Infant & Toddler Feeding Case Files
嬰幼餵哺檔案
Baby Friendly Hospital Initiative Hong Kong Association
Sept 2023

The Use of Foods and Medications to Enhance Breastmilk Production

Dr Amy FUNG Wai Han (MBBS)
Dr Sandra YAU Yat Wa (MBBS, MPH)
Dr Shirley LEUNG Sze Lee (FHKAM(Paed), FFPH(UK))

Editor's Notes:

Inadequate breastmilk production in postpartum women, which may lead to premature cessation of breastfeeding, is prevalent. Such a situation is undesirable as breastfeeding / breastmilk confers lots of benefits to infants, especially those born preterm. The first line of treatment is certainly the optimisation of the frequency and effectiveness of breastfeeding through skills support for mothers. Notwithstanding the effort, there remains a small proportion of mothers who fail to produce adequate breastmilk. As there are currently no approved drugs for inadequate lactation, which is an important unmet health need, clinicians face the dilemma of "to treat or not to treat" with the "off-label" use of galactogogues. In this article, one of the authors (AFWH) shares her experience of the "off-label" use of domperidone. The controversies surrounding its use are then discussed and the importance of a prudent approach to management, with careful weighing of the risks and benefits, is highlighted. In all circumstances, the principle of "do no harm" should prevail.

Case History

Mrs. Wong, a first-time mother, had been directly breastfeeding her baby, Emily, since delivery. However, latching was suboptimal, and she had mild nipple pain. As suckling became more and more ineffective, Mrs. Wong had to express breastmilk to ensure effective milk removal. At 3.5 months old, Emily refused breastfeeding. Tongue tie was diagnosed. Two weeks later, surgical release was performed which was uneventful. Although Emily was willing to suckle again, suckling remained ineffective thereafter. Mrs. Wong's daily milk production reduced from a peak of 900 ml/day to 270 ml/day after an episode of blocked duct. She decided to seek help when Emily was 4.5 months old. Optimising her lactation skills and the frequency of milk removal failed to increase milk production significantly. After Mrs. Wong had been counselled on the pros and cons, domperidone, a dopamine antagonist, was prescribed. Subsequently, the daily milk production increased to 700 ml, and Emily's suckling improved 2 weeks afterwards. The medication was later tailed off. No side effect had been reported. Emily is now 21-month-old and growing healthily with normal development.

The Need for Galactogoues

Perceived or actual low milk supply is one of the most common reasons for discontinuing breastfeeding world-wide. In a cohort of 1,417 Hong Kong mother-infant pairs, 34.5% reported "insufficient milk" being the reason for stopping breastfeeding in the first year, the top reason in the list.[1] Galactogogues (or lactogogues) are medications or substances believed to assist the initiation, maintenance, or augmentation of maternal milk production.[2]

Endocrine and Autocrine Control of Breastmilk Production[3,4]

Neuroendocrine Regulation of Prolactin Secretion

Prolactin level rises during pregnancy from about 10 ng/ml in the pre-pregnant state to approximately 200 ng/ml at term. The baseline level reduces gradually but does not drop back to pre-pregnant level in a lactating woman, with an average of about 50 ng/ml at 6 months. Prolactin level can double with the stimulus of suckling or milk expression, named prolactin burst.

In the non-lactating state, regulation of prolactin by the hypothalamus is essentially inhibitory. Prolactin, secreted by the anterior pituitary gland, acts on the prolactin receptors of dopamine (DA) neurons in the hypothalamus. Dopamine is then secreted into the portal blood and inhibits prolactin secretion, constituting a short-loop feedback system.

During lactation when a high level of blood prolactin is needed, prolactin continues to act on the DA neurons via the short-loop feedback system. However, instead of increasing dopamine secretion, the DA neurons switch to the release of enkephalin, which promotes prolactin secretion. Dopamine level remains low despite an elevated prolactin level.

On the other hand, suckling at the breast provides a powerful stimulus for prolactin secretion. Afferent information from stimulation of the nipple-areola is transmitted via the spinal cord to a specific population of neurons in the hypothalamus, which secrete a peptide that increases prolactin secretion.

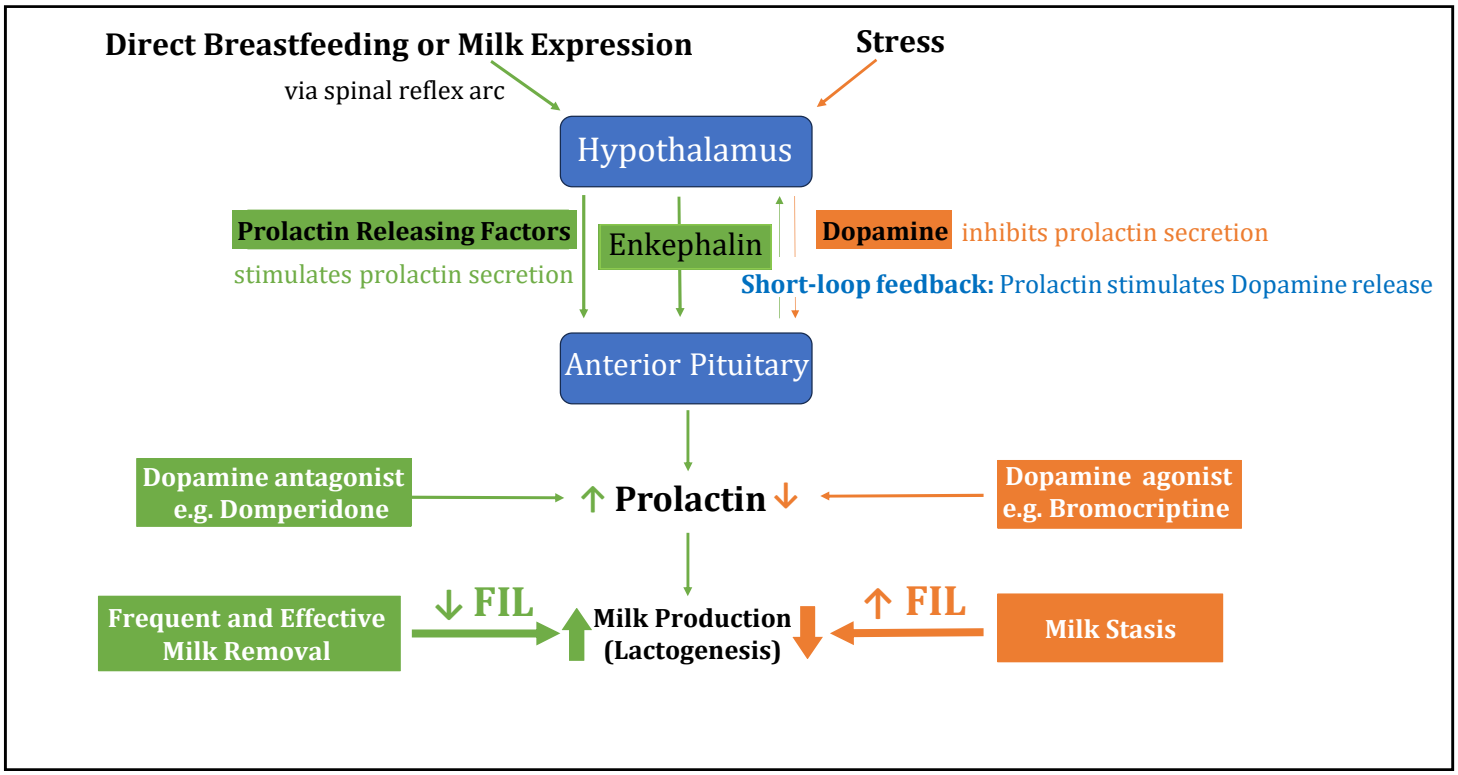
Autocrine Control (local feedback) of Breastmilk Production

After lactogenesis II, milk production is predominantly facilitated by effective removal of milk from the breast. Conversely, milk stasis leads to an increased concentration of the feedback inhibitor of lactation (FIL), which reduces milk production via a negative feedback mechanism by inhibiting the action of prolactin on lactocytes.

Actions of Galactogogues

Theoretically, agents or drugs that interfere with dopamine secretion would increase prolactin secretion. However, given that dopamine plays a relatively minor role in the regulation of prolactin secretion during lactation, and in view of the complex interplay between the endocrine and autocrine control of breastmilk production, it is uncertain to what extent alteration of dopamine secretion increases breastmilk production.

Diagram 1: Endocrine and Autocrine Control of Breastmilk Production



Herbals, Foods and Beverages as Galactogogues[2]

In many cultures, there are traditional foods and herbs that are meant to increase mother's strength and enhance lactation in the postpartum period. Innumerable plants are purported to be galactogogues. LactMed® has listed at least 44 common plants that have been used as galactogogues, such as fenugreek, goat's rue, milk thistle (Silybum marianum), oats, dandelion, millet, etc. Though these herbs have been used for centuries without apparent harm, there is little or no scientific evidence for their effectiveness and safety. The mechanisms of action are mostly unknown. Their placebo effect may have been the reason for widespread anecdotal experiences of their effectiveness due to more effective milk removal via improved let down reflex when mothers feel more confident after taking them. Use of these substances should be cautious because of the lack of standardised dosing preparations, possible contaminants, allergic potential, and drug interactions. Adverse effects for mother and infant dyads have been reported, for example, high dose fenugreek may cause lowering of blood sugar, thus increasing the chance of hypoglycaemia in diabetic mothers and may interact with warfarin to cause bleeding.[5]

Pharmaceutical Galactogogues

Domperidone and metoclopramide are dopamine receptor antagonists that are commonly used to treat symptoms of nausea and vomiting due to their stimulatory action on the motility of the upper gastrointestinal tract. They have also been used as galactogogues as their dopamine antagonistic action may increase serum prolactin level with positive effects in milk augmentation. Recent meta-analysis showed that metoclopramide was ineffective in augmenting breastmilk production in mothers of term or preterm infants.[6]

Controversies Surrounding the Use of Domperidone as a Galactogogue

Efficacy of Domperidone in Augmenting Breastmilk Production

There is evidence of increased baseline serum prolactin and increased milk production with domperidone use. However, it is uncertain if all women with low milk supply have low levels of prolactin and whether increasing prolactin may increase milk supply in women with both low and normal prolactin levels. A direct correlation between baseline prolactin levels and rate of milk synthesis or measured milk volume is not apparent.[2]

Three recent meta-analyses[7,8,9] of randomised controlled trials showed short-term use of domperidone had resulted in a modest increase in breastmilk production (of about 90 ml/day) compared to placebo. Amongst the 3 meta-analyses, there was a major overlap in the studies selected, which mainly examined mothers delivered preterm. It is uncertain if the result can be extrapolated to mothers deliver at term.

Safety of Domperidone Use in Mothers and Babies

In the above meta-analyses[7,8,9] which respectively included 194,239 and 328 mother-baby pairs, no significant adverse events were reported. Where quantitative data on adverse events was available, no significant difference between the domperidone and placebo groups was observed.

Drug Secretion into Breastmilk

Information gathered from a few small studies on domperidone secretion into breastmilk indicates that babies probably receive less than 0.1% of the maternal weight-adjusted dosage.[10]

Adverse Effects on Mothers

Domperidone is known to prolong the QT interval, which can lead to life-threatening ventricular arrythmias and sudden death. In 2004, the Food and Drug Administration (FDA) of the United States of America (USA) warned breastfeeding women of the risk of using domperidone to increase breastmilk production because of published reports of patients developing cardiac arrhythmias, cardiac arrest, and sudden death after receiving the intravenous form of domperidone.[11]

In the USA, domperidone is banned for any indications; whereas in some other countries, it is approved for use in a limited number of conditions but not enhancement of breastmilk production. For example, in 2014, the Medicines and Healthcare products Regulatory Agency (MHRA) of the United Kingdom (UK) issued guidance on the use of domperidone, specifying the only indication was for the treatment of nausea and vomiting. The maximum daily dose was limited to 30 mg and the duration of treatment limited to 7 days.[12] In 2019, MHRA announced that domperidone is no longer licensed for use in children younger than 12 years or those weighing less than 35 kg because of its lack of efficacy (compared to placebo) in symptom relief in acute gastroenteritis in this age group, hence its benefit did not outweigh the risk.[13]

In December 2022, Health Canada started a safety review of domperidone for its off-label use for augmentation of breastmilk production in postpartum women because of case reports of withdrawal symptoms after stopping or reducing the dose of domperidone. These case reports have documented women having severe anxiety, depression, intrusive disturbing thoughts and insomnia when stopping domperidone.[14]

Despite these safety concerns, clinicians around the world continue to use domperidone off-label on breastfeeding mothers. A study in British Columbia, Canada, using population-based health services data revealed that within a 10-year period between 2002 and 2011, 14% of women were prescribed domperidone at least once during the 6-month postpartum period.[15] Another Canadian cohort study (2004 – 2017) on 5 provinces showed that the prescription rate of domperidone increased from 7% in 2003 to reach a plateau of 12% in 2011.[16] An online, cross-sectional survey of Australian breastfeeding women conducted in 2019 found 19% (355 out of 1,876 responders) reported using domperidone.[17] However, the extent of selection bias in the study cannot be ascertained.

In the Canadian population-based retrospective cohort study which recorded 320,351 live births, a possible association between exposure to domperidone and hospitalisation for ventricular arrythmia (VA) in the postpartum period (Hazard Ratio = 2.25, 95% CI 0.84 – 6.01) was found, but the possibility of being confounded by BMI could not be ruled out. The strongest risk factor for postpartum VA hospitalization was identified as a prior history of VA. For those with a history of VA, the rate of hospitalisation for VA was 169 per 10,000 among those exposed to domperidone Vs 68 per 10,000 among the unexposed group. It is remarkable that all domperidone users with hospitalizations for VA had a prior diagnosis of VA.[15] However, the small number of mothers with the outcome (hospitalisation for VA) had cast doubt on the reliability of these estimates and precluded firm conclusions to be drawn. The more recent Canadian cohort study which included 1,190,987 live births from 5 provinces between 2004 and 2017 suggested domperidone use might be associated with a small increased ventricular tachycardia or sudden cardiac death (0.74 per 10,000 person-years vs 0.37 in the non-users).[16] Again, the small number of events renders these results inconclusive.

Considerations in Using Domperidone as Galactogogue

Clinicians who wish to use domperidone to augment breastmilk production in a lactating mother should take the following into consideration:

1. Current research on the efficacy and safety of both pharmaceutical and herbal galactogogues is inconclusive. The Academy of Breastfeeding Medicine (ABM) cannot recommend any specific galactogogue at this stage.[2]
2. Domperidone is not licensed for use as a galactogogue by the FDA. Prescription as a galactogogue constitutes off-label use in many countries including Australia, Canada, United Kingdom, Ireland and Japan.[2,18,19]
3. Mothers should be informed of the risks and benefits of using domperidone in an attempt to increase breastmilk production.

4. After identifying and managing treatable causes of low milk production, as well as optimizing lactation skills and milk removal frequency, clinicians may consider to prescribe domperidone, having ruled out any contraindications. The mother and infant should also be monitored closely for any side effects.[2,12,20]

Contraindications	Potential side effects
- History of cardiac disease - Pre-existing arrhythmia - Taking other medications known to prolong QTc interval (www.qtdrugs.org) e.g., Fluconazole, erythromycin or potent CYP3A4 inhibitors such as clarithromycin, ketoconazole - Severe hepatic impairment	headache, dry mouth, abdominal cramps, diarrhea, drowsiness, dizziness, change in mood, seizure (rare), arrhythmias (QTc prolongation), extra-pyramidal symptoms (rare), withdrawal symptoms following high doses

5. When prescribing domperidone:
   - Most studies used the dosage of 10 mg TDS for a duration of 7 to 14 days[2,10,21]
   - ABM recommends:[2]
     - ❖ To give the lowest possible dose for the shortest period
     - ❖ To consider tapering the dose when discontinuing the medication
     - ❖ If milk production wanes after stopping and improves with resumption of the medication, to taper to the lowest effective dose and discontinue later

Key Messages:

1. There is little or no scientific evidence of effectiveness and safety for herbal or food galactogogues.
   現時未有科研證據證明草本或食物催乳劑的有效性和安全性。

2. Some evidence shows domperidone, a pharmaceutical galactogogue, may help some mothers increase milk production but is associated with an increased, albeit small, risk of serious cardiac side effects.
   一些研究證據表明催乳藥 Domperidone 可能有助一些母親提升奶量，但會增加嚴重心臟副作用的風險，儘管風險很小。

3. When prescribing domperidone as a galactogogue, doctors should perform a thorough assessment to rule out any medical causes of low milk supply, contraindications, drug allergies and drug interactions.
   處方催乳藥 Domperidone 時，醫生須全面評估可引致奶量不足的醫學成因，並須檢視不適宜服藥、藥物敏感及藥物相衝的情況。

4. Medication should never replace non-pharmacological intervention to manage low milk production. Optimisation of suckling and milk expression skills should be implemented simultaneously.
   催乳藥絕不可代替其他非藥物方法去處理奶量不足。改善母乳餵哺及擠奶的技巧必須同步進行。

References:

1. Tarrant M, Fong DYT, Wu KM, Lee ILY, Wong EMY, Sham A, Lam C, Doggson JE. Breastfeeding and weaning practices among Hong Kong mothers: a prospective study. BMC Pregnancy and Childbirth 2010;10:27.
2. ABM Clinical Protocol #9: Use of galactogogues in initiating or augmenting maternal milk production, second revised 2018. Breastfeeding Medicine 2016;13(5):307-314.
3. Walker M. Breastfeeding Management for the Clinician Using the Evidence. 4th edition, Jones and Bartlett Learning 2017; P.118-120..
4. Grattan DR. The hypothalamo-prolactin axis. Journal of Endocrinology 2015; 226: T101-T122.
5. Anderson PO. Herbal use during breastfeeding. Breastfeed Med 2017; 12:507-509..
6. Metoclopramide. Drugs and Lactation Database (LactMed®) [Internet]. LactMed@NIH. Available from https://www.ncbi.nlm.nih.gov/books/NBK501352/
7. Grzeskowiak LE, Smithers LG, Amir LH, Grivell RM. Domperidone for increasing breast milk volume in mothers expressing breast milk for their preterm infants: a systematic review and meta-analysis. BJOG. 2018; 125:1371-8.
8. Taylor A, Logan G, Twells L, Newhook LA. Human Milk Expression After Domperidone Treatment in Postpartum Women: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. J Hum Lact. 2019 Aug; 35(3):501-509.
9. Shen Q, Khan KS, Du MC, Du WW, Ouyang YQ. Efficacy and Safety of Domperidone and Metoclopramide in Breastfeeding: A Systematic Review and Meta-Analysis. Breastfeed Med. 2021; 16:516-29.
10. Domperidone. Drugs and Lactation Database (LactMed®) [Internet]. LactMed@NIH. Available from https://www.ncbi.nlm.nih.gov/books/NBK501371/#LM495.REF.3
11. FDA Talk Paper: FDA Warns Against Women Using Unapproved Drug, Domperidone, to Increase Milk Production (Jun 2004). Available from https://www.fda.gov/drugs/information-drug-class/fda-talk-paper-fda-warns-against-women-using-unapproved-drug-domperidone-increase-milk-production
12. MHRA, 2014. Available from https://www.gov.uk/drug-safety-update/domperidone-risks-of-cardiac-side-effects
13. MHRA, 2019. Available from https://www.gov.uk/drug-safety-update/domperidone-for-nausea-and-vomiting-lack-of-efficacy-in-children-reminder-of-contraindications-in-adults-and-adolescents
14. CBC News Posted: Jan 30, 2023. Health Canada reviewing safety of controversial breastfeeding drug. Available from https://www.cbc.ca/news/canada/breastfeeding-lactation-drug-domperidone-health-canada-1.6731315
15. Smolina K, Mintzes B, Hanley GE, Oberlander TF, Morgan SG. The association between domperidone and ventricular arrhythmia in the postpartum period. Pharmacoepidemiol Drug Saf. 2016 Oct; 25(10):1210-1214.
16. Moriello C, Paterson M, Reynier P, Dahl M, Aibibula W, Fisher A, et al. Off-label postpartum use of domperidone in Canada: a multidatabase cohort study. CMAJ Open 2021; 9(2):E500-E509.
17. McBride GM, Stevenson R, Zizzo G, Rumbold AR, Amir LH, Keir A et al. Women's experiences with using domperidone as a galactagogue to increase breast milk supply: an Australian cross-sectional survey. Int Breastfeed J. 2023 Feb 7;18(1):11.
18. National Infant Feeding Network. Statement by the National Infant Feeding Network Dec 2014. The use of Domperidone in inadequate lactation.
19. Campbell-Yeo ML, Allen AC, Joseph KS, Ledwidge JM, Caddell K, Allen VM, et al. Effect of domperidone on the composition of preterm human breast milk. Pediatrics 2010;125(5):e107-e114.
20. EMA, 2014. Available from https://www.ema.europa.eu/en/medicines/human/referrals/domperidone-containing-medicines
21. Hale TW, Krutsch K. Hale's Medications and Mothers' Milk. 20th edition, Springer Publishing Company 2023; p.217-219.

Views expressed in this article are the authors' and do not necessarily reflect the opinion or position of the BFHIHKA.

作者在本文章表達的見解，未必代表愛嬰醫院香港協會的意見或立場

Baby Friendly Hospital Initiative
Hong Kong Association
愛嬰醫院香港協會

Website: www.babyfriendly.org.hk
Baby Friendly Hotline: 2838 7727 (9am-9pm)
General Enquiry: 2591 0782, Fax: 2338 5521
Email: info@bfhihka.org.hk
Address: 7th Floor, SUP Tower, 75-83 King's Road, Hong Kong

Supported by: unicef