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ABM Clinical Protocol #9: Use of Galactogogues in Initiating or Augmenting the Rate of Maternal Milk Secretion (First Revision January 2011)

The Academy of Breastfeeding Medicine Protocol Committee

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. These guidelines are not intended to be all-inclusive, but to provide a basic framework for physician education regarding breastfeeding.

Background

Galactogogues (or lactogogues) are medications or other substances believed to assist initiation, maintenance, or augmentation of the rate of maternal milk synthesis. Because perceived or actual low milk supply is one of the most common reasons given for discontinuing breastfeeding,[1–8] both mothers and health professionals have sought medication(s) to address this concern. Evaluation of evidence-based studies and emerging information regarding more serious potential side effects of some galactogogues have resulted in a recent shift in the Academy of Breastfeeding Medicine's recommendations regarding these drugs and herbs. In 2004, the previous version of this protocol used existing evidence that prescription galactogogues were effective and described when and how to use them.[9] Emerging data suggest that we should exercise more caution in recommending these drugs to induce or increase the rate of milk secretion in lactating women, particularly in women without specific risk factors for insufficient milk supply.

Human milk production is a complex physiologic 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, there has been no evidence for direct correlation of serum prolactin levels (baseline or percentage increase after suckling) with the volume of milk production in lactating women.[10–12]

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.[13] 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. The theory behind pharmaceutical galactogogues is that dopamine antagonists increase prolactin secretion[14] and subsequently increase the overall rate of milk synthesis. However, as mentioned above, no correlation exists between serum prolactin and increased milk volume.[10–12]

After secretory activation, the rate of milk synthesis is controlled locally in the mammary gland by autocrine control. Lactating breasts are never completely "empty" of milk, so the terms "drain, drainage, draining," etc., 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 a rapid (per feeding) effect and a delayed (several days) effect.[12] Even though the rate of milk synthesis is controlled locally at this stage of lactation, suckling-induced peaks of prolactin continue throughout the entire course of breastfeeding.

Potential Indications for Galactogogues

Galactogogues commonly have been used to increase a faltering rate of milk production, often due to the effects of maternal or infant illness and hospitalization or because of regular separation such as work or school. One very common area of use has been the neonatal intensive care unit, where the aim has been to stimulate initial secretory activation or augment declining milk secretion in these mothers. 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 for adoptive breastfeeding (induction of lactation in a woman who was not pregnant with the current child) and relactation (reestablishing milk secretion after weaning).

Many breastfeeding medicine specialists and lactation consultants have recommended these drugs and herbs, usually as a last resort when other non-pharmacological measures have not resulted in an increase in milk volumes. However, some providers may inappropriately recommend galactogogues prior to emphasizing the primary means of increasing the overall rate of milk synthesis (i.e., frequent feeding and complete milk removal at regular intervals) or evaluating other medical factors that potentially may be involved.

Pharmaceutical Galactogogues

Currently available pharmaceutical galactogogues are all dopamine antagonists and will increase prolactin levels via this mechanism.[12] A number of older studies documented increased baseline prolactin levels in lactating women who took metoclopramide or domperidone.[15–20] However, there are only a few randomized, placebo-controlled, blinded studies on each of these agents, and these studies are small.

Domperidone

Regarding domperidone, there are two well-designed randomized, placebo-controlled, blinded studies. One of the studies, published in 2010 ($n = 46$), shows that domperidone is associated with significantly increased volumes of expressed milk among women with premature infants less than 31 weeks' gestation; the study concluded at 14 days, so longer-term effects cannot be evaluated.[11] One very small study ($n = 6$) suggests that individual women may be "responders" or "non-responders" and that primiparas may respond to domperidone with higher prolactin levels than multiparas."[21]

Metoclopramide

For metoclopramide, only four randomized, placebo-controlled, blinded studies have been published, and they each have some problem(s) in design, small sample size, and/or patient selection.[22–25] Metoclopramide did not produce a statistically significant effect on infant weight gain in a randomized controlled trial of metoclopramide versus placebo in a 2008 study of 20 mothers who were relactating: 10 women received metoclopramide, and 10 received placebo; all received a course of standardized counseling regarding optimal breastfeeding technique.[24] These results replicated an earlier study with a total of 50 mothers.[25] All four of these higher-quality studies[22–25] found no differences in milk volumes and/or duration of breastfeeding between metoclopramide and placebo. Two found optimal breastfeeding instruction or counseling to be positively associated with a statistically significant increase in infant weight gain (and corresponding decrease in use of supplemental feedings).[24,25] The other two did not evaluate or assist with optimal breastfeeding routines.[22,23]

Summary

Despite widespread use of these pharmaceutical galactogogues, there are important reasons for reconsideration of this practice:

- Galactogogues do increase baseline serum prolactin, but there is no direct correlation between baseline prolactin levels and rates of milk synthesis or measured volumes of milk production.
- Previous studies up through 2006 have tended to show a pattern of increased milk production, but they have generally been of poor quality,[9,10] with the following weaknesses:
  - Lack of randomization, controls, or blinding
  - Small sample sizes
  - High dropout rates
  - Nonpharmacological measures were not optimized.
- Older reviews have cited studies with positive results while minimizing or ignoring studies with negative results.[9,26,27]
- A key systematic review in 2007[10] found two main problems.
  - Evidence for the use of pharmaceutical galactogogues is lacking: Only seven studies of various galactogogues met evidence-based criteria for review.
  - Potential significant side effects of the drugs should be weighed carefully against the lack of evidence (see Appendix for potential risks and benefits of specific drugs).
- Prescription drugs used as galactogogues constitute "off-label" use in most countries (they are not approved by regulatory agencies for this indication).

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 approximately 1 month. Many also have traditional foods and herbs for postpartum women that are meant to increase the mother's strength and enhance lactation.[28] Many of these herbal remedies have been used throughout history to enhance milk supply. Some herbs mentioned as galactogogues include fenugreek, goat's rue, milk thistle (*Silybum marianum*), oats, dandelion, millet, seaweed, anise, basil, blessed thistle, fennel seeds, marshmallow, and many others. Although beer is used in some cultures, alcohol may actually reduce milk production. A barley component of beer (even nonalcoholic beer) can increase prolactin secretion, but there are "no systematic studies" and "there is no hard evidence for causal effect."[29,30] The mechanism(s) of action for most herbals are unknown. Most of them have not been scientifically evaluated, but traditional use suggests safety and possible efficacy. The 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 (Levels of Evidence II-1,[31] II-3[32]).* The placebo effect may be the reason for widespread impressions (anecdotal experience) of a positive effect of fenugreek on increased milk volumes (Level of Evidence III, personal communications from K.A. Marinelli [2010], N. Wight [2010], C. Smillie [2009], and N.G. Powers

*Levels of Evidence are based on the United States Preventive Services Task Force "Quality of Evidence" (www.ncbi.nlm.nih.gov/books/NBK15430, last accessed December 20, 2010).

[2010]). The minimal specific data regarding these herbs are presented in the Appendix.

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 research settings), possible contaminants, allergic potential, and drug interactions. Several herbs, taken orally, will increase patient blood levels of warfarin, heparin, and other anticoagulants. There are several reports of severe maternal allergic reactions to fenugreek.[33]

Practice Recommendations

The following recommendations, based upon current evidence, apply to women experiencing difficulties with a low rate of milk production (e.g., the baby is not gaining weight normally or supplementation is being used because of low milk production, during either the initiation or maintenance of milk supply).

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

1. Evaluate and augment the frequency and thoroughness of milk removal. Use non-pharmacologic measures to increase the overall rate of breastmilk synthesis.
    a. For women with healthy term infants: Improve breastfeeding practices (Level of Evidence I).
        i. Recommend skin-to-skin contact between mother and baby to facilitate frequent feeding and stimulate oxytocin release (the milk ejection reflex [MER]).[34]
        ii. Encourage mother to perform self-breast massage in order to improve oxytocin release (MER) and milk removal.
        iii. Review or teach relaxation techniques to facilitate oxytocin release (MER) for improved milk removal.
        iv. Help the mother–infant dyad to achieve optimal latch-on.[10,24,25]
        v. Resolve nipple pain, if applicable, using the following strategies:
            (1) Optimal latch-on
            (2) Diagnosis and management of other causes of pain
            (3) Refer to a lactation specialist as needed.
        vi. Emphasize unrestricted frequency and duration of breastfeeding (if the infant has been shown to be effectively transferring milk).[24,25]
        vii. Advise the mother to reduce or stop unnecessary supplementation35 and provide strategies for how to do so.
            (1) Gradual tapering off of amounts of supplementation
            (2) Use of "supplementer system" (tube at the breast attached to a source of supplemental milk) if appropriate.
    b. For women with babies who are ineffective at milk removal or unable to feed at the breast (e.g., premature, hospitalized, hypotonic):
        i. Recommend and teach gentle hand expression of colostrum: The volume extracted by hand expression is greater than the volume extracted by full-size, automatic cycling breast pumps;[36] video and photographic illustrations of hand expression are available at newborns.stanford.edu/Breastfeeding/HandExpression.html[37] and www.breastfeeding.com/helpme/helpme_images_expression.html.[38]
        ii. Recommend milk expression with a full-size, automatic cycling breast pump, capable of draining both breasts at the same time ("hospital grade"), if available (Level of Evidence II-2).[39]
        iii. Recommend "hands-on pumping" (a combination of hand expression with double pumping); this technique was superior to double pumping alone in one randomized, controlled trial[40] and one observational study[41] (Level of Evidence I and II-3).
        iv. Recommend that women adjust the electric pump to their maximum comfortable vacuum, which enhances milk flow rate and milk yield and minimizes occurrence of tissue damage (Level of Evidence II-1).[42]
        v. Recommend hand expression if a hospital-grade pump is not available or if the woman prefers the manual technique; hand expression requires instruction and a period of practice until the mother becomes proficient.
        vi. Foot pump expression does not require electricity and may be another available alternative.[43]
2. Evaluate the mother for "medical" causes of hypogalactia: Pregnancy, medications, primary mammary glandular insufficiency, breast surgery, polycystic ovary syndrome, hypothyroidism, retained placenta, 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[12] (Level of Evidence II-2, II-3, and III).
3. Because current research of all galactogogues is relatively inconclusive and all of the agents have potential adverse effects, ABM cannot recommend any specific pharmacologic or herbal galactogogues at this time.
4. The healthcare provider who weighs the potential risks versus the potential benefits of these agents and chooses to prescribe a galactogogue should follow the guidelines below (Level of Evidence III) (see Appendix regarding details of prescribing specific galactogogues).
5. Inform women about available data concerning efficacy, timing of use, and duration of therapy of galactogogues (Level of Evidence I).[10] (Specific information is presented in the Appendix.)
6. Inform women about available data concerning potential adverse effects of galactogogues (see Appendix regarding details of specific galactogogues):
    a. Screen the mother for allergies to, contraindications to, or drug interactions with the chosen medication or other substance.
    b. 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.

c. Prescribe galactogogues at the lowest possible doses for the shortest period of time; do not exceed recommended therapeutic doses.
d. Consider gradually discontinuing the drug (tapering the dose) at the end of therapy; some studies stop the drug at the conclusion of therapy, and others gradually discontinue the drug, with no clear advantage to either method.
e. If milk production wanes after stopping the drug and improves again with resumption of the medication, attempt to gradually decrease the drug to the lowest effective dose and then discontinue the drug at a later date if possible.
f. Consider obtaining written documentation of informed consent when using any galactogogues.

Conclusions

Prior to the use of a galactogogue, thorough evaluation should be performed of the entire feeding process by a lactation expert. Reassurance may be offered, if appropriate. When intervention is indicated for the dyad, modifiable factors should be addressed: comfort and relaxation for the mother, frequency and thoroughness of milk removal, and underlying medical conditions. Medication should never replace evaluation and counseling on modifiable factors. As new evidence has emerged regarding various interventions to increase milk secretion in lactating women, the case for using pharmaceutical galactogogues has grown weaker. There remain selected indications for which some of these agents may be useful, but the data are insufficient to make definitive recommendations. One high-quality study has found domperidone useful in mothers of babies less than 31 weeks' gestation in the neonatal intensive care unit (see the Appendix). 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 in regards 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 baby is essential to monitor the status of lactation as well as any adverse effects of the drug(s) on mother or infant.

Recommendations for Further Research

Existing studies in this area 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. Most studies have been done in mothers of preterm infants using mechanical breast pumps rather than in 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 modern, 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 synthesis, and adverse drug effects.

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ABM protocols expire 5 years from the date of publication. Evidence-based revisions are made within 5 years or sooner if there are significant changes in the evidence.

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(Appendix follows →)

Appendix: Specific Galactogogues

Table 1. Possibly Effective for Selected Indications

	Domperidone	*Fenugreek*	*Metoclopramide*	*Silymarin*[a]
References	11,44,45,46–52	31,32,53–55	16–20,22–25,56	31,53
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	I (one study); other studies have inadequate methodology or excessive dropout rates	II-3 (one study in lactating women—abstract only)	III (mixed results in low-quality studies; effect on overall rate of milk secretion is unclear)	II-1 (one study in lactating women)
Suggested dosage	10 mg, orally, 3 times/day in the Level I study; higher doses have not been studied in this context.	"3 capsules," orally (typically 580–610 mg, but not stated in article), 3–4 times/day; strained tea, 1 cup, 3 times/day (¼ tsp of seeds steeped in 8 oz of water for 10 minutes)	10 mg, orally, 3–4 times/day	Micronized silymarin, 420 mg, orally, per day in study of diPierro et al.;[31] anecdotal, strained tea (simmer 1 tsp of crushed seeds in 8 oz of water for 10 minutes), 2–3 cups/day[54]
Length/duration of therapy	Started between 3 and 4 weeks postpartum and given for 14 days in the Level I study. In various other studies the range was considerable: Domperidone was started between 16 to 117 days postpartum and given for 2–14 days.	1 week	7–14 days in various studies	Micronized Silymarin was studied for 63 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 for pump-dependent mothers of premature infants less than 31 weeks' gestation in neonatal intensive care unit	Insufficient evidence; likely a significant placebo effect	Possible increased rate of milk secretion; possible responders versus non-responders	Inconclusive
Untoward effects	Maternal: Dry mouth, headache (resolved with decreased dosage), and abdominal cramps. Although not reported in studies of lactation, cardiac arrhythmias due to prolonged QTc interval are a concern and are occasionally fatal. This may occur with either oral[44] or intravenous	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 Fabacceae family such as chickpeas, soybeans, and green peas—possible anaphylaxis.	Reversible CNS effects with short-term use, including sedation, anxiety, depression/anxiety/agitation, motor restlessness, dystonic reactions, extrapyramidal symptoms. Rare reports of tardive dyskinesia (usually	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]
	administration and particularly with high doses, 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 breastmilk of mothers on domperidone.[45]	Theoretically: asthma, bleeding, dizziness, flatulence, hypoglycemia, loss of consciousness, skin rash, wheezing—but no reports in lactating women.	irreversible), causing the FDA to place a "black box warning" on this drug in the United States.	
Interactions	Increased blood levels of domperidone when combined with some substrates metabolized by CYP3A4 enzyme inhibitors, e.g., fluconazole, grapefruit juice, ketoconozole, macrolide antibiotics, and others	Hawthorne, hypoglycemics including insulin, antiplatelet drugs, aspirin, heparin, warfarin, feverfew, primrose oil, 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; no increased efficacy but increased untoward effects. b. Generally licensed for use as drug for gastrointestinal dismotility (not in the United States), where for this indication in some regions it is accepted that if no response at the initial dose may increase the dose. Some areas use as drug of choice when prolactin stimulation is felt to be needed. However, there are no studies of the safety or efficacy of this practice in lactating women. c. In the United States, the FDA has issued an advisory *against* the use of domperidone in lactating women.[46]	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 *S. marianum* (milk thistle).
CNS, central nervous system; CYP, cytochrome *c*; FDA, Food and Drug Administration.

Table 2. Controversial or not Recommended, Although Possibly Effective

	Human growth hormone	*Sulpiride*	*Thyrotropin-releasing hormone*
References	[57–60]	[61,62]	[19,61,64,65]
Chemical class or properties	Protein-based polypeptide hormone: Stimulates multiple growth, anabolic, and anticatabolic effects	Substituted benzamide (antipsychotic, antidepressant); antagonism of presynaptic inhibitory dopamine receptors	A tripeptide hormone that stimulates the release of TSH and prolactin by the anterior pituitary
Level of evidence	Level I[57,58], Level II[59]	II-1 (only two studies)	Level I[63]
Suggested dosage	0.2 IU/kg/day, given intramuscularly or subcutaneously	50 mg, orally, 2 times/day;[59] do not use higher doses because of sedation of mother and baby	1 mg 4 times daily by nasal spray
Length/duration of therapy	7 days, starting anywhere from 8 to 18 weeks postpartum	4-day course starting at 3 days postpartum;[59] no evidence to use for a longer course of treatment	10 days
Effects on lactation	Increased milk secretion in a selected population of normally lactating women with no feeding problems and with healthy thriving infants between 8 and 18 weeks postpartum	Increase in milk secretion in a selected population: Primiparous women with "total yield of milk not exceeding 50 mL for the first 3 postpartum days"	Increased milk secretion in elected population of primiparous women with insufficient milk supply at 5 days postpartum
Untoward effects	None observed in mothers or babies studied to date. Potentially: Joint swelling, joint pain, carpal tunnel syndrome, and an increased risk of diabetes, heart disease	Severe drowsiness; extrapyramidal effects listed in Table 1 for metoclopramide; weight gain	Elevated TSH and hyperthyroidism
Interactions	Other hormones including contraceptives, insulin, cortisol, and others too numerous to list	Levodopa, other drugs with CNS effects	Other hormones including contraceptives, insulin, cortisol, and others too numerous to list
Comments	Insufficient study; not practical—requires injection and is very expensive	Concern about untoward effects	Insufficient study; very expensive; no commercial product available

TSH, thyroid-stimulating hormone.

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