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The Use of Galactogogues in the Breastfeeding Mother

Alicia B Forinash, Abigail M Yancey, Kylie N Barnes, and Thomas D Myles

OBJECTIVE: To review data regarding the efficacy of galactogogues available in the US to increase breast milk production in postpartum mothers.

DATA SOURCES: Literature was sought using PubMed (1966-June 2012) and EMBASE (1973-June 2012). Search terms included breastfeeding, breast milk, lactation, galactogogue, metoclopramide, oxytocin, fenugreek, milk thistle, silymarin, growth hormone, thyroid releasing hormone, medroxyprogesterone, domperidone, goat's rue, beer, *Asparagus racemosus*, shatavari, *Medicago sativa*, alfalfa, *Onicus benedictus*, blessed thistle, *Galega officinalis*, brewer's yeast, and herbals.

STUDY SELECTION AND DATA EXTRACTION: All studies including humans and published in English with data assessing the efficacy of galactogogues for increasing breast milk production were evaluated.

DATA SYNTHESIS: Breast milk is considered the optimal food source for newborns through 1 year of age. Many factors influence overall maternal production, including maternal pain, illness, balance of time when returning to work, anxiety, or emotional stress. Although a variety of herbal and pharmaceutical options have anecdotal evidence of their ability to improve breast milk production, peer-reviewed studies proving their efficacy are lacking. Metoclopramide, oxytocin, fenugreek, and milk thistle have shown mixed results in improving milk production; however, the trials were small and had a variety of limitations.

CONCLUSIONS: Nonpharmacologic recommendations should be exhausted before adding therapy. Although anecdotal evidence encourages the use of metoclopramide, fenugreek, asparagus, and milk thistle for their galactogogue properties, efficacy and safety data in the literature are lacking. Oxytocin and domperidone are potentially available for compounding purposes, but safety data are limited. More studies are needed to evaluate the effects of available galactogogues on breast milk production.

KEY WORDS: breastfeeding, breast milk, fenugreek, galactogogue, herbals, lactation, metoclopramide, milk thistle, oxytocin, silymarin.

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Breastfeeding is considered the optimal source of nutrition for infants from birth to 1 year and is supported by the American Academy of Pediatrics (AAP) and the World Health Organization.[1,2] The 2012 AAP Policy on Breastfeeding recommends exclusive breastfeeding for 6 months, with continuation up to 1 year or longer. Breastfeeding has been associated with both short- and long-term benefits over formula feeding. In 2007, the Agency for Healthcare Research and Quality prepared a report summarizing the literature concerning the relationship between breastfeeding and its impact on infant and maternal outcomes.[3] A total of 9000 abstracts were reviewed; 43 studies focused on infant health outcomes, 43 studies on maternal health outcomes, and 29 systematic reviews or meta-analyses of more than 400 trials. Results of these studies indicated that exclusive breastfeeding for a minimum of 3 months decreased the risk of the infant developing acute otitis media and/or atopic dermatitis and, if the child were exclusively breastfed for greater than 4 months, the result was a decrease in hospitalizations secondary to lower respiratory tract infection. Additionally, if breastfeeding continued for greater than 6 months, there was a potential decrease in the occurrence of acute lymphocytic leukemia and acute myeloid leukemia. Studies have also shown a potential decrease in death from sudden infant death syndrome and the development of asthma, diabetes mellitus, and obesity. The Agency for Healthcare Research and Quality report also notes the potential benefits to the mother, including reduced risk of breast and ovarian cancers as well as decreased risk of diabetes mellitus type 2 as long as the mother did not have gestational diabetes.

Despite the AAP recommendations and perceived benefits, breastfeeding rates in the US continue to be low.[4] At

Author information provided at end of text.

birth, initiation of breastfeeding occurs for 75% of mothers; however, the rate of breastfeeding decreases to 44.6% at 6 months and 23.8% at 12 months. Exclusive breastfeeding rates are even lower at 35% and 14.8% at 3 months and 6 months, respectively. Many factors can contribute to difficulty feeding and may lead to early cessation of breastfeeding; these include structural abnormalities such as inverted nipples and oral clefts, infection, pain, poor latching, and insufficient milk production.[5] Factors that have been associated with a reduction in breast milk production include preterm delivery, maternal illness, anxiety, fatigue, and emotional stress. Because of the many documented benefits of continued breastfeeding for the infant and mother, different measures are taken to increase breast milk production. A variety of herbal and pharmaceutical products have been recommended as galactogogues, substances that promote lactation. The purpose of this article is to review data regarding the efficacy of galactogogues available in the US for increasing breast milk production in postpartum mothers.

Physiology of Breastfeeding

Many factors play a role in the development of breast milk. During early pregnancy, estrogen and progesterone develop key components of the breast tissue for lactation; estrogen stimulates milk duct development and progesterone forms lobules that are responsible for milk production. Prolactin is the predominant hormone that stimulates mammary glands; however, high progesterone and estrogen progesterone levels during pregnancy suppress prolactin's action on milk production during pregnancy. Additionally, prolactin and human chorionic somatomammotropin stimulate the production of enzymes required for milk production. After delivery, estrogen and progesterone levels significantly decrease, allowing prolactin to fully stimulate the alveoli for milk production. Cortisol, insulin, vasoactive intestinal peptide, growth hormone, and thyroid-releasing hormone stimulate prolactin and influence the composition of milk, whereas dopamine inhibits prolactin, suppressing its action.[6,7] Milk secretion is primarily controlled by oxytocin, which stimulates the myoepithelial cells to contract and release stored milk into the ducts (ie, letdown). Milk must be ejected from the lumen of the alveoli into the milk ducts to reach the infant. Infant suckling stimulates production of prolactin as well as oxytocin. Milk secretion continues until suckling ends. Interestingly, even if the alveoli still contain milk, once suckling stops, no more milk can be released. It is important to allow plenty of time for feeding or breast pumping to empty the breasts. When all of the milk is released, the breast stimulates additional milk production for the next feeding. This feedback mechanism leads to an overall increase in supply over time.[6,7]

Literature Selection

A search of PubMed (1966-June 2012) and EMBASE (1973-June 2012) was performed with the terms breastfeeding, breast milk, lactation, galactogogue, metoclopramide, oxytocin, fenugreek, milk thistle, silymarin, growth hormone, thyroid-releasing hormone, medroxyprogesterone, domperidone, goat's rue, beer, *Asparagus racemosus*, shatavari, *Medicago sativa*, alfalfa, *Onicus benedictus*, blessed thistle, *Galega officinalis*, brewer's yeast, and herbals. Limits of English language and human subjects were applied to the searches. References of all articles were reviewed to identify additional relevant articles. All relevant articles were included despite limitations due to the limited supply of published data evaluating these therapies. These products are commonly recommended in practice by both maternal and pediatric health care providers. Case reports, case series, and abstracts were excluded unless they were the only published literature on the topic. Medications that are not available in the US were excluded from this review.

Herbal Products

Natural herbal medications, such as fenugreek (*Trigonella foenum-graecum*), milk thistle (silymarin; *Silybum marianum*), *A. racemosus* (shatavari), alfalfa (*M. sativa*), blessed thistle (*O. benedictus*), goat's rue (*G. officinalis*), fennel (*F. vulgare*), and brewer's yeast, are often recommended to breastfeeding mothers to increase milk production. However, data on herbal products are limited and often based on anecdotal evidence. Fenugreek, milk thistle, and asparagus are frequently recommended and are the only herbal galactogogues that have some, although minimal, published clinical data on use in humans.[8,9]

FENUGREEK

Fenugreek is a member of the pea family and is often used as artificial maple flavoring.[10] The galactogogue property of fenugreek was first reported in the 1940s. Although its exact mechanism of action is unknown, there are 2 proposed mechanisms. The first is that it increases sweat production, leading to an increase in milk supply given that the breast is considered to be a modified sweat gland (Figure 1).[10,11] The second thought is that milk flow is increased by fenugreek phytoestrogens and diosgenin, a steroid sapogenin, components.[12] The recommended dose of fenugreek is 2-3 capsules (580-610 mg per capsule) 3-4 times per day, and it may be discontinued once milk supply has increased to the desired level.[10,11] Many women have reported results within 24-72 hours.[8,10,11]

Fenugreek is often prescribed to nursing mothers, based on anecdotal reports. One physician observed the successful use of fenugreek in more than 1200 patients. Unfortu-

nately, detailed information was not available in regard to gestational age, time of initiation, or specific results.[10] Two studies showed that fenugreek appears to stimulate breast milk production (Table 1).[12-14] Limitations of these reports include lack of reporting maternal and infant adverse effects, adherence, and doses of fenugreek used. Confounding factors that affect breastfeeding success, including caloric and fluid intake of mother, other medications used, frequency and duration of breastfeeding, and stress/pain level of the mother, were not controlled in these studies. One study evaluating 10 exclusively pumping women was presented only in abstract form; full evaluation of the data is therefore not possible.[13] The second study, a randomized trial, also included a small sample size and focused mainly on birth weight, loss of birth weight, and time to regain birth weight.[12] Milk volume produced was measured only on the third day after delivery and the study concluded when the infant reached birth weight, so the full efficacy of fenugreek was unable to be determined. The biggest limitation of this study is that the galactogogue tea included other herbal components thought to have galactogogue properties, including fennel and goat's rue; thus, it is difficult to conclude that benefit is solely from fenugreek.[12,15]

Although it appears that fenugreek may have some benefit, randomized clinical trials are needed to determine its specific role as a galactogogue. Safety data are minimal since adverse events and tolerability were not reported. Currently, the Food and Drug Administration (FDA) lists fenugreek as generally regarded as safe (GRAS); however, these data are not specifically aimed at the nursing mother and infant.[10,16] Additionally, no information has been published to describe the safety or relative infant dose of fenugreek consumption through breast milk. There are reports of mild gastrointestinal symptoms in the mother, mainly diarrhea, and there is potential for hypoglycemic effects.[10,11] The fenugreek seed can lead to a maple-like odor that can be mistaken in infants for maple-syrup urine disease, which is a metabolism disorder in which the body is unable to break down certain parts of proteins.[9,17] Women who are pregnant should not use fenugreek, as it has been shown to stimulate uterine contractions.[8,16]

MILK THISTLE

Another popular herbal galactogogue is milk thistle (silymarin, St. Mary's milk), which has been used for more than 2000 years for a variety of ailments.[18] It is theorized that milk thistle galactogogue effects are secondary to an increase in prolactin levels, as seen in female rats (Figure 1).[19] Clinical data are limited to 1 placebo-controlled trial[14] conducted in Peru (Table 1).[12-14] Limitations of this study include a small sample size, indirect measurement of milk production by weighing the infant before and after feeding, as well as not

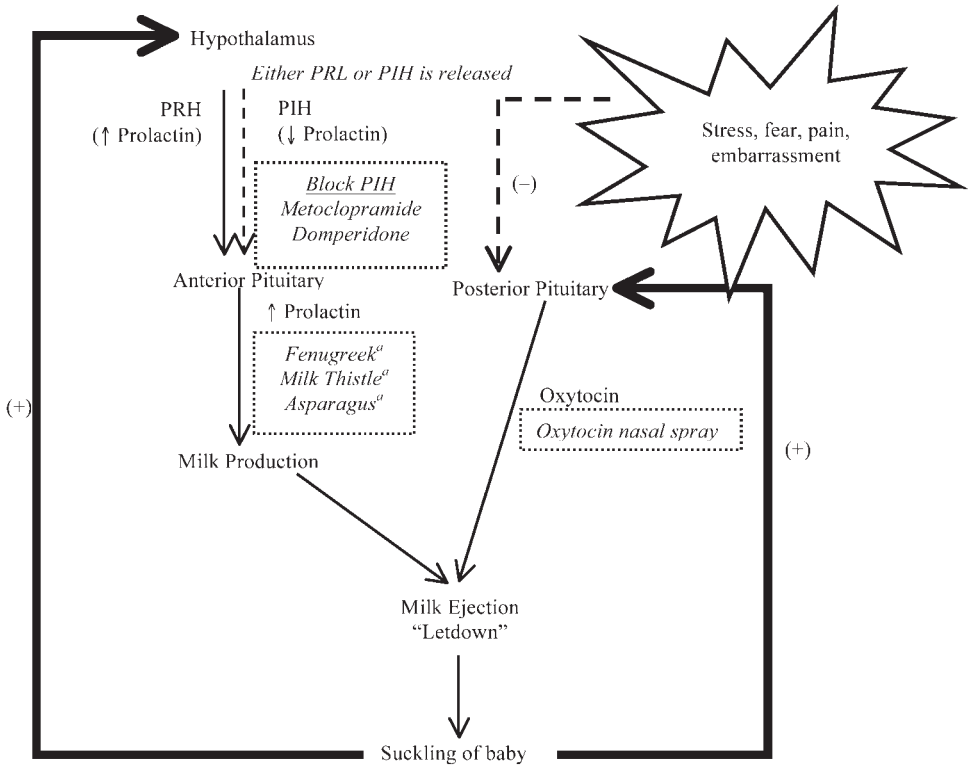

Figure 1. Physiology of lactation and potential medication mechanisms of action. PIH = prolactin inhibiting hormone; PRH = prolactin releasing hormone. [a]Exact mechanism of action unknown but known to increase prolactin.

including detailed information on both the mother and infants, infant weight gain, adverse event data, and adherence. Randomized controlled trials evaluating the benefit of milk thistle are needed to show its benefit, safety, and potential role as a galactogogue. As with many herbal agents, safety data are minimal and, unlike fenugreek, milk thistle is not listed as GRAS by the FDA. No data are available describing the relative infant dose of milk thistle after breast milk consumption.[18]

SHATAVARI

Shatavari is a popular galactogogue used in India. The exact mechanism of action is unknown but could possibly be secondary to the presence of steroidal saponins, which potentially increase prolactin levels.[20] Two studies have been conducted to determine whether prolactin increased with shatavari; unfortunately, the results were conflicting.[20,21] Both studies looked at milk production as a secondary outcome; however, this was determined indirectly by weighing the infant before and after treatment. Once again, study results were conflicting. Other limitations of the trials included small sample size, omission of detailed information on adherence, reasons for drop-outs, and information about adverse events for both mother and infant. As with milk thistle, shatavari is not listed as GRAS by the FDA.[22] There is also recent evidence showing teratogenicity in animal studies, thus shatavari should be avoided in pregnant females.[23] No data are available describing relative infant dose of shatavari after breast milk consumption.[22,23] Randomized controlled trials are needed to determine the benefit, safety, and potential role as a galactogogue.

Potentially Available from Compounding Pharmacies

OXYTOCIN

Before oxytocin nasal spray was voluntarily removed from the US market in 1995 and worldwide in 1999, it was commonly used to promote milk letdown in women with decreased milk production. Supplemental oxytocin increased breast milk production because it causes contraction of the myoepithelial cells that surround areola tissue in the breast (Figure 1).[24] Three randomized, double-blind studies have been conducted evaluating the impact of oxytocin nasal spray immediately prior to each breastfeeding session to increase breast milk production (Table 2).[25-31] Oxytocin nasal spray 3 IU per spray prior to each feeding from birth to 5 days postpartum showed significant differences in overall breast milk production. Production increased 3- to 5-fold with oxytocin nasal spray compared with placebo in primiparous mothers and 2-fold in multiparous mothers.

Oxytocin appears to be generally well tolerated, but minor epistaxis was reported by 1 woman in 1 study.[25] No infant adverse events were reported; however, safety cannot be assumed since only a small number of exposures occurred. Limitations of these studies include small sample size, short duration, minimal to no information on infant weight gain reported, evaluated only the effects in preterm delivery, and overall medication adherence was not verified.[24-27] The first trial also used an indirect method for measuring production by breast engorgement instead of actual milk production.[25] Overall, oxytocin improved milk production when used in late preterm deliveries compared with historical controls but

Table 1. Comparison of Herbal Galactogogue Clinical Trials[a]

Reference	Regimen	Patients	Infant Age (FT/PT)	Milk Attainment	Effect on Milk Production	Infant Weight
Turkyilmaz 2011[12]	Fenugreek tea, ≥3 cups daily	Fenugreek tea (n = 22) Control (n = 22) Placebo (n = 22)	1 day (FT)	Nursing, except day 3 postdelivery by mechanical breast pump	Day 3 postdelivery: fenugreek 73.2 ± 53.5 mL; control 38.8 ± 16.3 mL; placebo 31.1 ± 12.9 mL (p = 0.004) 7.3 ± 2.7 mL; placebo 9.9 ± 3.5 mL	Lactation consultant for all groups
Swafford 2000[13]	Fenugreek 3 capsules daily[16]	10		Breast pump	Daily average increase from 207 to 464 mL (p = 0.004)	
Di Pierro 2008[14]	Micronized milk thistle 420 mg/day for 63 days	Milk thistle (n = 25) Control (n = 25)		Nursing, then pumping to void the gland	Milk thistle 601.92 mL (day 0), 989.76 mL (day 30), and 1119.24 mL (day 60); an 85.95% increase Placebo 530.36 mL (day 0), 649.76 mL (day 30), 700.56 mL (day 60); a 32.09% increase	

FT = full-term delivery; PT = preterm delivery.
[a]No data have been reported on maternal or infant adverse events.

Table 2. Comparison of Clinical Trials with Prescription Products

Reference	Regimen	Patients	Infant Age (FT/PT)	Milk Attainment	Effect on Milk Production	Infant Weight	Maternal ADRs	Infant ADRs	Notes
Oxytocin Nasal Spray (within 5 minutes prior to each pump)									
Huntingford 1961[25]	Oxytocin before feeding for up to 10 days	Oxytocin (n = 24) Placebo (n = 24)	Day 1 (unknown whether FT/PT)		Milk production day 7: oxytocin, mean 3.4 oz; placebo, mean 2.3 oz ($p < 0.001$)	Day 4: Oxytocin, –147 g Placebo, –207 g ($p = 0.01$)	Minor epistaxis (n = 1)		Oxytocin 4-5 IU (no spray amount provided) Randomized, double-blind Average length of use: oxytocin 70 hours (before 14 feedings); placebo 78 hours (before 16 feedings) No significant difference in primary outcome of level of breast engorgement (clinical observation)
Ruis 1981[26]	Oxytocin before pumping for 5 days	Oxytocin (n = 8) Placebo (n = 4)	Day 1 (PT)	Pump	Primiparous: 3- to 5-fold increase Multiparous: 2-fold increase Oxytocin: 1964 ± 308 mL Placebo: 510 ± 142 mL ($p = 0.0002$)				Oxytocin 3 IU 1 spray, pump 10 minutes, instill 2 sprays, pump 10 minutes, repeat for other breast Randomized, double-blind Gestation age <38 weeks
Fewtrell 2006[27]	Oxytocin prior to pumping for 5 days	Oxytocin (n = 27) Placebo (n = 24)	(PT)	Pump every 3 hours	Day 5: Oxytocin median 667 g Placebo median 530 g ($p = 0.9$)		None	None	Oxytocin 100 µL (~4 IU/dose) Randomized, double-blind, intention-to-treat, maintained 80% power Mean gestational age 29 weeks Received education on lactation
Domperidone									
Campbell-Yeo 2010[28]	Domperidone 10 mg 3 times/day or placebo for 2 weeks	Domperidone (n = 22) Placebo (n = 24)	3-4 weeks (PT)	Pump	Baseline to 14-day milk volume: Domperidone 184.4-380.2 mL (266.8%) Placebo 217.7-250.8 mL (18.5%) $p < 0.005$		Domperidone: none	None	Gestational age <31 weeks Milk volume increased within 48 hours
Wan 2008[29]	Domperidone: 10 mg 3 times/day or 20 mg 3 times/day for 2 weeks Crossover	Domperidone (n = 6)	16-117 days (mean 53) (PT)	Pump	Baseline: mean 8.7 g/h^{-1} 30 mg: mean 23.6 g/h^{-1} ($p = 0.0217$) 60 mg: mean 29.4 g/h^{-1} ($p = 0.0047$)		Abdominal cramps (30 mg: 1; 60 mg: 2) Constipation (60 mg: 1) Dry mouth (30 mg: 3; 60 mg: 5) Depressed mood (60 mg: 1) Headache (30 mg: 1; 60 mg: 3)		Conducted in Australia Randomized, double-blind Gestational age, mean 26.5 weeks (24-29.4) 2 nonresponders
da Silva 2001[30]	Domperidone 10 mg 3 times/day for 1 week	Domperidone (n = 11) Placebo (n = 9)	Mean 31-33 days (PT)	Pump	Domperidone: 112.8 mL to 162.2 mL (44.5%; $p < 0.05$) Placebo: 48.2 mL to 56.1 mL (16.6%)		None	None	Conducted in Canada Randomized, double-blind Gestational age mean, 29.1 weeks

Petraglia 1985[31]	Domperidone 10 mg 3 times/day for 3-10 days	Group A: Domperidone (n = 8) Placebo (n = 7) Group B: Domperidone (n = 9) Placebo (n = 8)	Group A: 2 days Group B: 2 weeks		Domperidone: day 2, 347 ± 36 mL Placebo: day 2, 335 ± 30 mL Domperidone: day 10, 673 ± 44 mL Placebo: day 10, 398 ± 45 mL ($p < 0.01$) Group A: Domperidone: day 2, 105 ± 35 mL Domperidone: day 5, 475 ± 51 mL ($p < 0.05$) Group B: Domperidone: day 2, 371-417 mL; day 5, 631-708 mL	None	None	Group A: history of lactation problems Group B: Primiparous with insufficient lactation after 2 weeks Feedings 6-7 times/day Infants weighed pre- and postfeedings to determine milk amount Milk supply significantly higher with domperidone vs placebo at days 4, 6, 8, and 10

ADRs = adverse drug reactions; FT = full-term delivery; PT = preterm delivery.

no improvement in early preterm deliveries compared with placebo.

Currently, oxytocin is available in intramuscular and intravenous injection forms in the US; however, it lacks the indication for lactation purposes. Oxytocin powder is still available for compounding pharmacies and could potentially be used as a galactogogue. Available data do not describe the relative infant dose and theoretical infant dose in breast milk.[32]

DOMPERIDONE

In addition to oxytocin, domperidone is a potential galactogogue available in powder formulation for potential compounding. Domperidone is a dopamine antagonist and can increase prolactin levels (Figure 1). Domperidone 10 mg orally every 8 hours for 2 weeks has been shown to increase milk supply in 48 hours, and it has a low relative infant dose of 0.04% and a subtherapeutic theoretical infant dose of 0.18 µg/kg/day.[28-31,33] Domperidone significantly increased milk production in women with preterm deliveries (Table 2).[25-31] It appears to be generally well tolerated, but abdominal cramps, headaches, constipation, and depression have been reported, although rates were higher when the dose was increased to 20 mg every 8 hours. No infant adverse events were reported; however, safety cannot be assumed since only a small number of exposures occurred. Limitations of these domperidone studies include small sample size; location, having been conducted in other countries; and potential confounders that may have affected milk supply, such as fluid and calorie intake, frequency of pumping, medical history, and concomitant medications, were not provided.

Despite effectiveness, this formerly commercially available product was removed from the market in 2004. The FDA released a statement expressing concerns for domperidone safety in lactating women due to potential for cardiac arrhythmias and sudden cardiac death in 2004 and again in 2009.[34,35] This risk was discovered in oncology patients with hypokalemia receiving intravenous domperidone; however, the FDA issued warnings specific to lactating mothers to avoid the use of domperidone.

Prescription Products

METOCLOPRAMIDE

Metoclopramide is a commonly prescribed galactogogue that acts through dopamine antagonism to increase prolactin levels and stimulate increased milk production (Figure 1).[36-41] In one study, milk supply increased 52% after 2 days of treatment.[38] Metoclopramide has been studied as 10 mg given orally 3 times a day for 5 days to 4 weeks, but most commonly 7-14 days, initiated with onset of lactation or later for partial or complete lactation failure in both preterm and full-term infants (Table 3).[36-48] Metoclopramide

Table 3. Comparison of Metoclopramide Clinical Trials

Reference	Metoclopramide Regimen	Patients	Infant Age (FT/PT)	Milk Attainment	Effect on Milk Production	Infant Weight	Maternal ADRs	Infant ADRs	Notes
Guzman 1979[36]	10 mg 2 times/ day for 4 weeks	Metoclopramide (n = 11) Placebo (n = 10) who could start metoclopramide during week 2 Control (n = 30)	2 days (FT)		Data not collected; considered good for all groups; supplemental formula not needed				All had history of decreased lactation Metoclopramide group started medications before starting lactation
Ertl 1991[37]	10 mg 3 times/day for 5 days	Metoclopramide (n = 11) Placebo (n = 11)	1 day (FT)	Not noted; milk samples by expression	No baseline values Day 5: metoclopramide, 276.4 ± 36.6 mL; placebo, 150.0 ± 25.3 mL ($p < 0.01$)				Pumping or weighing of babies
Ehrenkranz 1986[38]	10 mg 3 times/day for 7 days, then tapered over 2 days	Metoclopramide (n = 17)	32 ± 3.7 days (PT)	Electrical or hand breast pump	Metoclopramide 93.3 ± 18 mL (day 1) to 197.4 ± 23 mL (day 7) ($p < 0.001$)		Diarrhea (1), nervousness (1), tiredness (1)	None	All babies premature; mean gestational age 30.4 ± 0.7 weeks
Kauppila 1981[39]	5, 10, or 15 mg 3 times/day for 2 weeks	5 mg (n = 10) 10 mg (n = 13) 15 mg (n = 14)	8-62 days (FT)	Nursing	5 mg: 12.1 mL (92.4 vs 104.5) Placebo: 4.4 mL (96.8 vs 92.4) 10 mg: 42.5 mL (96.3 vs 138.8) ($p < 0.001$) Placebo: 10.5 mL (96.3 vs 106.8) 15 mg: 50 mL (80.3 vs 130.3) ($p < 0.05$) Placebo: –0.3 mL (80.3 vs 80)	5 mg: 380 ± 153 g Placebo: 331 ± 144 g 10 mg: 439 ± 143 g Placebo: 385 ± 132 g 15 mg: 480 ± 138 g Placebo: 449 ± 162 g	Tiredness (1), headache (1), anxiety (1), hair loss (2), intestinal disorders (2)		Crossover vs placebo for each strength of metoclopramide Lactational response measured by weighing infant –8 dropouts
Kauppila 1981[40]	10 mg 3 times/day for 3 weeks, off 1 week, repeat for 2 weeks	(n = 17)	18-141 days (mean 40.8) (unknown whether FT/PT)	Nursing	Baseline vs end of treatment First treatment: 194 mL (433 ± 55 mL vs 626 ± 76 mL; $p < 0.001$) Second treatment: 214 mL (390 ± 73 mL vs 606 ± 56 mL; $p < 0.01$)	Baseline, mean 4653 g Gain, mean 5%/week	Tired (5), nausea (2), headache (1), vertigo (1), gas (1)	Gas (1)	
Kauppila 1985[41]	10 mg 3 times/day for 3 weeks	(n = 11) Placebo (n = 14)	4-20 weeks (unknown whether FT/PT)	Nursing	285 ± 75 mL to 530 ± 162 mL/day ($p < 0.01$) Placebo: no change		Tired (4), tired plus headache (1), tired plus nausea (1)	None	Randomized controlled Conducted in Finland
Lewis 1980[42]	10 mg 3 times/day for 7 days	(n = 10) Placebo (n = 10)	7-10 days (14 FT, 3 PT per group)	Not noted	Similar rates of breastfeeding at 10 days, 6 weeks, and 3 months postpartum		None	None	Published as letter to the editor Randomized controlled All delivered via caesarean section
De Gezelle 1983[43]	10 mg 3 times/day for 8 days	(n = 7) vs control (n = 6)	1 day (FT)	Nursing every 3 hours	50.7 ± 14.6 g (day 3) to 84.3 ± 28.8 g (day 8) vs control: 41.7 ± 24 g (day 3) to 41.7 ± 25.6 g (day 8) Day 3, NS Day 8, $p < 0.05$		None	None	Production estimated by weighing baby before and after second daily feeding

Gupta 1985[44]	10 mg 3 times/day for 10 days	(n = 32) Complete lactation failure (12) Partial lactation failure (20)	Unknown (FT/PT)	Nursing	Complete lactation failure: 4 no response; 8 had response (supplemental feedings decreased from 505.83 ± 60.20 mL to 223.75 ± 64.75 mL at 8 weeks) Partial lactation failure: 13 required supplementary feedings, but decreased from 270.5 ± 36.87 mL to 153.07 ± 38.85 mL at 8-week follow-up; 7 eliminated supplementary feedings within 5-11 days of initiating metoclopramide		None	None	Conducted in India All infants managed in specialized care center for prematurity (6), birth weight <2500 g (9), low birth weight for gestational age (3), neonatal infection (5), hyperbilirubinemia (3), maternal pre-eclampsia (7) 4 nonresponders in complete lactation failure group had complete failure of lactation for 30 days prior to study entry
Hansen 2005[45]	10 mg 3 times/day for 10 days	(n = 28) vs placebo (n = 29)	3 days (PT)	Electric breast pump	Metoclopramide not associated with significant increase in milk volume compared with placebo on each of 17 study days		Facial rash and itching (1)	1 death at day 10, not related to study drug	Randomized controlled All received education from lactation nurse Women recorded length of time pumping each time (results not provided) Preterm infants with gestational age 23-34 weeks at delivery Milk volume exact data not presented (only represented in graph)
Seema 1997[46]	10 mg 3 times/day for 10 days	(n = 25) vs control (n = 25)	<4 months (unknown whether FT/PT)	Nursing	Not noted Relactation successful in 49 (98%) mothers	No significant difference for 12-14 weeks of follow-up			Conducted in India All received vitamin supplementation and lactation education 76% of mothers did not start breastfeeding "soon after delivery" 86% baseline had complete lactation failure; 14% were partial failure Infant weight exact data not presented (only represented in graph) Birth weight estimated to nearest 5 g
Sakha 2008[47]	10 mg 3 times/day for 15 days	(n = 10) vs control (n = 10)	Unknown (FT)	Nursing	Data not provided	No difference between groups over 15 days Metoclopramide 351.1 g vs control 328.5 g			Randomized controlled Conducted in Iran All received training for breastfeeding
Fife 2011[48]	10 mg 3 times/day for 8 days	(n = 13) vs placebo (n = 13)	Within 6 hours (PT)	Pumping every 3 hours	All increased significantly from baseline No differences between groups		Moderate to very severe reports Fatigue (10), nervous (3), constipation (2), depression (2), headache (1), diarrhea (1) No difference compared with placebo	None	Randomized controlled 3 metoclopramide and 4 placebo dropouts Did not maintain power (10 pts. per group) Preterm infants delivered ≤34 weeks gestation All pts. received lactation education Milk volume exact data not presented (only represented in graph)

ADRs = adverse drug reactions; FT = full-term delivery; PT = preterm delivery.

has been studied in 13 trials with mixed results; however, the most recent, a randomized controlled trial with strong trial design, failed to maintain power, which may have contributed to the lack of significant differences found between groups.[48] Metoclopramide crosses into breast milk, but this would result in subtherapeutic infant exposure because of a low relative infant dose of 4.4%; the theoretical infant dose is 18.75 µg/kg/day.[49] One study estimated that the maximum exposure of the infant to metoclopramide would be 45 µg/kg/day, whereas typical pediatric dosing is 100-500 mg/kg/day for reflux.[42,49] The only adverse event reported in infants has been intestinal gas. Limitations of these studies include small sample sizes, short duration, and indirect measurement of milk production by weighing the infant before and after feeding, as well as not reporting maternal and infant adverse events, infant weight gain, and adherence. Additionally, no data were provided about several factors known to influence milk supply, including length or frequency of breastfeeding, caloric and fluid intake, and stress/pain evaluation of the mother, nor was information regarding adherence reported. Several studies were conducted in different countries, making it difficult to evaluate the influence of culture, diet, and other differences that might exist. Overall, metoclopramide has been evaluated as a galactogogue in 213 mothers, with mixed results. When comparing various patient characteristics (preterm vs full-term), time of initiation (within 14 days postpartum vs later), or trial characteristics (milk production measured by weighing the infant vs pumping; randomized controlled trials vs other designs), no subgroup strongly demonstrated efficacy or overall efficacy.

Metoclopramide should not be used for all patients. The labeling has a boxed warning for risk of tardive dyskinesia when the drug is used for more than 3 months.[50] Women with a history of tardive dyskinesia or seizures or who are at risk for developing tardive dyskinesia should avoid using this product. Metoclopramide may also increase the risk for serotonin syndrome when used with other medications that act on serotonin. A few examples include selective serotonin receptor inhibitors, serotonin-norepinephrine receptor inhibitors, monoamine oxidase agonist inhibitors, and tramadol. Metoclopramide is renally eliminated and requires dose reductions to 50% the normal dose when creatinine clearance is less than 40 mL/min. Patients with pheochromocytoma should also avoid metoclopramide because of the potential for hypertensive crisis. Despite the AAP listing of metoclopramide as a drug with effects that are unknown but that may be of concern, it received a lactation category of L2 (safer: been studied in a limited number of breastfeeding women without an increase in adverse events in the infant, and/or evidence of demonstrated risk in infant is remote) in *Medications in Mother's Milk* and is considered medication with small risk in *Drug Use in Pregnancy and Lactation*.[49-51]

Other Medications

Several other medications have been suggested as galactogogues and/or have properties that may improve lactation. First-generation antipsychotics and risperidone produce increased prolactin levels and may increase milk supply. However, without a diagnostic indication for their use, we do not recommend initiating therapy for breast milk production alone because of potential maternal and infant adverse events.[32]

Beer has been recommended for nursing mothers since the 1800s. Beer is thought to increase milk production by increasing prolactin levels.[52,53] However, studies have shown that breastfeeding infants consume 20% less milk 3-4 hours after the ingestion of beer by the mother, which was unrelated to the number or duration of feedings but was likely secondary to decreased quantity produced.[54,55] Additionally, some of the alcohol consumed by the mother is transferred to her milk and consumed by the infant. Alcohol consumption has detrimental effects on the infant, including disruption in sleep patterns and effects on gross motor development.[55] Therefore, beer is no longer recommended as a galactogogue.[2]

Although not touted as a galactogogue, depot-medroxyprogesterone (DMPA) has been shown to have favorable effects on milk supply in women using the drug for contraceptive purposes.[56-58] It is speculated that galactogogue properties may be secondary to an increase in prolactin levels.[58] To date, no studies looking at DMPA galactogogue effects as a primary outcome have been completed.

Human growth hormone (GH) in doses ranging from 0.1 to 0.2 IU/kg/day (maximum of 16 IU/day) for 7 days has also been used as a galactogogue because of its proposed ability to increase prolactin levels.[59,60] GH lacks FDA indication for use as a galactagogue and has several limitations for use. First, it is injected subcutaneously, which would require mothers to prepare and inject it multiple times per day. Second, GH is expensive. Also, the FDA is conducting an investigation on the safety of GH use during childhood, with specific concerns for increased mortality due to bone tumors and cardiovascular events in children exposed to GH.[61] Considering these factors, GH is not recommended for use as a galactogogue.

Thyroid-releasing hormone (TRH) has also been used as a galactogogue. TRH is secreted in breast milk and, to date, 3 of 4 studies have reported no benefit to using TRH as a galactogogue. TRH dosing in these studies ranged from 1 mg as a nasal spray 4 times daily for 10 days, 5 mg twice daily for 5 days, 20 mg twice daily for 2 weeks, to 20 mg twice daily for 3 weeks. Each study reported an increase in triiodothyronine and thyroxine; however, the studies have not reported incidences of hyperthyroidism in the mothers or infants.[62-65] Unfortunately, the study periods have not been long enough for the effects of elevations in

triiodothyronine and thyroxine to be fully evaluated, and there is a potential for mothers and infants to develop hyperthyroidism. Because of this risk and lack of evidence overall of increased breast milk production, TRH is not recommended for use as a galactogogue at this time.

Discussion

Breast milk is considered to be the optimal food source for newborns through 1 year of age. Although it is a natural food source, women often encounter difficulties when attempting to breastfeed and turn to supplemental sources of nutrition, such as formula, for their infant prior to the infant's first birthday. Although there are a variety of herbal and pharmaceutical options that have anecdotal evidence supporting their ability to improve breast milk production, peer-reviewed studies proving their efficacy and safety are lacking.

When approaching lactation difficulties, health care providers should provide recommendations in a stepwise fashion. Nonpharmacologic measures should first be used to increase breast milk production. All mothers should receive extensive education about proper breastfeeding techniques, including latching, positioning, and length of feeding, since these factors can significantly affect breastfeeding. Stress contributes to decreased milk production by decreasing oxytocin release.[6,7,14] Because of this, relaxation techniques, deep breathing, gentle massages, eating or drinking enjoyable foods and beverages, and listening to music while breastfeeding have been shown to initiate the milk ejection reflex as has looking at things that remind her of the baby, such as a picture or blanket, while pumping.[66] Other methods that encourage complete emptying of the breasts include massaging and warming the breasts while pumping.[67-69] Techniques to increase milk supply include increasing feeding/pumping time, decreasing intervals between feedings, increasing duration of pumping, and increasing caloric and fluid intake. Some studies have shown that pumping both breasts simultaneously may increase breast milk production as well as save the mother time.[66,70]

If nonpharmacologic interventions fail to improve supply, the health care provider could consider recommending metoclopramide or fenugreek; however, both medications lack strong evidence to support efficacy. Metoclopramide and fenugreek have some clinical evidence of their usefulness in increasing breast milk production in lactating women and they appear to be safe for the breastfeeding infant. Although fenugreek is rated as GRAS, it is important for the health care provider to remember that it has minimal safety data when used as a galactogogue. As for safety, metoclopramide is considered by AAP to be a medication with unknown effects, but its use may be of concern; however, other breastfeeding sources have granted it category L2 status, medication with small risk.[49,51]

Studies focused on breastfeeding are limited and often lack the rigor and design that are expected in medical research. Limitations of lactation studies often include small sample sizes, short duration, and indirect measurement of milk production by weighing the infant before and after feeding. Additionally, trials commonly lack control for factors known to influence milk supply, including length or frequency of breastfeeding, caloric and fluid intake, warming and massaging of breasts, and evaluation of maternal levels of stress/pain. Currently, there are no available data evaluating repeat courses or effects on lactation after medication discontinuation for any medication.

Summary

Although anecdotal evidence encourages the use of metoclopramide, fenugreek, asparagus, and milk thistle for their galactogogue properties, efficacy and safety data in the literature are lacking. When examining the limited reported data on potentially subtherapeutic exposure to the infant, it is likely that metoclopramide and fenugreek can be used; however, exposed infants should be monitored for any adverse events. Oxytocin and domperidone are potentially available for compounding purposes, but safety data are limited. Unfortunately, at this time there is not enough efficacy and/or safety evidence to support using other proposed galactogogues such as milk thistle, goat's rue, beer, brewer's yeast, alfalfa, asparagus, domperidone, oxytocin, GH, TRH, or DMPA. Additionally, potential risk for maternal and/or infant harm has not been fully elucidated. More studies are needed to evaluate the effects of available galactogogues on breast milk production.

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EXTRACTO

Uso de Estimulantes de Producción de Leche Materna en Madres que Amamantan

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Ann Pharmacother 2012;46:1392-404.

OBJETIVO: Revisar los datos existentes sobre la eficacia de productos disponibles en los Estados Unidos y utilizados para estimular la producción de leche materna.

FUENTE DE DATOS: Se realizó una búsqueda en PubMed (1966–junio 2012) y EMBASE (1973–junio 2012) utilizando los términos amamantar, leche materna, lactancia, metoclopramida, oxitocina, hormona de crecimiento, hormona estimulante de la tiroides, medroxiprogesterona, domperidona, hierbas, galactogogue, fenugreek, milk thistle, silymarin, goat's rue, beer, asparagus racemosus, shatavari, medicago sativa, alfalfa, onicus benedictus, blessed thistle, galega officinalis, y brewer's yeast.

SELECCIÓN DE ESTUDIOS Y EXTRACCIÓN DE DATOS: Se evaluaron todos los estudios que incluyeran humanos, publicados en el idioma inglés y que evaluaran la eficacia de productos utilizados para estimular la producción de leche materna.

SÍNTESIS DE DATOS: A pesar que existe evidencia anecdótica que indica que varias opciones farmacéuticas y productos herbarios causan un aumento en la producción de leche materna, no existe suficiente evidencia en la literatura que apoye su eficacia. Estudios con metoclopramida, oxitocina, fenugreek, y milk thistle han tenido resultados inconsistentes relacionados con la producción de leche materna. Las muestras estudiadas son pequeñas y sus diseños tienen varias limitaciones.

CONCLUSIONES: La leche materna es considerada la mejor fuente de alimento para niños desde su infancia hasta el primer año de edad. Varios factores influyen la producción de leche materna, incluyendo presencia de dolor, enfermedades, tiempo disponible, ansiedad, y estrés emocional. Se deben agotar las recomendaciones no farmacológicas antes de añadir algún otro tratamiento. A pesar que existe evidencia anecdótica que fomenta el uso de metoclopramida, fenugreek, asparagus, y milk thistle para aumentar la producción de leche materna, es necesaria evidencia científica que apoye su eficacia y seguridad. La oxitocina y domperidona pudieran estar disponibles para la preparación de mezclas extemporáneas potencialmente útiles, pero los datos sobre la seguridad de su uso son limitados. Son necesarios estudios que evalúen el efecto de los productos disponibles en la producción de leche materna.

Traducido por Astrid J García-Ortiz

RÉSUMÉ

L'Usage des Galactogogues chez la Mère qui Allaite

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Ann Pharmacother 2012;46:1392-404.

OBJECTIF: Revoir les données concernant l'efficacité des galactogogues disponibles aux États-Unis et utilisés pour favoriser une production accrue de lait maternel après l'accouchement.

SOURCES DE DONNÉES: Une revue de la documentation scientifique a été effectuée par le biais de PubMed (1966 à Juin 2012) et EMBASE (1973 à Juin 2012). Les termes de recherche de langue anglaise incluaient: breastfeeding, breast milk, lactation, galactogogue, metoclopramide, oxytocin, fenugreek, milk thistle, silymarin, growth hormone, thyroid releasing hormone, medroxyprogesterone, domperidone, goat's rue, beer, asparagus racemosus, shatavari, medicago sativa, alfalfa, onicus benedictus, blessed thistle, galega officinalis, brewer's yeast, et herbals.

SÉLECTION DES ÉTUDES ET EXTRACTION DES DONNÉES: Toutes les études de langue anglaise incluant des sujets humains et des données évaluant l'efficacité des galactogogues pour augmenter la production de lait maternel ont été évaluées.

SYNTHÈSE DES DONNÉES: De l'information anecdotique est disponible pour une variété d'options pharmaceutiques et botaniques concernant leur utilité pour améliorer la production de lait maternel. Cependant la documentation scientifique démontrant leur efficacité est insuffisante. Les options tels que le métoclopramide, l'oxytocine, le fenugreek, et le milk thistle ont démontré des résultats conflictuels en ce qui a trait à leur capacité d'augmenter la production de lait maternel. Cependant, les essais cliniques sont de faible envergure et présentent plusieurs limites.

CONCLUSIONS: Le lait maternel est considéré comme l'option nutritive optimale pour les nouveaux nés jusqu'à l'âge de 1 an. Plusieurs facteurs influencent la production de lait maternel incluant les douleurs postpartum et subséquentes, la maladie, le temps disponible lors d'un retour au travail, l'anxiété, et le stress émotionnel. Les options non pharmacologiques doivent être épuisées avant d'ajouter une thérapie médicamenteuse. Bien que des données anecdotiques encouragent

l'utilisation de métoclopramide, de fenugreek, d'asparagus racemosus, et de milk thistle pour leurs propriétés galactogogues, les données concernant leur efficacité et leur innocuité sont insuffisantes dans la documentation scientifique. L'oxytocine et le dompéridone sont des traitements potentiellement disponibles pour des fins de préparations magistrales mais les données d'innocuité sont limitées. Des études additionnelles sont nécessaires afin d'évaluer les effets des galactogogues présentement disponibles sur la production de lait maternel.

Traduit par Chantal Guévremont