Health
Organization

Spring 2018

Research Article

Intrapartum Administration of Synthetic Oxytocin and Downstream Effects on Breastfeeding: Elucidating Physiologic Pathways

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Abstract

The importance of breastfeeding as a public health priority has increased as new research reinforces the health benefits to both mother and nursing, even continuing years after weaning. However, many women do not nurse as long as they intend. Birth practices, such as labor medications and the routine separation of mother and baby are two of the several intrapartum influences on breastfeeding outcomes. This paper seeks to elucidate the physiologic mechanisms affecting breastfeeding outcomes of the commonly administered intrapartum drug, synthetic oxytocin.

A modified ascending, link tracing methodology was used to identify studies about breastfeeding and human lactation which describe possible physiologic

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