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ABM Clinical Protocol #9: Use of Galactogogues in Initiating or Augmenting Maternal Milk Production, Second Revision 2018

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A central goal of the Academy of Breastfeeding Medicine is the development of clinical protocols for managing common medical problems that may impact breastfeeding success. These protocols serve only as guidelines for the care of breastfeeding mothers and infants and do not delineate an exclusive course of treatment or serve as standards of medical care. Variations in treatment may be appropriate according to the needs of an individual patient.

Background

Galactogogues (or lactagogues) are medications or other substances believed to assist initiation, maintenance, or augmentation of maternal milk supply. Because perceived or actual low milk supply is one of the most common reasons given for discontinuing breastfeeding,[1–4] both mothers and health professionals have sought medication(s), in addition to other nonpharmacological interventions, to address this concern.

Human milk production is a complex physiological process involving physical and emotional factors and the interaction of multiple hormones, the most important of which is believed to be prolactin. Despite the fact that prolactin is required for lactation, once lactation is established, there is no direct correlation between serum prolactin levels (either baseline levels or percentage increase after suckling) and the volume of milk produced in lactating women.[5,6] However, most lactating women have a higher baseline prolactin level than nonlactating women for a number of months and continue to experience suckling-induced peaks when breastfeeding.

Lactation is initiated with parturition, expulsion of the placenta, and falling progesterone levels in the presence of very high prolactin levels. Systemic endocrine control of other supporting hormones (estrogen, progesterone, oxytocin, growth hormone, glucocorticoids, and insulin) is also important.[7] These hormonal changes trigger secretory activation (lactogenesis II) of the mammary secretory epithelial cells, also called lactocytes. Prolactin secretion functions in a negative feedback system in which dopamine serves as an inhibitor. Therefore, when dopamine concentration decreases, prolactin secretion from the anterior pituitary increases.[7]

Once secretory activation has occurred and the mother's milk supply has been established, the rate of milk synthesis is mainly controlled locally in the mammary gland by autocrine control. Lactating breasts are never completely empty of milk, so the terms drain, drainage, and draining are more appropriate. If the breasts are not drained regularly and thoroughly, milk production declines. Alternatively, more frequent and thorough drainage of the breasts typically results in an increased rate of milk secretion, with both immediate (per feeding) and delayed (several days) effects.[8,9]

Potential Indications for Galactogogues

Galactogogues have commonly been used to increase low (or perceived low) milk supply. Physiologically, low milk supply is often related to suboptimal milk removal with reasons including problems with infants draining the breast, inappropriate breastfeeding management, maternal or infant illness and hospitalization, and regular mother–infant separation, for example, work or school. In addition, galactogogues have frequently been used in the neonatal intensive care unit in mothers with preterm infants, where the aim has been to stimulate initial secretory activation or augment declining milk secretion. Mothers who are not breastfeeding, but are expressing milk by hand or with a pump, often experience a decline in milk production after several weeks. Galactogogues have also been used in women inducing lactation when they have not been pregnant with the current child, in women relactating after weaning, or in transgender women.[10]

Many breastfeeding medicine specialists and lactation consultants have recommended various drugs and herbs when other nonpharmacological measures have not resulted in an increase in milk volume. However, some providers may inappropriately recommend galactogogues before emphasizing the primary means of increasing the overall rate of milk synthesis (i.e., frequent and effective milk drainage at regular intervals) or evaluating other medical factors that may potentially be involved (see point 1 in the Practice Recommendations section).

Pharmaceutical Galactogogues

Human growth hormone[11–13](lB, llA) (quality of evidence [levels of evidence IA, IB, IIA, IIB, III, and IV] is based on levels of evidence used for the National Guidelines Clearing House[14] and is noted in parentheses), sulpride[15,16](llB), and thyrotropin-releasing hormone[17,18](lB) may be helpful as galactogogues in some populations, but are not currently used in most countries. Domperidone and metoclopramide are the most commonly used pharmaceutical galactogogues at present. Both are dopamine antagonists that increase prolactin secretion. A number of older mainly observational or controlled studies documented increased baseline prolactin levels in lactating women who took metoclopramide or domperidone and provide some evidence for their effectiveness.[19,20](llA, lll)

However, high-quality evidence is lacking. The numbers of women in randomized, placebo-controlled blinded studies (RCTs) with each of these agents are small. Studies also tended to have high dropout rates, differed in patient selection (i.e., some were expressing for preterm infants, not all women had documented low milk supply), and differed in dose and duration of the galactogogue and application of other nonpharmacological measures before starting the galactogogue. Most studies also had limited follow-up.

Domperidone

A Cochrane systematic review[21](lA) published in 2012 included two studies with a total of 59 mothers with preterm infants and found a moderate benefit (mean increase of 99 mL per day) when using domperidone, 30 mg per day, for 7 or 14 days. Other systematic reviews have similar findings,[22] with the most recent review that included one finding a mean increase of 88.3 mL per day (95% confidence interval 56.8–119.8).[23](lA) There have been four RCTs using domperidone since the Cochrane review. In one study of 45 women, 22 were given domperidone, 30 mg per day, for 4 days postcesarean section and were found to have increased milk production during that time compared with the control group.[24](lB)

In a second study of only 15 women with low milk supply who were expressing for preterm infants, there was a 300-mL per day difference in milk production for women given domperidone, 60 mg per day, for 4 weeks compared with women given domperidone, 30 mg per day, for a similar length of time.[25](lB) A third trial in the United Kingdom compared the effects of domperidone, 30 mg per day, with metoclopramide, 30 mg per day. Women had 24-hour milk production measured from 10 days before the commencement of medication administration and during the 10 days of medication administration.[26] The 51 women were expressing for their preterm infants and had documented low milk supply. They all received high-quality breastfeeding assistance throughout the study. Milk production almost doubled from the steady premedication level with both medications and plateaued after about 7 days of treatment.[26](lB)

The fourth and largest trial to date (EMPOWER) included 90 women who had low milk supply when expressing for preterm infants. They were randomized between 8 and 21 days postpartum to receive domperidone, 30 mg per day, for 28 days or a placebo for 14 days and then domperidone, 30 mg per day, from day 15 to 28.[27] At 14 days, 77.8% of women in the first group had increased their milk production by 50% compared with 57.8% in the second group. By 28 days, there were no significant differences between the two groups, nor were there differences at term or at 6 weeks post-term.[27](lB) The results of one older very small study ($n = 6$) suggested that individual women may be responders or nonresponders and that primiparas may respond to domperidone with higher prolactin levels than multiparas.[28](lB)

With respect to potential risks, there is evidence that domperidone increases the QTc interval and it has been implicated in ventricular arrhythmias and sudden cardiac death, particular in older and unwell adults.[29,30](lA, lV) The risk for domperidone to increase the incidence of arrhythmias in postpartum women with no other risk factors appears to be very small, but may increase with other factors such as a past history of ventricular arrhythmias, high BMI, higher dosages, and concomitant use of medications that inhibit CYP3A4.[31](lll) In this large study of more than 225,532 postpartum women, the only women who developed ventricular arrhythmias while taking domperidone had a past history of ventricular arrhythmias.[32] See Table 1 for further information.

Metoclopramide

Five randomized, placebo-controlled blinded studies researching the effect of metoclopramide have been published between 1980 and 2011.[33–37](lB) Of these, participants in three studies commenced metoclopramide within 4 days of birth without a diagnosis of low milk supply,[33,34,37] one study investigated women who were relactating,[36] and one recruited women whose infants had not gained 500 g within the first month of life.[35] None of these studies found differences in milk volumes and/or breastfeeding duration between metoclopramide and placebo groups, even with optimal breast expression and counseling.[37] However, as mentioned above, Ingram et al.[26] found similar positive effects with metoclopramide and domperidone.

In addition, a number of older randomized controlled trials,[38–41](lB, llA) controlled trials,[42,43](llB) and observational studies[20,44–46](lll) reported a significant increase in milk yield using metoclopramide, 5–20 mg, three times a day for periods of 5 days to 4 weeks. The one study that compared different doses of metoclopramide found no response with 15 mg per day, but similar responses with 30 and 45 mg per day. The scientific rigor of these older studies may not be as strong as more recent studies, so their results should be interpreted with caution. As for potential risks, metoclopramide may cause neurological side effects in the mother. Further information can be found in Table 1.

Summary

Despite the widespread use of these pharmaceutical galactogogues, there are important issues to consider:

1. Pharmaceutical galactogogues do increase baseline serum prolactin, and there is evidence for increased milk production with domperidone use (and perhaps metoclopramide). However, the population that would most benefit from this treatment is still uncertain as it is unknown if all women with low milk supply have low levels of prolactin and whether increasing prolactin increases milk supply in women with both low and normal prolactin levels. In addition, there does not appear to be a direct correlation between baseline

Table 1. Commonly Used Galactogogues

	Domperidone	*Fenugreek*	*Metoclopramide*	*Silymarin*[a]
References	21,24–27,29–31,47,61	56,62–66	20,26,33–37,39–41,45	67–70
Chemical class or properties	Dopamine antagonist	A commonly used spice; active constituents are trigonelline, 4-hydroxyisoleucine, and sotolon.	Dopamine antagonist	Flavolignans (presumed active ingredient)
Level of evidence	Five Level 1B studies; others have inadequate methodology or excessive dropout rates	IIA-IIB (three studies in lactating women) most not of high quality; mixed results	IB-IIB high-quality and low-quality studies give mixed results; effect on overall rate of milk secretion is unclear, but may be effective	IIB (one study in lactating women)
Suggested dosage	10 mg, orally, 3 times per day used in most of the Level IB studies; one Level 1B study compared 10 mg 3 times per day with 20 mg 3 times per day and found higher milk production using the higher dose. Doses >60 mg per day have not been studied in this context.	Herbal tea (200 ml 3 times per day); 570–600 mg 3 times per day.	10 mg, orally, 3 to 4 times per day	Micronized silymarin, 420 mg, orally, per day in the study by Di Pierro et al.[67]; silymarin-phosphatidylserine and galega (5 g per day); anecdotal, strained tea (simmer 1 tsp of crushed seeds in 8 oz of water for 10 minutes), 2–3 cups per day[71]
Length/duration of therapy	Various commencement times from 2 days to 3 to 4 weeks postpartum in Level 1B studies. Duration of therapy between 7 and 28 days. Maximum effect usually reached by 7–14 days.	1–3 weeks	7–14 days in various studies	Micronized silymarin was studied for 63 days; silymarin-phosphatidylserine and galega were used for 28 days
Herbal considerations	—	Need reliable source of standard preparation without contaminants	—	Need reliable source of standard preparation without contaminants
Effects on lactation	Increased rate of milk secretion in both pump-dependent mothers of preterm infants and other mothers with low milk supply.	Insufficient evidence; likely a significant placebo effect	Possible increased rate of milk secretion; possible responders versus nonresponders	Inconclusive. Possible increase in milk secretion in the short term
Potential side effects	Maternal: Dry mouth, headache (resolved with decreased dosage), and abdominal cramps. One case reported of psychomotor withdrawal symptoms from a dose of 160 mg per day.[72] Although not reported in studies of lactation, rare complications (1.3/10,000 postpartum women) of cardiac arrhythmias due to a prolonged QTc interval have been reported, but all these women had a past history of ventricular arrhythmias.[31] Risk	Generally well tolerated. Diarrhea (most common), unusual body odor similar to maple syrup, cross-allergy with Asteraceae/Compositae family (ragweed and related plants), peanuts, and Fabaceae family such as chickpeas, soybeans, and green peas—possible anaphylaxis. Theoretically, asthma, bleeding, dizziness, flatulence, hypoglycemia, loss of consciousness, skin rash, or wheezing—but no reports in lactating women.	Reversible CNS effects with short-term use, including sedation, anxiety, depression/agitation, motor restlessness, dystonic reactions, and extrapyramidal symptoms. Rare reports of tardive dyskinesia (usually irreversible), causing the FDA to place a black box warning on this drug in the United States.	Generally well tolerated; occasional mild gastrointestinal side effect; cross-allergy with Asteraceae/Compositae family (ragweed and related plants)—possible anaphylaxis

(*continued*)

Table 1. (Continued)

	Domperidone	*Fenugreek*	*Metoclopramide*	*Silymarin*[a]
	may increase with a previous history of cardiac arrhythmias, high doses, high BMI, or concurrent use of drugs that inhibit domperidone's metabolism (see Interactions, immediately below). Neonatal: Very low levels in milk and no QTc prolongation in premature infants who had ingested breast milk of mothers on domperidone.[73] In the United States, the FDA has issued an advisory against the use of domperidone in lactating women.[47]			
Interactions	Increased blood levels of domperidone when combined with some substrates metabolized by CYP3A4 enzyme inhibitors, for example, fluconazole, macrolide antibiotics, grapefruit juice, cannabinoids, antipsychotics, and others	Hawthorne, hypoglycemics, including insulin, antiplatelet drugs, aspirin, heparin, warfarin, feverfew, primrose oil, and many other herbals	Monoamine oxidase inhibitors, tacrolimus, antihistamines, any drugs with CNS effects (including antidepressants)	Caution with CYP2C9 substrates—may increase levels of the drugs. Possible increased clearance of estrogens (decreased blood levels). Possible increased levels of statins.
Comments	a. Do not advise exceeding maximum recommended dosage. b. Generally licensed for use as a drug for gastrointestinal dismotility where doses of 20 mg 3 or 4 times per day may be recommended if no response to lower doses. Some areas use this dose initially to stimulate prolactin. However, there is only one study using this dose in lactating women. c. Tapering of dose usually recommended.	If patient develops diarrhea, reducing the dose is often helpful.	Some studies suggest tapering off the dose at the end of treatment.	No prescription required

[a]Silymarin (micronized silymarin) or *Silybum marianum* (milk thistle).
CNS, central nervous system; CYP, cytochrome *c*; FDA, Food and Drug Administration.

prolactin levels and rates of milk synthesis or measured volumes of milk production.

2. Potential side effects (minor and significant) should be weighed carefully against any potential benefit.
3. Prescription medications used as galactogogues constitute off-label use in most countries (they are not approved by regulatory agencies for this indication). Domperidone is not approved by the Food and Drug Administration (FDA) for use in the United States, except for some specific circumstances. The FDA has explicitly recommended against the use of Domperidone to increase milk production.[47,48]

Herbals, Foods, and Beverages as Galactogogues

In non-Western cultures, postpartum women are assisted in a number of ways that are intended to ease their transition to motherhood and to optimize breastfeeding. Many cultures keep new mothers very warm and insist on a period of rest of ~1 month. Many also have traditional foods and herbs for

postpartum women that are meant to increase the mother's strength and enhance lactation.[49–52](IV)

Many of these herbal remedies have been used throughout history to enhance milk supply. Some herbs commonly mentioned as galactogogues include fenugreek, goat's rue, milk thistle (*Silybum marianum*), oats, dandelion, millet, seaweed, anise, basil, blessed thistle, fennel seeds, marshmallow, moringa leaf, shatavari, and torbangun among others.[22,53](IA) LactMed (https://toxnet.nlm.nih.gov/newtoxnet/lactmed.htm) has further information about the effect on lactation of some of these herbs. Although beer is used in some cultures to increase milk supply, hops appear to be the active ingredient, while alcohol may actually reduce milk production.[54](IA) A barley component of beer (even nonalcoholic beer) can also increase prolactin secretion.[55]

While the fact that these herbs have been used for centuries without apparent harm is reassuring, there is also little or no scientific evidence for their effectiveness or safety.[56] The mechanisms of action for most herbals are unknown, and available studies for herbs, herbal medicines, or herbal galactogogues suffer from the same deficiencies as the studies for pharmacologic agents: small numbers of subjects, lack of information regarding breastfeeding advice, and lack of randomization, controls, or blinding. The placebo effect when taking herbal preparations may be the reason for widespread anecdotal experience of their effectiveness. Because of the limited data available, only two herbal preparations have been included in Table 1.

It is important to note that caution is required for the use of herbal preparations because of the lack of standardized dosing preparations (other than in research settings), possible contaminants, allergic potential, and drug interactions. Adverse effects for both mother and infant from several herbs have been reported,[56](IV) and some will increase patient blood levels of warfarin, heparin, and other anticoagulants, while others may affect insulin resistance and blood sugars. There are several reports of severe maternal allergic reactions to fenugreek.[57](III)

Practice Recommendations

The following recommendations, based upon current evidence, apply to women experiencing difficulties with a low rate of milk production (e.g., the infant is not gaining weight normally or supplementation is being used because of low milk production during either the initiation or maintenance of milk supply). It is always important to ensure that low weight gain is due to insufficient calories from low milk supply and not other infant causes.

Specific information about individual drugs and herbs is summarized at the end of these recommendations in Table 1.

1. Evaluate the mother for medical causes of low milk supply: pregnancy, medications, primary mammary glandular insufficiency, breast surgery, polycystic ovarian syndrome, hypothyroidism, retained placenta, ingestion of placenta capsules, theca lutein cyst, loss of prolactin secretion following postpartum hemorrhage, heavy smoking or alcohol use, or other pertinent conditions. Treat the condition as indicated if treatment is available.[58] For many of these women, a galactogogue should not be recommended or prescribed.
2. Assess and increase the frequency and effectiveness of milk removal. Use nonpharmacologic measures to increase the overall rate of breast milk synthesis. For women whose infants are not effective at milk removal or are unable to feed at the breast (e.g., premature, hospitalized, hypotonic, and anatomical problems), regularly expressing by hand and/or breast pump is necessary. Ensure that the expressing technique and any breast pumps used are effective. Galactogogues will not increase the milk supply if there is infrequent or inadequate breast drainage.
3. Although there are more high-quality studies of domperidone and some studies of herbal galactogogues since the last revision of this protocol, current research of both pharmaceutical and herbal galactogogues is still relatively inconclusive and all agents have potential adverse effects. Therefore, ABM cannot recommend any specific galactogogue at this time.
4. If the healthcare provider chooses to prescribe a galactogogue after weighing potential risks versus potential benefits of these agents, they should follow the guidelines below.[56,59,60](IV)
   a. Inform women about available data concerning efficacy, timing of use, and duration of therapy of galactogogues.
   b. Inform women about available data concerning potential adverse effects of galactogogues.
   c. Screen the mother for contraindications to, allergies to, or drug interactions with the chosen medication or other substance.

If prescribing domperidone:

   i. It is particularly important to screen mothers for a past history of cardiac arrhythmias and concomitant use of medications such as fluconazole, erythromycin, and other macrolide antibiotics (Table 1).
   ii. While no studies have been undertaken, some practitioners perform an electrocardiogram on women of concern before commencement of the medication and at 48 hours. If there is prolongation of the QTc interval, the medication is ceased.

   d. Provide ongoing care to, supervise ongoing care of, or transfer care of both mother and infant to ensure appropriate follow-up and attention to any side effects.
   e. Prescribe galactogogues at the lowest possible doses for the shortest period of time; do not exceed recommended therapeutic doses.
   f. Consider gradually discontinuing the drug (tapering the dose) rather than abruptly discontinuing the therapy; some studies simply stop the drug at the conclusion of therapy and others gradually discontinue the drug, with no clear advantage to either method.
   g. If milk production wanes after stopping the drug and improves again with resumption of medication, attempt to gradually decrease the drug to the lowest effective dose and then discontinue the drug at a later date if possible.
   h. Consider documenting that there has been a discussion about contraindications and that the mother has been provided with information about the benefits and risks of any galactogogue being prescribed.

Conclusions

Before the use of a galactogogue, a lactation expert should thoroughly evaluate the entire feeding process and maximize

nongalactogogue management. In the absence of evidence for low milk supply, the mother should be reassured. When intervention is indicated, modifiable factors should be addressed: maternal anxiety and mental health issues, comfort and relaxation for the mother, frequency and effectiveness of milk removal, and any underlying medical conditions.

Medication should never replace evaluation and counseling on modifiable factors. There remain selected indications for the use of galactogogues, but the current data are insufficient to make any definitive recommendations. A number of high-quality studies have found domperidone to be useful in mothers of preterm infants (Table 1), although there is concern about rare, but significant, adverse effects. Herbal galactogogues are problematic because of lack of regulation of preparations and insufficient evidence of efficacy and safety.

Clinicians should prescribe galactogogues with appropriate caution with regard to drug-to-drug (or drug-to-herb) interactions as well as an overall risk-to-benefit approach and complete informed consent. Close follow-up of both mother and infant is essential to monitor the status of lactation as well as any adverse effects of the drug(s) on the mother or infant.

Recommendations for Further Research

At present, there are ongoing studies investigating the effects of insulin resistance on milk supply and whether metformin can act as a galactogogue in women with insulin resistance and low milk supply. We await with interest the outcome of these studies.

However, existing studies about galactogogues cannot be considered conclusive, and many of the recommendations are based primarily on expert opinion, small studies, and studies in which nonpharmacologic breastfeeding support was suboptimal and not standardized. Most studies have been conducted on mothers of preterm infants using mechanical breast pumps rather than on mothers of term infants whose problems usually arise in the first few days to weeks postpartum. There is a clear need for well-designed, adequately powered, randomized controlled trials using adequate doses of galactogogues in populations of women in which both the experimental and control groups receive up-to-date, appropriate lactation support.

These studies need to be done in mothers of both term and preterm infants and need to measure clinically relevant outcomes such as infant weight gain, need for artificial feeding (supplements other than mother's own milk), quantification of maternal milk production, and adverse drug effects. In addition, research should be undertaken investigating cultural practices and foods that have been used to stimulate and maintain milk production over many centuries.

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ABM protocols expire 5 years from the date of publication.

The content of this protocol is up to date at the time of publication. Evidence-based revisions are made within 5 years or sooner if there are significant changes in the evidence.

Previous versions of this protocol were authored by Nancy Powers and Anne Montgomery.

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