

The Effect of Early Limited Formula on Breastfeeding, Readmission, and Intestinal Microbiota: A Randomized Clinical Trial

Valerie J. Flaherman, MD, MPH¹, Nicole R. Narayan, PhD², Dennis Hartigan-O'Connor, MD, PhD²,
Michael D. Cabana, MD, MPH¹, Charles E. McCulloch, PhD³, and Ian M. Paul, MD, MSc⁴

Objective To determine whether using 10 mL formula after each breastfeeding before copious maternal milk production affects breastfeeding duration, readmission, and intestinal microbiota through 1 month of age.

Study design In this randomized controlled trial, we enrolled 164 exclusively breastfeeding newborns, 24-72 hours old, whose weight loss was ≥ 75 th percentile for age, and whose mothers had not yet begun mature milk production. Enrolled newborns were assigned randomly to either supplement breastfeeding with early limited formula (ELF), 10 mL of formula after each breastfeeding stopped at the onset of copious maternal milk production (intervention), or to continue exclusive breastfeeding (control). Outcomes assessed through 1 month included breastfeeding duration, readmission, and intestinal microbiota.

Results At 1 week of age, 95.8% of infants receiving ELF and 93.5% of control infants were still breastfeeding ($P > .5$); readmission occurred for 4 (4.8%) control infants and none of the infants receiving ELF ($P = .06$). At 1 month of age, 86.5% of infants receiving ELF and 89.7% of control infants were still breastfeeding ($P > .5$); 54.6% of infants receiving ELF and 65.8% of controls were breastfeeding without formula ($P = .18$). ELF did not lead to decreased abundance of *Lactobacillus* or *Bifidobacterium* and was not associated with expansion of *Clostridium*.

Conclusion In this population of healthy newborns with weight loss ≥ 75 th percentile, ELF did not interfere with breastfeeding at 1 month, breastfeeding without formula at 1 month, or intestinal microbiota. ELF may be an important therapeutic option for newborns with the potential to reduce readmission rates. (*J Pediatr* 2018;■■■:■■■-■■■).

Trial Registration Clinicaltrials.gov NCT02313181.

Public health initiatives from the Centers for Disease Control and Prevention, the Surgeon General, and the World Health Organization have discouraged hospitals, providers, and parents from using formula for newborns during the birth hospitalization.¹⁻⁵ To support these initiatives, the Joint Commission established quality measures aimed at reducing the use of formula for breastfed newborns.⁶⁻⁸ Since these measures were implemented in 2010, rates of exclusive breastfeeding have risen substantially in US hospitals.^{3,9} However, rising rates of exclusive breastfeeding have presented clinical challenges in newborn management, doubling the risk of hyperbilirubinemia, dehydration, and readmission.¹⁰⁻¹² The increased risk is partly attributable to the low enteral intake of exclusively breastfed newborns in the first few days after birth, when mothers produce about 1-5 mL of colostrum per feeding.^{13,14} Newborns with pronounced weight loss in the first few days are at high risk of hyperbilirubinemia and dehydration, perhaps because more pronounced weight loss is a marker of low enteral intake.¹⁵⁻²⁰

Increasing enteral volume by supplementing breastfed newborns with formula could ameliorate morbidity, especially for those with pronounced weight loss, but has been discouraged by guidelines as the result of several concerns. First, numerous studies have demonstrated that receiving both breast milk and formula in the first few days after birth increases the risk of breastfeeding cessation.²¹⁻²⁶ Second, some evidence suggests that the use of formula along with breastfeeding reduces the health benefits associated with breastfeeding, perhaps by altering the abundance of beneficial intestinal microbiota such as *Lactobacillus* and *Bifidobacterium*, which have been associated with reduced risk of infectious and allergic disease.²⁷⁻³² Some studies have also reported that the use of formula increases the abundance of taxa such as *Clostridia* that are associated with increased risk of eczema.³³⁻³⁵ Third, the use of formula to supplement breastfeeding can impact maternal experience. If formula feeding is perceived by mothers as easier or “better” than breastfeeding, this may impact maternal breastfeeding self-efficacy.³⁶⁻³⁸ Citing

From the ¹Department of Pediatrics, University of California San Francisco, San Francisco; ²Department of Medical Microbiology and Immunology, University of California Davis, Davis, CA; ³Department of Epidemiology and Biostatistics, University of California San Francisco, San Francisco; and ⁴Department of Pediatrics, Penn State College of Medicine, Hershey, PA

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BSES-SF	Breastfeeding Self-Efficacy Scale–Short Form
ELF	Early limited formula
ELF-TLC	Early Limited Formula for Treating Lactation Concerns
EPDS	Edinburgh Postnatal Depression Scale
SMNHC	Satisfaction with Maternal and Newborn Health Care Following Childbirth
STAI-SS	State Trait Anxiety Inventory (State Subscale)
UCSF	University of California San Francisco

these concerns, current guidelines recommend avoiding supplementation and continuing exclusive breastfeeding even in the setting of pronounced weight loss, unless supplementation is determined to be medically necessary.^{39,40}

Each year, about 80 000 newborns in the US require readmission after discharge from the birth hospitalization.^{11,41} The majority of these neonatal readmissions are related to hyperbilirubinemia or dehydration, 2 conditions potentially ameliorated by formula supplementation.^{11,12,41} Developing a strategy to balance the beneficial effect of formula on dehydration and hyperbilirubinemia while avoiding any detrimental effect on maternal experience, on breastfeeding duration, or on the presence of key intestinal taxa such as *Lactobacillus*, *Clostridium*, and *Bifidobacterium* might improve newborn outcomes.

In a small randomized trial, our group previously studied the use of early limited formula (ELF), a strategy using 10 mL of extensively hydrolyzed formula fed via syringe after each breastfeeding and discontinued after the onset of copious maternal milk, and reported that ELF improved rates of breastfeeding and of breastfeeding without formula at 3 months.⁴² Other existing studies regarding the impact of formula on the short-term and long-term risks and benefits of breastfeeding have not specifically examined the impact of small volumes of formula, administered during the period of low maternal milk volumes, followed by the resumption of exclusive breastfeeding. Our study, Early Limited Formula for Treating Lactation Concerns (ELF-TLC), was designed to test the hypothesis that the ELF approach improves length of breastfeeding duration for infants with pronounced weight loss compared with the currently recommended strategy of continued exclusive breastfeeding.

Methods

Between January 2015 and September 2016, ELF-TLC enrolled healthy, exclusively breastfeeding term (≥ 37 week) singletons born at the University of California San Francisco (UCSF) Medical Center (San Francisco, California) and at Penn State Milton S. Hershey Medical Center (Hershey, Pennsylvania). We included infants with weight loss ≥ 75 th percentile on The Newborn Weight Tool (www.newbornweight.org) whose mothers had not yet begun copious milk production.⁴³ We excluded infants with birth weight < 2500 g, those the clinical team had recommended should not breastfeed, and those who had received formula, required a greater level of care than a Level 1 nursery, had mothers who were < 18 years old or could not speak English, were not expected to be discharged home with their parents, or were observed for narcotic abstinence syndrome. We also excluded infants who had lost $\geq 10\%$ of their birth weight because such infants routinely were supplemented in both enrolling institutions. Weight measurement obtained during routine hospital care was used to determine eligibility for enrollment. A study nurse obtained informed consent from mothers for themselves and their infant. The ELF-TLC trial was approved by the UCSF Committee on Human Research, the Human Subjects Protection Office at Penn State College of Medicine, and the University of California Davis

institutional review board and is registered at clinicaltrials.gov (ClinicalTrials.gov: NCT02313181).

We randomly assigned 164 mother–infant pairs either to breastfeed with ELF or to continue exclusive breastfeeding with a safety control intervention. An independent biostatistician generated the randomized allocation sequence using a password-encoded Excel spreadsheet (Microsoft Corporation, Redmond, Washington) stratified on location and on method of delivery. A study nurse accessed this sequence following enrollment to determine treatment assignment.

All study nurses at both sites received training from the Principal Investigator before the study commencement and at the midpoint of enrollment. Immediately after enrollment and treatment assignment, all mothers breastfed with support from a study nurse. After this supported breastfeeding, mothers randomly assigned to ELF were taught to feed their infants 10 mL of formula using a feeding syringe after each breastfeeding until the onset of copious breast milk. Extensively hydrolyzed formula (Nutramigen; Mead Johnson Nutrition, Inc, Glenview, Illinois) was used for the intervention because of the reported beneficial effect of extensively hydrolyzed formula on bilirubin levels⁴⁴ and because our pilot study indicated its color, odor, and expense might help families distinguish it from standard cow's milk formulas.⁴² Mothers randomly assigned to the control group were instructed to continue exclusive breastfeeding as recommended by existing guidelines unless directed by a healthcare provider to begin formula and/or discontinue breastfeeding. Mothers assigned to the control group were taught infant safety techniques (including household water temperature, car seat position, and safe infant sleep environment) for 15 minutes by the study nurse to reduce any confounding by providing an equal amount of time and attention to control participants and ELF participants.

The enrolling nurse surveyed all mothers for covariates related to breastfeeding, including maternal country of birth, previous breastfeeding experience, race/ethnicity, and planned duration of breastfeeding and also assessed measures including the Breastfeeding Self-Efficacy Scale–Short Form (BSES-SF), the State Trait Anxiety Inventory (State Subscale) (STAI-SS), the Edinburgh Postnatal Depression Scale (EPDS), and the Satisfaction with Maternal and Newborn Health Care Following Childbirth (SMNHC).^{38,45–47} All infants received usual care before and subsequent to the study nurse visit at enrollment.

A research assistant blinded to study group assignment assessed 1-week and 1-month outcomes via telephone call, including the outcomes of continued breastfeeding with and without formula, neonatal readmission, STAI-SS, and EPDS. In addition, at 1 week the research assistant verbally administered the BSES-SF and SMNHC. A score of ≥ 40 on the STAI-SS was defined as a positive screen for anxiety, and a score of ≥ 12 on the EPDS was defined as a positive screen for depression, as was any answer other than “never” to the EPDS item querying mothers about self-harm. Screening tests were scored within 24 hours of survey administration, and positive screens were reported by study staff to the mother's obstetric team or primary care provider.

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