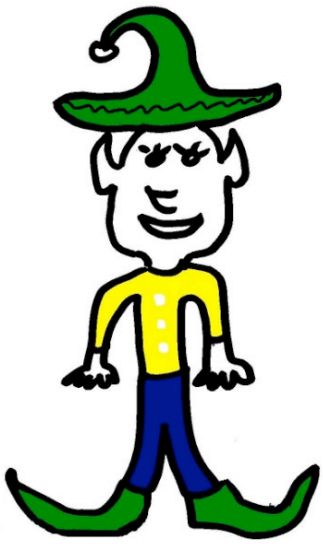
The Early Limited Formula Treating Lactation Concerns (ELF-TLC) Study



PI: Valerie Flaherman, MD, MPH
Co-Investigators: Michelle Rait, RN, MS(c), Michael Cabana, MD, MPH, Charles McCulloch, PhD, Ian Paul, MD, MSc, Jessica Beiler, MPH

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The University of California at San Francisco
Penn State Hershey Children's Hospital

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I. PRINCIPAL HYPOTHESES TO BE TESTED

Breastfeeding provides many important health benefits to mothers and babies, and longer duration of breastfeeding is associated with much greater health benefits. However, the large majority of mothers and babies who begin breastfeeding shortly after birth actually stop breastfeeding well before the recommended duration of 12 months. Early breastfeeding problems occurring in the first few days after birth can have a major impact on overall breastfeeding duration. Weight loss is one such problem and can be rapid. In this study, we define rapid early weight loss as weight loss ≥75th percentile at the most recent weight as defined by an hourly nomogram demonstrating weight loss percentiles for exclusively breastfed newborns during the birth hospitalization. The PI of this study has previously shown that the brief, temporary use of small amounts of formula was helpful for infants with rapid early weight loss in overcoming early breastfeeding problems, and may allow these to continue breastfeeding through at least 3 months. The proposed research will build on this previous work and prospectively evaluate the impact of a small, controlled amount of Early, Limited Formula (ELF) on breastfeeding duration for mothers and newborns in a randomized controlled trial involving 164 mother-infant breastfeeding dyads. ELF may help mothers and babies transition through the brief period of early low milk production into successful, long-term breastfeeding. Our study will also report the effect of ELF on maternal experience including anxiety and depression and will examine the effect of ELF on healthcare utilization when compared with current standard of care, continued exclusive breastfeeding.

A. Proposed Hypotheses: For babies 18-72 hours old with rapid early weight loss, we hypothesize that the temporary use of 10 mL of formula fed by syringe immediately after each breastfeeding prior to the onset of mature milk production will improve breastfeeding duration and maternal experience and reduce overall healthcare utilization.

Outcomes to be studied for newborns include:

Primary outcome:
- Any breastfeeding at 6 months

Secondary outcomes:
- Any breastfeeding at various time points through 12 months
- Predominant breastfeeding >80% as defined by the Infant Feeding Practices II Study
- Any feeding other than breast milk at various time points through 6 months
- Volume of formula used in the past 24 hours at 1, 3 and 6 months of age

Outcomes to be studied for mothers include:
- Anxiety
- Breastfeeding self-efficacy
- Milk supply concern
- Parenting self-efficacy
- Postpartum depression

Outcomes to be studied for the health care system include:
- Infant office visits, emergency room visits and re-hospitalizations in the first month
- Maternal satisfaction with the quality of care in the first month

Additionally, we expect that ELF will have particularly positive effects on breastfeeding duration for mothers who are low-income and are therefore at higher risk of breastfeeding discontinuation. A subgroup analysis will be performed specifically for this population.

Specific hypotheses include:

- **Primary hypothesis:** ELF improves rates of any breastfeeding at 6 months.
- **Additional hypotheses:** ELF improves rates of any breastfeeding at 12 months.
- ELF improves predominant breastfeeding at 3 and 6 months.
- ELF improves rates of breastfeeding without concurrent formula at 3 months.
- ELF improves rates of breastfeeding without concurrent formula at 3 months for low-income mothers with household incomes <200% of the Federal Poverty Level
- ELF reduces the total volume of formula used in the first week.
- ELF reduces maternal state anxiety at 1 week.
- ELF ameliorates maternal milk supply concern.
- ELF improves maternal breastfeeding self-efficacy and parenting self-efficacy.
- ELF reduces the frequency of postpartum depression.
- ELF reduces health care utilization in the first month after birth.
- ELF improves maternal satisfaction with quality of care.

II. BACKGROUND AND RATIONALE

A. Introduction

National Breastfeeding Targets For Initiation Have Been Met, but Breastfeeding Rates at All Time Points After Initiation Are Lagging. Breastfeeding reduces infant morbidity and mortality[1-6] and benefits maternal health by reducing the incidence of breast[7] and ovarian cancer.[8] Longer duration of breastfeeding improves all these outcomes.[9, 10] At least 12 months of breastfeeding are recommended by the Centers for Disease Control and Prevention (CDC), the World Health Organization (WHO) and the American Academy of Pediatrics (AAP),[11-13] and Healthy People 2020 includes national breastfeeding goals at 0, 3, 6 and 12 months of age.[14] Healthy People 2020's target for breastfeeding initiation is 75%, and it is being met, with 76% of U.S. mother-infant pairs initiating breastfeeding.[13, 15, 16] However, most discontinue breastfeeding far before recommended: only 49% breastfeed through 6 months, and only 27% breastfeed through 12 months.[16, 17] Rates of breastfeeding are even lower for low-income U.S. mothers, with only 33% of low-income mothers breastfeeding at 6 months.[18]

Initial Physiologically Low Volumes of Milk Can Trigger a Cascade That May Lead to Breastfeeding Discontinuation. Immediately after birth, mothers begin production of early milk called colostrum that is high in nutrient concentration but very low in volume. Since each colostrum feeding averages 1-5 mL,[19, 20] exclusively breastfed newborns typically lose weight until copious mature milk production begins at about 2-5 days of age.[21, 22] While this weight loss generally does not cause serious medical problems, it can nevertheless raise maternal levels of anxiety, often even if clinicians have provided appropriate reassurance and education.[23-26] This is important because high levels of maternal anxiety in the postpartum period substantially increase the risk of breastfeeding discontinuation.[27] Furthermore, concerns about breastfeeding on day-of-life 3 also substantially increase risk of discontinuation.[28] Therefore, although newborn weight loss may not cause immediate medical consequences, it may risk generating a train of events that can end in breastfeeding discontinuation.

Hospitals Discourage Formula Use for Those Attempting to Breastfeed. Formula can ameliorate weight loss for newborns,[21, 22, 29] but using formula for breastfed newborns has been strongly associated with reduced breastfeeding duration in multiple observational studies.[9, 30-39] For this reason, current public health efforts have focused on discharging newborns with no formula use, whatsoever.[11, 40-44] The CDC,[13] the Surgeon General,[40] the WHO's Baby Friendly Hospital Initiative and the Joint Commission's Perinatal Care Core measure all promote discharging newborns without any formula use.[11, 41-44] Local and state agencies have been encouraging both academic and community hospitals to increase rates of exclusive breastfeeding during the birth hospitalization,[45-50] and rates of in-hospital formula supplementation have been falling across the nation.[51-55] However, since the evidence supporting these policies is observational,[9, 30-39] it is likely to have some confounding.[56] Mother-baby pairs with a greater determination to breastfeed would be less likely to use

formula and more likely to continue breastfeeding, and mother-baby pairs with latch or nipple problems would be more likely to use formula and less likely to continue breastfeeding.

The experimental evidence in this area has been limited, in part due to the difficulty in randomizing newborns to alternative feeding approaches.[57] *The only published clinical trial of formula use restriction reported that restricting formula during the birth hospitalization had no effect on breastfeeding duration.*[58] A cluster randomized trial found that the Ten Steps of the Baby Friendly Hospital Initiative[11] were effective at improving breastfeeding duration, but this study did not randomly assign formula restriction separately from the nine other interventions of the Ten Steps.[1] No previous studies have examined specific strategies for formula use and their effect on breastfeeding duration, according to a 2011 Cochrane systematic review.[57]

Natural History of Milk Production and Infant Weight Loss Suggests that Carefully Managed "Early Limited Formula" (ELF) May Benefit Many Mother-Newborn Pairs. Although low colostrum volume and associated newborn weight loss are physiological, they can potentially cause three interrelated problems for the breastfeeding dyad. First, low intake volumes and associated weight loss raise a newborn's risk of eventually meeting criteria for hyperbilirubinemia and dehydration, the most common morbidities of the newborn period.[59-64] Second, newborn weight loss with or without the development of associated morbidity may increase maternal anxiety and negatively impact other aspects of maternal experience, including breastfeeding self-efficacy and milk supply concern.[23, 25, 26, 65] Third, rapid weight loss in the beginning of the first week raises the risk of meeting criteria for excess weight loss later in the first week.[66] Excess weight loss, which typically develops around day 4-7, is usually defined as the loss of ≥10% birth weight and is usually treated with unrestricted volumes of formula fed to the point of infant satiation. This is important because once mature milk production begins, using formula to the point of infant satiation may have a detrimental impact on breastfeeding by causing breast milk stasis that activates the breast's Feedback Inhibition Loop (FIL) and reduces the volume of breast milk produced.[67, 68] Altogether, these three problems may lead to reduced breastfeeding duration, increased health care utilization and decreased maternal satisfaction with the quality of care. See Figure 1 for the potential effects of low early newborn intake.

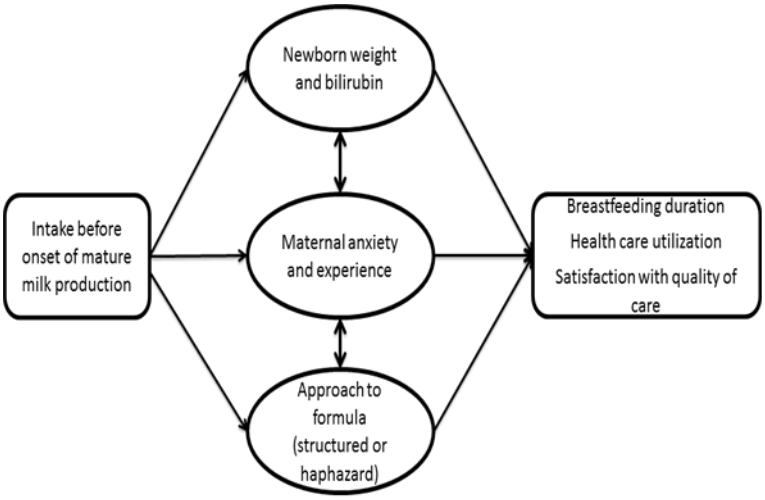


Figure 1: Potential effects of early newborn intake on shorter-term outcomes and subsequent outcomes

Our group's recent published analyses have reported that babies with rapid early weight loss are at greatly increased risk of this sequence of events, with an odds ratio of 3.30 (1.79, 6.07) for eventually developing excess weight loss.[29, 69] Since excess weight loss usually develops around days 4-7, such infants are at risk of receiving large volumes of formula *at or after* the onset of mature milk production, in a pattern that is likely to activate FIL and have a detrimental effect on breastfeeding. For such newborns, earlier use of limited volumes of formula, prior to the onset of mature milk production, might prevent excess weight loss and allow the discontinuation of formula at the onset of mature milk production. Such an approach to these particular infants, who we can now systematically identify, might avoid any activation of FIL and thus maintain the mother's milk supply.

Using small amounts of formula to supplement breastfeeding prior to copious maternal milk production could potentially ameliorate early newborn weight loss and reduce the need to use formula later in the first week. Since copious mature milk becomes available on average around 56 hours after birth,[21, 22] slightly later than mean age at discharge from U.S. birth hospitalizations,[70-72] if formula were to be used to ameliorate newborn weight loss and improve subsequent outcomes, the optimal time for beginning formula would likely be prior to the onset of mature milk production and therefore *prior* to hospital discharge. **Our group's recently published pilot data reported that random assignment to Early Limited Formula (ELF)—10 mL of**

formula after each breastfeeding prior to the onset of mature milk production—resulted in significantly *higher* rates of breastfeeding at 3 months than did the control assignment of standard of care, continued exclusive breastfeeding (95% vs. 68%, *p*=.04).

The carefully managed use of ELF prior to the onset of mature milk production could have effects on infants, mothers and the health care system. For babies with rapid early weight loss, using small volumes of formula before the availability of mature milk could provide nutrition and volume that might ameliorate weight loss, reduce the risk of morbidity associated with weight loss and reduce the need for large-volume formula supplement later in the first week. All these effects together might lead to improved duration of breastfeeding, so that babies can gain all the health benefits of breastfeeding. Since 21% of exclusively breastfeeding newborns have rapid early weight loss,[29] an effective strategy for early formula use for such infants could have substantial public health impact.

ELF might also reduce maternal anxiety. The postpartum period is a vulnerable time for maternal mental health; hormonal shifts combine with the profound lifestyle changes of motherhood to influence mood.[73] Low-income mothers are at even higher risk of mental-health problems.[74, 75] Rapid newborn weight loss can increase maternal anxiety and milk supply concern,[23, 25, 26, 28] which are associated with reduced breastfeeding duration.[27, 28, 76, 77] This team recently reported that mothers of newborns with excess weight loss were three times more likely to have a positive anxiety screen than mothers of newborns without excess weight loss.[23] The relationship between maternal anxiety attributable to newborn weight loss and other aspects of maternal experience such as breastfeeding self-efficacy, parenting self-efficacy, milk supply concern and postpartum depression has not previously been examined, but these aspects of maternal experience may be interrelated. Breastfeeding self-efficacy, milk supply concern, parenting self-efficacy and postpartum depression have each been correlated with both maternal anxiety and breastfeeding outcomes.[76, 78-86] If temporary early formula is effective at ameliorating newborn weight loss and thereby reduces maternal anxiety levels, it is possible that temporary early formula would have a synergistic effect that could improve breastfeeding self-efficacy, parenting self-efficacy and milk supply concern and potentially reduce postpartum depression.

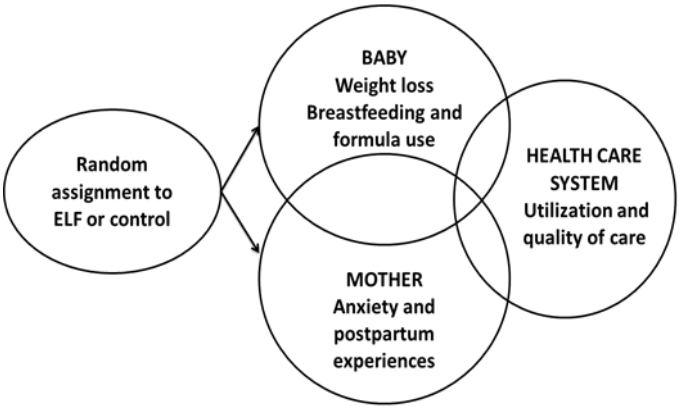


Figure 2: Effect of Feeding Approach on Baby, Mother and the Health Care System

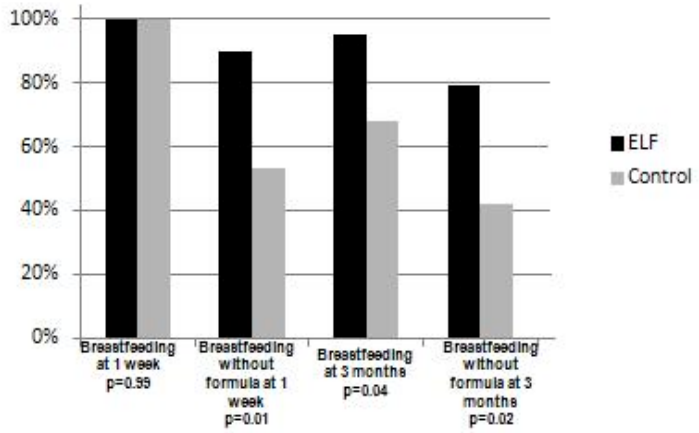
ELF might also have an effect on the health care system, potentially affecting health care utilization and maternal satisfaction with the quality of care. Excess weight loss increases a newborn's risk of rehospitalization and treatment for hyperbilirubinemia.[59, 62, 63, 87] Since quality of care is rated lower by the parents of children with poorer health status,[88] it is possible that newborn weight loss might also cause parents to rate lower the quality of care. The effect of ELF on the baby, mother and health care system will not be independent: ameliorating newborn weight loss might reduce maternal anxiety; lower maternal anxiety levels might lead to longer breastfeeding duration; and less weight loss and maternal anxiety might lead to lower health care utilization. (Figure 2)

The ELF strategy may appear counterintuitive in light of the observational evidence that early formula is associated with decreased breastfeeding duration and in light of current public health efforts aimed at reducing formula use during the birth hospitalization. However, it may be that a more nuanced approach to formula use, rather than an all-or-nothing strategy, could allow babies to obtain benefit from formula prior to mature milk production, discontinue formula at the onset of mature milk production and transition to sustained breastfeeding. Our ELF pilot results suggest that this is possible, but before any intervention using early limited volumes of formula can be recommended on a national scale, it will be critically important to demonstrate in a large-scale trial that early formula can be used in a way that supports breastfeeding.[89]

Supportive Pilot Data for the Innovative Intervention "Early Limited Formula" (ELF)

The ELF regimen is a well-defined protocol which incorporates four previously untested elements: (1) using a limited volume of 10 mL of formula after each breastfeeding; (2) beginning at 24-48 hours, (3) administering the formula with a syringe as opposed to a bottle with a nipple, (4) discontinuing formula at the onset of mature milk production and (5) using extensively hydrolyzed formula. Each ELF feeding uses 10 mL formula, much less than the 30-60 mL in a typical newborn formula feeding, in order to avoid satiating newborns and encourage frequent breastfeeds. ELF does not begin before 24 hours, giving mothers and babies a chance to experience exclusive breastfeeding. Since becoming accustomed to a rubber nipple may cause nipple confusion and interfere with proper latch at breast,[90] ELF uses a syringe to feed formula and does not use a bottle. Discontinuing formula once mature milk production begins may allow vigorous infant breastfeeding demand at that time, maximizing breast milk extraction and reducing feedback inhibition from milk stasis. In addition, the ELF technique uses extensively-hydrolyzed formula, which, while palatable to newborns, has a slightly unpleasant odor that may seem less desirable to parents. Extensively-hydrolyzed formula has the additional benefit of reduced risk of atopic and allergic disease when compared with cow's-milk-based and soy-based formulas.[91-93]

Figure 3: Results from the ELF pilot



Recently, our group conducted a pilot study of 40 exclusively breastfeeding newborns who had rapid early weight loss and randomly assigned these newborns either to ELF or to continued exclusive breastfeeding. Our results showed that those randomly assigned to ELF were more likely to be breastfeeding at 3 months than those randomly assigned to the control group of continued exclusive breastfeeding (95% vs. 68%, *p*=.04).[94] Additionally, we found that newborns in the ELF intervention group were much more likely to be breastfeeding without using any formula at 1 week than control newborns (90% vs. 53%; *p*=.01). ELF intervention infants remained more likely to be breast-feeding without formula than controls at 3 months (79% vs. 42%; *p*=.02). (Figure 3)

It is possible that using formula before the onset of mature milk production to reduce the use of formula at 1 week of age may be a powerful approach to supporting breastfeeding. Funded by Dr. Flaherman's Career Development Award from the NICHD (HD059818), our pilot offers a preliminary indication that ELF may help mothers meet Healthy People 2020 goals for breastfeeding at 6 and 12 months. The ELF protocol might also result in less overall volume of formula used through infancy. In this pilot, infants who were assigned to ELF used much less formula in the first month than infants who were assigned to the control group.

Tailoring Feeding Strategies to Best Pursue Healthy People 2020 Goals: Our work will be the first to explore whether feeding strategies can be tailored to the characteristics of the individual newborn. Although most exclusively breastfeeding newborns would obtain no benefit from formula, a subset meeting screening criteria may benefit from ELF. Our screening method for early identification of infants at risk for an extreme weight loss nadir demonstrates the strong relationship between rapid early weight loss (≥5% at <36 hours) and later excess weight loss (eventual loss ≥10%) described above.[95] Our group's most recent research suggests that weight loss ≥75th percentile may be an even stronger predictor of breastfeeding problems.[96] (Appendix II) By identifying infants at risk of such problems, we can be selective in providing ELF alternative feeding strategies, and as a result, we hope to help more newborns meet Healthy People goals for breastfeeding through 12 months.

A Potential Paradigm Shift in Newborn Care: Based upon strong preliminary data, the proposed study will offer direct, specific evidence of the effect of small amounts of formula followed by resumption of exclusive

breastfeeding on clinically relevant infant outcomes including breastfeeding duration and total formula use for those at-risk for unsafe neonatal weight loss. We will also examine the impact of our intervention on maternal experience including an assessment of the effect of ELF on maternal anxiety, breastfeeding self-efficacy, milk supply concern, parenting self-efficacy and depression and on health care system outcomes including health care utilization and maternal satisfaction with quality of care. In this way, we hope to provide a more comprehensive understanding of the potential health outcomes related to ELF.

Preliminary Studies:
Early Limited Formula Pilot. Dr. Flaherman was Principal Investigator for this pilot study[97] with the results described above. *The pilot data shows the potential beneficial effect of ELF on breastfeeding duration. This study also demonstrates our ability to work with a second enrollment site to recruit patients during the birth hospitalization, randomize to an intervention, and follow maternal and infant breastfeeding outcomes, as well as demonstrating our ability to teach a control intervention.*

Nurses for Infants Through Teaching and Assessment After the Nursery (NITTANY). Dr. Paul was principal investigator for the NITTANY trial (HRSA/MCHB R40MC 06630), which reported that among 1169 enrolled newborns, those randomly assigned to a nurse home visit were more likely to be breastfeeding at 2 weeks (92.3% compared to controls 88.6%, *p*=.04) and 2 months (72.1% compared to controls 66.4%, *p*=.05) but not 6 months. In this study, 55% of mothers were breastfeeding at 6 months.[98] NITTANY also found that high maternal anxiety scores are strongly associated with reduced breastfeeding duration.[27] *This study estimates breastfeeding rates at 6 months for the Penn State site and demonstrates the ability of our Penn State investigators to recruit mothers during the birth hospitalization, randomly assign them to an intervention and follow breastfeeding and anxiety outcomes.*

B. SPECIFIC AIMS

SPECIFIC AIM 1:

Establish that *early limited formula* improves breastfeeding duration and reduces formula use for newborns with rapid early weight loss ≥75th percentile. Early limited formula will be shown to **improve** breastfeeding duration and **reduce formula use for those enrolled** in a prospective trial based on data collected by the PI presented above under *Preliminary Studies*. A randomized, controlled trial will be conducted over a period of 36 months to demonstrate that early limited formula improves breastfeeding duration and reduces formula use. Secondary outcomes of importance will include maternal experiences including volume of formula used and breastfeeding duration and formula use at 1 week and 1, 3, 6 and 12 months. In secondary analysis, we will also report the relationship between ELF and breastfeeding duration by percentile zone of weight loss (≥95th, ≥90th, and 75th percentiles).

SPECIFIC AIM 2:

Establish that *early limited formula* reduces maternal anxiety. Maternal anxiety is highly correlated with perception of insufficient milk supply and with newborn weight loss, and all these together greatly increase a dyad's risk of breastfeeding discontinuation. It is possible that the temporary use of early limited formula will ameliorate maternal anxiety and allow sustained breastfeeding. In this aim, we will also explore whether ELF is effective at modifying other aspects of maternal experience such as breastfeeding self-efficacy, parenting self-efficacy, milk supply concern and postpartum depression.

SPECIFIC AIM 3:

Prospectively evaluate the effect of early limited formula on the healthcare system. Low enteral intake and corresponding newborn weight loss are highly correlated with the two most common causes of healthcare utilization after the birth hospitalization: jaundice and dehydration. It is possible that increasing enteral intake and ameliorating weight loss may reduce the incidence of jaundice and dehydration, potentially leading to fewer outpatient visits, fewer emergency room visits and fewer hospital readmissions. We will also measure the effect of ELF on maternal satisfaction with the quality of care.

EXPLORATORY AIM:

Prospectively evaluate the effect of early limited formula on the infant intestinal microbiome. We will collect and store infant stool specimens at 1 week and 1 month of age. Specimens will be stored at the University of California Davis for future analysis of the effect of ELF on the intestinal microbiome.

III. PROTOCOL

In the ELF-TLC study, the effectiveness of ELF will be evaluated prospectively and compared with standard of care, which is continued exclusive breastfeeding, using a randomized, controlled study design. We will attempt to improve breastfeeding duration and reduce morbidity in the neonatal/postpartum period using small volumes of formula after each breastfeeding, discontinued at the onset of mature milk production. Although previous studies have shown that early formula use is associated with decreased breastfeeding duration, ELF incorporates five previously untested elements that may allow ELF to improve infant nutrition and hydration without interfering with the natural breastfeeding process. These elements are: (1) ELF uses a limited volume of formula, only 10 mL of formula after each breastfeeding. This volume is much less than the 30-60 mL in a typical newborn formula feeding, and thus may avoid satiating newborns and encourage frequent breastfeeds; (2) ELF begins at 18-72 hours, after mother and baby have had some time for exclusive breastfeeding; (3) ELF formula is fed with a syringe as opposed to a bottle with a nipple, which may reduce nipple confusion and allow good latch at breast (4) All ELF formula is discontinued at the onset of mature milk production. Discontinuing formula once mature milk production begins may allow vigorous infant breastfeeding demand at that time, maximizing breast milk extraction and reducing feedback inhibition from milk stasis; and (5) using extensively hydrolyzed formula, which, while palatable to newborns, has a slightly unpleasant odor that may seem less desirable to parents.

Over an 18-month period we will prospectively enroll a cohort of 164 healthy, term singleton newborns and their mothers admitted to the hospital nursery who are exclusively breastfeeding and have weight loss of ≥75th percentile for age based on an hourly nomogram demonstrating percentiles of newborn weight loss generated from a large sample of exclusively breastfed newborns.(ref) Previous data have indicated that newborns with this level of weight loss are at greatly increased risk of eventually losing 10% or more of their birth weight and therefore requiring supplementation with large volumes of formula, sometimes known as “rescue formula use”. In this study, patients will be randomized to receive either early limited formula or to continue breastfeeding exclusively unless otherwise instructed by a health care provider. For each newborn and mother, information from the pregnancy, obstetrical record, and the nursery course will be collected. Data also will be recorded regarding duration of breastfeeding, compliance with and extent of early limited formula use, maternal anxiety, newborn readmissions, ED visits, outpatient visits and maternal satisfaction with care. Maternal breastfeeding self-efficacy, parenting self-efficacy, milk supply concern and postpartum depression will also be assessed.

A. STUDY GROUPS AND SUBJECTS

Of the approximately 2000 newborns born at UCSF each year and 1800 newborns born at Hershey Medical Center each year, we estimate that about 40% will meet study entry criteria of breastfeeding exclusivity and weight loss ≥75th percentile before 48 hours of age. Therefore, over an 18-month recruitment period, of 2000 newborns admitted to the nursery at UCSF and 1800 newborns admitted to the nursery at Hershey, approximately 1520 mother/baby pairs will be eligible for enrollment (800 at UCSF and 720 at Hershey). Our enrollment targets are 84 mother-baby pairs for UCSF and 80 mother-baby pairs for Hershey. At randomized assignment, pairs will be stratified by site (UCSF or Hershey), income (<200% Federal Poverty Level (FPL) or ≥200% FPL) and parity (primiparous or multiparous). About 32% of mothers are estimated to have household incomes <200% of the FPL. About 50% of mothers of eligible babies are expected to be primiparous.

Covariates will include maternal demographic factors such as ethnicity/race, age, marital status, education, and insurance type. Also, we will collect data on maternal clinical features such as previous breastfeeding experience, birth outside of the U.S., education, income, language preference, prior participation

in a breastfeeding class, previous breast surgery, pre-pregnancy body mass index, intended duration of any and exclusive breastfeeding, multiple birth, importance attributed to breastfeeding, planned time of return to employment and whether or not the mother saw a lactation consultant while in the hospital and data on infant factors including gestational age, birth weight, weight loss at enrollment and latch score.

B. INCLUSION CRITERIA

Based on sample size calculations, we will enroll 164 mother/infant pairs meeting these inclusion criteria:

1) Full term, healthy singleton infant (≥ 37 0/7 weeks gestational age) in well newborn nursery
2) Exclusively breastfeeding (has not received any feedings other than breast milk)
3) Infant is 18-72 hours old
4) Infant has weight loss of ≥75th percentile on delivery mode specific nomogram (Appendices IIa, IIb; available at www.newbornweight.org) documented at 12-72 hours of age
5) English-speaking mother

C. EXCLUSION CRITERIA

1) Mothers or infants for whom breastfeeding is not recommended by the clinical team
2) Mothers who have already begun to produce mature breast milk[99]
3) Any formula or water feeding prior to enrollment
4) Infants who have already lost ≥10% of their birth weight
5) Family with no active telephone number (home or cellular)
6) Plan for infant adoption or foster care
7) Mothers <18 years of age
8) Infant receiving scoring for Narcotic Abstinence Sydrome

D. RATIONALE FOR INCLUDING THOSE WHO HAVE LOST ≥75th PERCENTILE OF BIRTH WEIGHT

Weight loss of ≥75th percentile is by definition not unusual and will occur in 25% of babies. The proportion experiencing this level of weight loss is likely higher in academic medical centers such as UCSF and HMC, where mothers are more likely to have pre-existing conditions that may interfere with optimal breastfeeding. However, although such weight loss can be normal for healthy term infants, it may predict an increased risk of eventual weight loss of 10% or more of birth weight.[100] Infants with 10% weight loss are at much greater risk of hypernatremic dehydration, and for this reason treatment with ad lib volumes of formula is usually begun if an infant has lost 10% or more of their birth weight.

This is important, because ad lib formula administration at the time of 10% weight loss, which usually occurs around day 3-5 after birth, may have important negative consequences. Ad lib formula administration may interfere with a baby's interest in breastfeeding, and extensive formula use at 3-5 days of age may coincide with the onset of mature maternal milk production. Since vigorous infant suckling is necessary at the onset of mature milk production to sustain a strong maternal milk supply, ad lib formula administration at 3-5 days of age can be very damaging to sustained breastfeeding. Since early weight loss of ≥75th percentile may predict increased risk of eventual weight loss of ≥10%, early weight loss of ≥75th percentile may therefore also predict a greatly increased risk of ad lib formula administration at 3-5 days of age. The use of ELF might preclude the development of 10% weight loss, allow unconstrained exclusive breastfeeding at the onset of mature milk production and therefore reduce the likelihood that sustained breastfeeding will be damaged by ad lib formula begun at 3-5 days.

E. RATIONALE FOR EXCLUDING THOSE WHO HAVE RECEIVED FORMULA OR WATER

Exclusive breastfeeding without any supplementary formula or water is recommended by multiple public health organizations and is standard of care for healthy term newborns. This study is designed to compare such exclusive breastfeeding to the carefully managed formula of ELF, so therefore we will not enroll infants who are not exclusively breastfeeding. Oral medications are not excluded from WHO and CDC definitions of exclusive breastfeeding, so any babies who have received Sweetease or other similar for analgesia can still be included in this study.

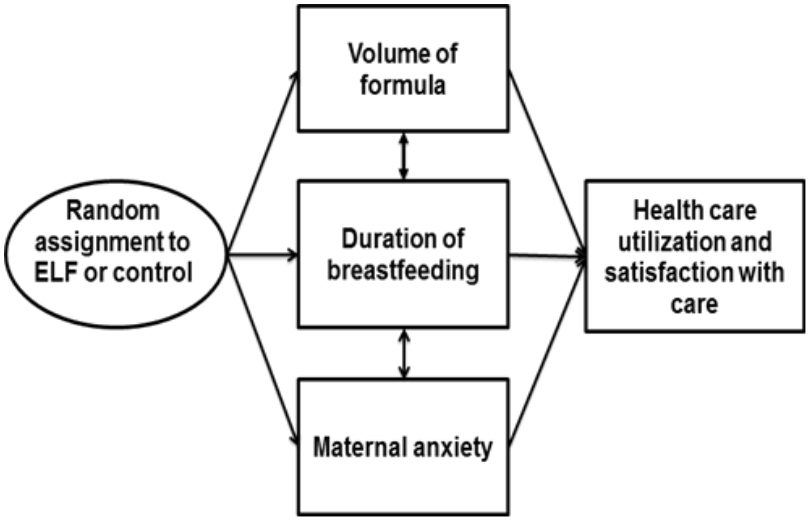
F. OUTCOME MEASURES AND THE RATIONALE FOR CHOOSING THEM

The primary outcome in this investigation will be the duration of breastfeeding, which will be assessed at 1 week and at 1, 3, 6 and 12 months. If this intervention is successful at improving rates of breastfeeding at 6 months of age, we may be able to provide evidence to support changes in practice that will allow more mothers and babies to reach the Healthy People 2020 goals of breastfeeding through 6 months and through 12 months. Another important outcome in this study will be formula use, and we will be assessing both any use of formula at 1 week and 1, 3, 6 and 12 months of age and the total volume of formula used. If the use of small volumes of formula in the period prior to the onset of mature milk production is successful at improving breastfeeding rates at 1, 3, 6 and 12 months of age, the overall volume of formula used for each baby randomly assigned to ELF will be very much lower than the overall volume of formula used for each control who discontinued breastfeeding prior to 1, 3, 6 or 12 months of age.

The immediate postpartum period is a time of high state anxiety levels for mothers, and we will assess how ELF affects maternal state anxiety by using the State Trait Anxiety Inventory (STAI). It may be that using small volumes of formula after each breastfeeding prior to the onset of mature milk production may reduce maternal anxiety about breastfeeding, potentially leading to improved overall maternal mental health. In order to further assess the potential impact of ELF on maternal mental health, we will also examine the outcome of postpartum depression using the Edinburgh Postnatal Depression Survey (EPDS). Measuring this important outcome will also allow us to identify any mothers who need additional supportive services and refer them to care during this vulnerable period (see Section IV.E.). We will also assess the effect of ELF on maternal breastfeeding self-efficacy and maternal milk supply concern, because both of these are important predictors of breastfeeding duration. Additionally, we will examine the effect of ELF on healthcare utilization including office visits, ER visits and hospital readmission. We acknowledge that clinicians have varying thresholds for readmission and follow-up, but believe this study will allow for a “real world” evaluation of readmission since guidelines for management of conditions such as hyperbilirubinemia are not universally followed. As such, data will be collected on the reasons for hospitalization, office visits and ER visits, including bilirubin levels when jaundice is the cause for a readmission.

Because the first few days after the birth is a critical period for the successful establishment of breastfeeding, we anticipate that early intervention with ELF might potentially affect breastfeeding rates throughout the first year. For this reason, we will follow outcomes related to breastfeeding duration for 12 months. Since we anticipate that the potential effect of ELF on maternal anxiety and healthcare utilization are unlikely to extend beyond 1 month, we will follow these secondary outcomes at 1 week and 1 month. See Table 4 for a summary of study outcome assessment. The potential relationships between the intervention and the assessed health outcomes are displayed in Figure 4.

Fig 4. Relationship between ELF and maternal, infant and health systems outcomes



G. STUDY CONTACT WITH PARTICIPANTS

This study will have only one in-person visit, occuring at the time of enrollment with the study RN. At that time, baseline information will be collected, the study RN will teach either the intervention or the control, and brief outcomes related to the intervention or control will be collected. Subsequently, there will be 5 followup calls at: 1 week, 1 month, 3 months, 6 months and 12 months.

1) Visit (24-48 HOURS) – Newborn Nursery

a) Newborn and Maternal chart review in newborn nursery/maternity floor to determine eligibility based on inclusion and exclusion criteria
b) Obtain informed consent
c) Complete enrollment data collection forms (Item C can be deferred until after Item K if mother is currently ready to breastfeed)
   - INFANT: record birth weight, gestational age and weight loss at enrollment
   - MOTHER: record age, parity, race/ethnicity, method of delivery, previous breastfeeding experience, birth outside of the U.S., education, income, language preference, prior participation in a breastfeeding class, previous breast surgery, pre-pregnancy body mass index, intended duration of any and exclusive breastfeeding, multiple birth, importance attributed to breastfeeding, planned time of return to employment and inpatient access to a lactation consultant. Record additional data on lactation including: time of first breastfeeding, number of breastfeedings in the first 24 hours, planned method of feeding, planned length of breastfeeding, whether mother is having breastfeeding problems now, what problem mother is having, whether or not mother is pumping, hand expressing or using a nipple shield. For mothers who have previous breastfeeding experience, whether they had a problem and what it was.
d) Ascertain when mother is next planning to breastfeed her infant and tell mother study nurse will return at that time. Exchange contact information so that mother can notify study nurse if feeding occurs earlier than planned.
e) Return at the time of the next breastfeeding.
f) Support mother in breastfeeding her infant and provide breastfeeding education. Mother should attempt both breasts unless she wishes to use only one. Provide breastfeeding education to all mothers on the following topics while supporting and advising breastfeeding: hunger cues, hand expression, positioning, latch and breastfeeding duration. Encourage all mothers to breastfeed 8-12 times/day at least until weight gain is established. Review normal patterns of voiding, stooling, weight loss and milk production. Detailed description of breastfeeding education is in Table 1 below. In the event that the newborn is unable latch after 15 minutes of attempt, move ahead to Item G after 15 minutes. Total breastfeeding teaching time on average is estimated to require about 30 minutes.
g) Distribute handout summarizing this teaching. (Appendix 1)
h) Record LATCH score, approximate volume expressed during hand expression and positions taught.
i) Randomize subject to treatment groups
j) Based on randomization arm, teach EITHER intervention (Table 2) or control (Table 3) as detailed below.

Table 1: Breastfeeding education for both groups in the ELF Study
Hunger cues: Newborns can give a variety of hunger cues. Mothers should try to breastfeed as soon as early hunger cues occur, such as when babies turn their heads back and forth, open their mouths, move their mouths from side to side (rooting), or suck their hands or thumbs. Waiting for later hunger cues such as crying can make it more difficult to obtain a good latch.
Hand expression: Teach using the press/compress/release method described by Jane Morton at the web site http://newborns.stanford.edu/Breastfeeding/HandExpression.html. This website should also be recommended to parents for future viewing.
Positioning: Teach cradle, cross-cradle or football as desired by mother. If the mother's physical condition allows it, teach an alternate position on the second breast.
Latch: Show mother how to wait for baby's mouth to open wide. Bring baby towards breast, not breast toward baby. Baby should engulf as much of the areola as possible in a manner with a bit more areola in the direction of the baby's chin. Once latched, there should be 180° angle where the baby's upper lip meets the lower lip. If

initial latch is suboptimal, re-attempt after showing mother how to break suction by inserting her 5th digit in the corner of the baby's mouth. Alternatively, or in addition to breaking the latch, study nurse may teach mother how to pull baby's chin down once latched to improve latch.
Duration: Baby should breastfeed 10-20 minutes from each breast. Teach mother that babies naturally pause often during early breastfeeding, and should suck approximately 50% of the time that they are latched. If baby is not sucking 50% of the time, can stimulate baby by rubbing back or soles of feet, or blowing on baby's head. Do not rub baby's cheek when latching, this can generate rooting towards cheek which can interfere with latching. If baby still does not suck 50% of the time and breastfeeding has been less than 10 minutes on a breast, remove baby from breast, remove clothes and blankets and let baby lie in crib for a minute until he wakes up, then attempt breastfeeding again to complete at least 10 min per breast of attempted breastfeeding. After 20 minutes, mother should remove baby from breast.
Frequency: Educate mothers to breastfeed 8-12 times per day, approximately every 2-3 hours at least until weight gain is established. Teach mothers that cluster feedings are normal, where baby may breastfeed every hour for a few hours, and then sleep for a few hours. However, mothers should not let babies breastfeed for more than 40 minutes at a time. After 40 minutes of breastfeeding, mothers should take a break for at least 20 minutes or so to allow recovery of both mother and baby. During the day, it's best not to have baby sleep more than 2-3 hours without a feeding. If baby is breastfeeding 8-12 total in 24 hours, it's okay to go as long as 5 hours at night without breastfeeding at one time during the 24-hour period. During the first 2 weeks after delivery, if more than 5 hours elapse at night without breastfeeding, mothers should wake babies and feed.
Voiding: Babies should void at least once per day of age, so that a 3-day-old baby should void at least three times on the third day, a 4-day-old baby should void at least four times on the fourth day, etc. By 7 days of age, babies should be voiding 8-12 times per day. Urine that is the color of brick dust is normal during the first week after birth because many babies are not fully hydrated.
Stooling: Babies should stool at least once per day of age, so that a 3-day-old baby should stool at least once on the third day, a 4-day-old baby should stool at least twice on the fourth day, etc. By 7 days of age, babies should be stooling 8 times per day. Stool will be initially black (meconium), and then transition to yellow/mustard color when mature milk is in.
Weight loss: All breastfed newborns lose weight daily for the first few days after birth. Babies are born with extra fluid and weight loss is normal and universal. Frequent breastfeeding will encourage weight gain.
Milk production: Mothers do not produce mature milk until 2-5 days after birth, or 2-7 days for primiparous mothers. Before mature milk production, mothers produce an early milk called colostrum that is high in protein and antibodies. Colostrum can be clear, yellow or even orange. Colostrum helps establish the healthy bowels associated with breastfeeding, and it benefits babies to swallow as much colostrum as possible.

Table 2: Early Limited Formula Teaching (Intervention Group)
Formula preparation: Wash hands. Gently agitate the bottle of extensively hydrolyzed formula, Enfamil® Nutramigen®. Select a new feeding syringe. Open formula bottle. Insert feeding syringe and remove 10 mL of formula. (*While in hospital:* mother should discard remaining formula. *When home,* mother should refrigerate remaining formula for later use. Previously refrigerated formula should be drawn up in a new syringe and then held under warm running water for a few minute to bring it to room temperature.)
The following steps should be first performed by the study nurse, using about 5 mL of the formula. After about 5 mL have been ingested, all of the following steps should be repeated by at least one parent.
Position baby: Baby should be comfortably reclining with head slightly higher than body. Baby can be propped on mother or father's legs, or held in cradle position by one parent and fed ELF by other parent, or can sit in car seat if available.
Initiating sucking reflex: Wash hands again. Nurse should put on gloves, parents feed without gloves. Place appropriately-sized finger, palmar side up, in baby's mouth. Mothers often use the index finger; fathers often use the pinky finger. Soft part of finger should make contact with baby's hard palate, and sucking reflex will be activated. (Note: if baby sucks only a little bit and then falls asleep, check placement of finger and proceed to next step). Leave finger in place for next step.
Feeding: Without moving sucking finger, place tip of syringe in the corner of baby's mouth. Depress feeding syringe slightly to release about 0.3 mL of formula into mouth. That means, for each mL of formula ingested, syringe will be depressed about 3 times. Babies drink only a small amount of formula at any given time, and it

will take about 30 swallows for baby to ingest all formula. After depressing syringe and releasing about 0.3 mL of formula, wait for baby to swallow and then wait for the next suck. Once the next suck occurs, depress syringe and release formula again. The sequence may occur quite rapidly at the very beginning of feeding, and then may become slower as feeding progresses. If baby is feeding rapidly at beginning, try to keep up with demand by depressing syringe slightly after each swallow/suck cycle. If baby is not feeding rapidly, carefully wait until formula is swallowed and the next suck occurs before depressing syringe.
Leaking: Some formula may leak from side of mouth, please wipe as this occurs.

Table 3: Safety Teaching (Control Group)[101]
Car seat safety: Baby should always be placed in rear-facing car seat in the back seat of the car. Baby must remain in seat throughout travel. Straps in the car seat should be adjusted to fit snugly around baby, following manufacturer's instructions. Car seat must be firmly and correctly affixed to car. You can find a location to check the position of your car seat on http://www.safercar.gov/cpsApp/cps/index.htm. Discuss common situations in which correct car seat use may be difficult and troubleshoot how parents might address these (e.g. baby is crying when car is on highway—find a safe place to pull over and comfort baby; using a taxi, take the time to install the seat properly; etc.)
Parent car safety: Always wear your seat belt. This helps maintain better control of the car in case of an accident. Do not drive under the influence of alcohol or drugs. Many postpartum medications can make mothers sleepy, and new mothers may also be very sleepy even without medications. Do not drive with your baby if you have any concerns about alertness. Avoid distracted driving and never handle your cell phone while driving.
Smoking: Even occasional exposure to cigarette smoke can damage babies' lungs, and smoke exposure is highly correlated with Sudden Infant Death Syndrome (SIDS). Keep your home and vehicle smoke-free, and do not allow anyone to smoke in your home or vehicle. If you or someone living in your house smokes, it's important to quit now. Even if you only smoke outside, smoke can cling to your hair and skin and your baby can be exposed.
Falls: Keep one hand on your baby at all times while changing diapers and clothes. Babies can move and even start to roll, and injuries can occur unexpectedly, so vigilance about falls is necessary.
Home: Install smoke detectors and carbon monoxide detectors and carefully follow instructions on timing of when to change batteries. Set home water temperature to <120°F. Avoid drinking hot liquids while holding baby. Never place hot liquids next to baby on changing table or in crib.
Sleep: Place baby to sleep on back in crib with slats ≤2 3/8" apart. No pillows, bumpers, stuffed animals or fluffy bedding in crib. The safest place for baby to sleep is in a crib, cradle, co-sleeper, or bassinet next to your bed. Babies should never sleep in the parents' bed if there has been any use of drugs or alcohol.

Phone follow-up assignments: The first two participants randomly assigned to ELF each month will receive 1-week phone follow-up from the Penn State team, who will enter the responses directly into RedCAP. All other phone follow-up calls will be made by the UCSF team.

2) <u>Follow-up call (8 days of age) – Telephone Call</u>

a) Breastfeeding
- Breastfeeding status (yes/no)
- Reasons for discontinuing breastfeeding (if applicable)
- Formula use in last 24 hours (yes/no)
- Volume of formula used
- Any other feedings
- Day and time at onset of mature milk production

For the first two participants randomly assigned to ELF each month, we will also ask questions about:
- ELF use on day of enrollment
- ELF use on subsequent days

b) Breastfeeding Self-Efficacy Scale—Short Form[84]
c) Infant Satisfaction and Satiety Scale[102]
d) Parenting Sense of Competence Scale[103]

e) State Trait Anxiety Inventory (STAI)[104] - State Portion only –if score ≥40, refer to Primary Care Provider (PCP) if mother has one, obstetrical service if no PCP.
f) Edinburgh Postnatal Depression Scale (EPSD)[105] - If score ≥12, refer to PCP if mother has one, obstetrical service if no PCP. If Penn State team has made the follow-up call and identified an EPDS ≥12, the Penn State team member will call Dr. Flaherman to report.
g) Outpatient visits, emergency room visits, inpatient hospitalizations and their associated reasons/diagnoses, with weights and bilirubin levels if available

3) **Follow-up call (1 month of age) – Telephone Call**
All items completed on paper forms by interviewer contemporaneously with interview
a) Breastfeeding
- Breastfeeding status (yes/no)
- Reasons for discontinuing breastfeeding (if applicable)
- Formula use in last 7 days (yes/no)
- Volume of formula used in a typical feeding in the last 7 days
- Typical frequency of formula feedings in the last 7 days
- Any other feedings

b) Breastfeeding Self-Efficacy Scale—Short Form
c) Infant Satisfaction and Satiety Scale
d) STAI - State Portion only –if score ≥40, refer to PCP if mother has one, obstetrical service if no PCP.
e) EPSD - If score ≥ 12, If score ≥ 12, refer to PCP if mother has one, obstetrical service if no PCP.
f) Outpatient visits, emergency room visits, inpatient hospitalizations and their associated reasons/diagnoses, with weights and bilirubin levels if available

4) Follow-up call (3 months of age) – Telephone Call
All items completed on paper forms by interviewer contemporaneously with interview
a) Breastfeeding
- Breastfeeding status (yes/no)
- Reasons for discontinuing breastfeeding (if applicable)
- Formula use in last 7 days (yes/no)
- Volume of formula used in a typical feeding in the last 7 days
- Typical frequency of formula feedings in the last 7 days
- Any other feedings

b) Breastfeeding Self-Efficacy Scale—Short Form
c) Infant Satisfaction and Satiety Scale

5) Follow-up call (6 months of age) – Telephone Call
All items completed on paper forms by interviewer contemporaneously with interview
a) Breastfeeding
- Breastfeeding status (yes/no)
- Reasons for discontinuing breastfeeding (if applicable)
- Formula use in last 7 days (yes/no)
- Volume of formula used in a typical feeding in the last 7 days
- Typical frequency of formula feedings in the last 7 days
- Any other feedings

b) Breastfeeding Self-Efficacy Scale—Short Form
c) Infant Satisfaction and Satiety Scale

6) **Follow-up call (12 months of age) – Telephone Call**
All items completed on paper forms by interviewer contemporaneously with interview
a) Breastfeeding
- Breastfeeding status (yes/no)
- Reasons for discontinuing breastfeeding (if applicable)

Table 4. Summary of study outcome assessment

Outcome	Measurement tool	Time of assessment					
		Baseline	1 wk	1 mo	3 mo	6 mo	12mo
Aim 1—Infant							
Clinical and demographic screening information	ELF-TLC instrument	X					
Any breastfeeding	National Immunization Survey (NIS)[106] breastfeeding items		X	X	X	X	X
Type of feeding other than breast milk, if any	Infant Feeding Practices Study (IFPS) breastfeeding items[107]		X	X	X	X	
Formula volume used	IFPS breastfeeding items[107]		X	X	X	X	
Latching	LATCH score	X					
Aim 2—Mother							
Anxiety	State Anxiety Scale of the State-Trait Anxiety Inventory[104]	X	X	X			
Breastfeeding self-efficacy	Breastfeeding Self-Efficacy Scale—Short Form[84]	X	X				
Milk supply concern	Infant Satisfaction and Satiety subscale of H&H Lactation Scale[102]	X	X				
Postpartum depression	Edinburgh Postnatal Depression Survey[105]	X	X	X			
Aim 3—Health care system							
Health care utilization	Maternal report of office visit, emergency visit, re-hospitalization		X	X			
Maternal satisfaction with quality of care	Satisfaction with Health Care Following Childbirth Scale[108]		X				

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IV. PROTOCOL IMPLEMENTATION

A. RECRUITMENT

During the maternity and newborn hospital stay at UCSF and HMC, study personnel will identify eligible mothers and babies through a review of the electronic medical record. Once dyads are identified as meeting each of the inclusion criteria, informed consent will be obtained from the mother.

B. PARTICIPANT RETENTION

It is expected that dropouts may occur over the course of the 12-month follow-up period. The vast majority of those dropouts are unlikely to occur in the first month of the study, but by the 6-month outcome assessment a 10% dropout rate was included in sample size calculations. To minimize drop-outs, we will obtain multiple phone numbers for each participant and will obtain the phone number of at least one contact who does not live with the participant. We will have a dedicated call-back number and use multiple reminder calls to obtain robust follow-up. To further protect against loss to follow-up for breastfeeding duration, we will obtain permission at enrollment to request medical records for babies with missing data to gain information on breastfeeding duration and formula use.

C. STUDY NURSE TRAINING

The nurses responsible for teaching the intervention or control will be research nurses with experience in breastfeeding teaching. Prior to the start of this study, all nurses will receive education on the support of breastfeeding mothers and in particular on the teaching of ELF and safety education. The PI Dr. Flaherman is board certified as both a pediatrician and a lactation consultant and will lead this educational initiative. All nurses as well as study staff have received training on cultural competency.

D. HEALTHCARE UTILIZATION ASSESSMENT

Maternal and infant healthcare utilization will be primarily assessed via maternal report using a healthcare utilization survey. Though maternal report has been shown to be a reliable indicator of actual healthcare utilization,[109] a subset of mother/infant dyads that receive all care at either UCSF or HMC and their affiliated clinics will have their utilization objectively assessed using the hospital scheduling and/or billing databases. The concordance between self-report and documented visits will be determined for this subset. In case the concordance is not sufficient, included in the informed consent will be permission to access the outpatient medical record including clinics outside of the HMC system.

E. MICROBIOME

Infant stool will be collected at 1 week and 1 month from infants enrolled at UCSF and will be stored by investigators at UC Davis for future analysis of the effect of our intervention on infant microbiota.

E. RISKS/BENEFITS

Risks to the subjects.

Human subjects involvement and characteristics. This study will involved a total of 164 healthy term newborns and their mothers who are patients at UCSF Medical Center and the Penn State Milton S. Hershey Medical Center. We will include newborns 18-72 hours old who have weight loss ≥75th percentile based on the weight loss nomogram stratified for delivery mode since this criterion may predict increased risk of breastfeeding problems. We will exclude those requiring Level II or Level III care, newborns whose mothers have conditions that are contraindications to breastfeeding (e.g. HIV, active TB, receipt of chemotherapy) and those who have lost ≥10% birth weight. All eligible mother-infant pairs will be approached for potential recruitment and enrollment. Since this study will examine the effect of a breastfeeding intervention in the newborn period, our study participants will be neonates. Participants will be randomly assigned to either the intervention or the control group. The intervention group will receive 10 mL of formula in addition to breastfeeding, while the control group will breastfeed exclusively unless otherwise directed by a health care provider. UCSF is the primary site and plans to enroll 84 newborns; Penn State plans to enroll 80 newborns. Data from both sites will be entered directly onto the password-protected server of UCSF's Research Encrypted Data Capture (REDCap). Protected Health Information (PHI) will be removed from the data before it is exported to the UCSF Principal Investigator, Valerie Flaherman, MD, MPH, for analysis.

Sources of materials. The research material will consist of survey responses and medical history reports. Dr. Flaherman, PI, Dr. Cabana (co-investigator) and Dr. Paul (site PI for Penn State) will have access to protected health information, as will the project managers and research nurses from the two sites and the research assistant at UCSF. All identifiable private information will be maintained on a password-protected server maintained by UCSF's REDCap.

Potential risks. Since both exclusive breastfeeding and mixed feeding with formula and breast are common in the newborn period, we do not anticipate any additional medical risks to the patients that exceed the usual risks surrounding the postpartum period for newborns. However, loss of privacy may be a risk, as we will collect some information individuals might prefer to keep private, such as income, education, previous breastfeeding experience and parenting self-efficacy. Eligible participants who do not want to enroll in the study will receive usual care, and may choose to breastfeed exclusively, to breastfeed with some formula use or to stop breastfeeding.

Protection Against Risk: To protect against the risk of loss of privacy, all potential participants will be approached in their private hospital room, which house all mothers at both study sites. Study investigators will also consent, enroll and teach the intervention in the participant's private hospital room. To protect against a

loss of confidentiality of data, all data will be entered into UCSF's RedCAP, a research database server with password-protection maintained by UCSF. All paper records, including signed informed consent, will be kept in either a locked filing cabinet in Dr. Flaherman's locked office at UCSF, or a locked filing cabinet in the locked office of the project manager at Penn State. The study investigator will obtain informed consent from mothers for themselves and their newborns. Improving outcomes for newborns is the main outcome of this study and therefore it is necessary to enroll neonates in this study. See below for Data Safety and Monitoring Plan.

Potential benefits of the proposed research to the subjects and others. All study participants will receive breastfeeding support at enrollment, which will supplement and not replace breastfeeding support available during the course of their usual clinical care. In addition, parents of participants may have the benefit of knowing that they are helping contribute to a greater understanding of the impact of early infant feeding on subsequent health outcomes. The study risks of loss of privacy and loss of confidentiality may therefore be balanced by the potential benefit of breastfeeding support and the potential feeling of satisfaction from helping contribute to knowledge of the impact of early feeding.

The maternal mental health outcomes of anxiety and depression will be assessed in this study at 1 week and 1 month using the State Trait Anxiety Inventory (STAI) and the Edinburg Postpartum Depression Scale (EPDS). In order to insure adequate protection of mothers from the risk of adverse mental health outcomes, STAI and EPDS total scores will be calculated within 24 hours of maternal interview. Mothers with positive screening tests on either the STAI (STAI score ≥40) or the EPDS (EPDS score ≥12) will be referred to their primary care provider immediately for further evaluation. If no primary care provider has been identified for an individual mother, she will be referred to her obstetrician for further evaluation. The study risks of loss of privacy and loss of confidentiality may therefore be balanced by the increased surveillance and referral for anxiety and depression, in addition to the potential benefit of breastfeeding support and the potential feeling of satisfaction from helping contribute to knowledge of the impact of early infant feeding.

Importance of the knowledge to be gained. Breastfeeding for at least 12 months reduces infectious disease in infancy and reduces maternal risk of breast and ovarian cancer, but most mothers and infants stop breastfeeding in the first few months after birth. In this proposed study, we aim to examine whether a specific feeding strategy might improve breastfeeding duration. Since the risks to privacy and confidentiality are relatively small for participants in this study, the risks to participants are reasonable in relation to the importance of the knowledge to be gained.

F. ANTICIPATED RESULTS

If our randomized trial shows that ELF improves breastfeeding duration, it might be possible to use ELF to help meet Healthy People 2020 targets for breastfeeding at 6 and 12 months and allow more mothers and babies to obtain all the benefits of continued breastfeeding. Our results could also potentially inform the modification of breastfeeding guidelines from the WHO,[11] the CDC,[13] the AAP[110] and the Joint Commission,[41-43] so that the use of formula could be tailored to the needs of individual infants based on their individual clinical presentation. In addition to improving U.S. breastfeeding rates, such a tailored strategy might also ameliorate maternal anxiety and reduce health care utilization, potentially leading to improvement in maternal satisfaction with the quality of health care.

If the use of this intervention helps breastfeeding rates meet Healthy People 2020 targets, this project could have a substantial impact on population health by reducing rates of infectious disease during infancy and by decreasing future rates of maternal breast and ovarian cancer.

V. ADVERSE EVENTS

A. DEFINITIONS

An adverse event shall be defined as any detrimental change in the patient's condition, whether it is related to perinatal care or to another unrelated illness.

B. ADVERSE EVENTS

Adverse events may be grounds for withdrawal from the study if the patient is no longer able to effectively participate in the study. Subjects experiencing minor illnesses that are considered part of normal childhood such as acute otitis media, upper respiratory infections, and gastroenteritis not resulting in a hospitalization will not be recorded as adverse events. Adverse events that will be recorded include jaundice/hyperbilirubinemia requiring phototherapy, intravenous fluid administration, and laboratory evaluations of any kind not related to a prenatal diagnosis (e.g. renal ultrasound to follow up on antenatal hydronephrosis, hip ultrasound due to intrauterine breech position or abnormal neonatal hip exam). Participants may continue in the study provided that the nature, severity, and duration of the illness are recorded. Examples of minor illnesses for mothers that will be considered adverse events include mastitis, urinary tract infections, and surgical wound infections. Medications are allowed for treatment of these conditions in accordance with the judgment of the responsible study physician.

Documentation of an adverse event will be recorded on an Adverse Event Report Form and will include the following information:

1. Description of the illness
2. Dates of illness
3. Treatment of illness and dates (medications, doses, and dose frequency)
4. Whether emergency treatment or hospitalization was required
5. Treatment outcome

Though neonatal re-hospitalizations are an outcome measure for the study, they will be treated as serious adverse events (SAEs). Expected causes of re-hospitalizations are included in other portions of this protocol. The SAE rate for neonates is expected to be <5%.

C. CRITERIA FOR DISCONTINUING SUBJECTS FROM THE STUDY

Subjects who cannot be contacted after repeated attempts by phone will be sent a letter by mail asking them to contact the study staff. If this letter is not responded to within 2 weeks, the subject will be discontinued from the study.

D. DROPOUT STATUS

Any family who withdraws consent to participate will be assigned dropout status.

VI. DATA SAFETY AND MONITORING PLAN

A. PROTECTION OF HUMAN SUBJECTS

For this randomized trial examining the effect of different feeding strategies in infancy, we do not anticipate any medical risks for enrolled participants beyond the usual risks for mothers and infants in the immediate postpartum period. However, it is possible that early limited formula affects breastfeeding duration, so that either our intervention group or our control group might eventually have reduced breastfeeding duration, which could potentially affect their receipt of the health benefits associated with breastfeeding. We will therefore undertake a midcourse review halfway through enrollment to assess the data. We anticipate that recruitment and enrollment for this project will take 12 months, and we therefore anticipate reaching 50% enrollment at about 6 months. Since, after 6 months of enrollment, few of our enrolled participants will have reached our primary outcome of breastfeeding at 6 months, our midcourse review will assess rates of breastfeeding at 1 month. When 50% of our participants (82 participants) have completed 1-month follow-up, Drs. Flaherman, Paul, McCulloch and Cabana will examine the accrued data for data quality and completeness and will assess whether our intervention has had a significant effect on breastfeeding duration through 1 month. If our midcourse review shows that our intervention has had a significant effect on breastfeeding prevalence at 1 month, we will revise our consent form to include specific information about the potential for shorter breastfeeding duration at 1 month based on treatment assignment. Dr. Flaherman will take responsibility for all adverse events and serious adverse events and will report any of these within 24 hours to the UCSF Committee on Human Research, the Pennsylvania State Medical College Institutional Review Board and the Maternal Child Health Bureau.

In addition, because our study assesses maternal mental health outcomes, we will undertake a limited review of data completeness and quality once 10% of our participants have completed their final study mental health assessment at 1 month postpartum. This will enable any problems assessing maternal mental health to be identified in a timely fashion. If we identify systematic sources of incomplete data regarding mental health, we will repeat training of outcomes assessment for our research staff and reassess data completeness and quality in a similar fashion once the next 10% of participants have completed 1-month follow-up.

B. INCLUSION OF WOMEN AND MINORITIES

The ELF study will enroll breastfeeding women and their healthy term newborns. We will not be able to enroll fathers since males cannot breastfeed. We anticipate that about half of infants will be female. We will recruit ELF participants from the nurseries and postpartum wards at UCSF Medical Center and Penn State Hershey Medical Center. Based on our preliminary data, approximately half of our participants will be non-Hispanic white, and approximately half will be either Hispanic or non-white. Our two previous randomized trials of breastfeeding newborns at UCSF recruited participants with the following racial/ethnic distribution: 44% Asian, 23% white non-Hispanic, 20% white Hispanic, 10% African-American, 3% Pacific Islander, 0% American Indian/Alaskan Native. Our previous randomized trial of newborns at Penn State recruited participants with the following racial/ethnic distribution: 84% non-Hispanic white, 6% Black, 4% Hispanic, 4% Asian, 0% Pacific Islander and 0% American Indian/Alaskan Native.

C. INCLUSION OF CHILDREN

Improving outcomes for newborns is the main objective of this trial and therefore this population will be primarily studied.

VII. COST, LIABILITY, AND PAYMENT

There is no cost to the participating subjects. UCSF will mail each family a $20 gift card upon completion of each follow-up call at 1 week and at 1, 3, 6 and 12 months, for a total of $100 and a $5 gift card upon receipt of each stool collected at 1 week and 1 month (UCSF only).

VIII. STATISTICAL DESIGN AND ANALYSIS

A. DATA RECORDING AND DATA MANAGEMENT

Research staff will record participant data on the data collection forms, review the forms for completeness and legibility and will use password-encrypted Research Electronic Data Capture to allow entry on site at enrollment and immediately after each follow-up. This will further allow transfer of data between Penn State and UCSF. We will de-identify the data and transfer into Stata SE 11.2 (Stata Inc., College Station, TX) for analysis.

B. RANDOMIZATION AND STRATIFICATION

Michele Marini, MS, an independent biostatistician not otherwise affiliated with the study, will develop the randomization scheme using permuted blocks. The allocation sequence for randomization will be generated by an independent statistician through a secure computerized allocation system using a block randomization technique with randomly permuted blocks of 2 and 4 participants stratified on site, income (<200% Federal Poverty Level (FPL) or ≥200% FPL) and parity (primiparous or multiparous). As a result, the nurse will not have any foreknowledge of group assignment.

After entering the secure Microsoft Excel application and entering the delivery type, a randomization assignment (either ELF or safety education) will be returned for the mother-infant dyad. *Thus, randomization will occur after consent has been obtained and after lactation education has been completed.* Of note, though the stratifying variable will yield 3 strata with unequal numbers between strata, within each individual stratum there will be approximately equal numbers and balance between the treatment groups.

C. SAMPLE SIZE, POWER CALCULATIONS, AND STATISTICAL ANALYSIS

Based on the data from PI Flaherman's pilot study where breastfeeding rates were 40% higher for mothers and infants who received ELF than for those who were assigned to control, 74 mother-infant dyads are required in each arm of the randomization (148 in both arms) to prospectively demonstrate 40% increase in breastfeeding rates at 6 months with 90% statistical power and α=0.05. These calculations are based on the chi-square test. We will also attempt to analyze the data using a Cox proportional hazards model, which may have slightly greater power to detect a difference. Included in the calculation of these figures is the assumption that currently, many mother-infant pairs are advised to breastfeed exclusively but instead use some formula, usually in an unstructured manner. This crossover of assignment has been considered, and the sample size calculation reflects the fact that similar crossover occurred in our pilot study. A low dropout rate is anticipated given the low rate in previous similar studies, and the fact that patients will be knowingly enrolling in a research study involving the assessment of breastfeeding. In order to account for the possibility of 10% dropout, we will recruit 164 infants to have final follow-up on at least 148.

For the chief secondary outcome, maternal anxiety, the required sample size is 155 per cohort to have 90% statistical power and α=0.05 to test a 5-point difference in maternal state anxiety as measured by the STAI. Since anxiety outcomes will only be assessed in the first month of the study, we anticipate that enrolling 164 mothers will allow us to assess outcomes on anxiety for at least 155 mothers.

This study also seeks to examine the effect of ELF on health care utilization. Assessment of these will also occur in the first month only, when we estimate 95% follow-up, giving 155 outcomes. In site PI Paul's NITTANY study, 42% of newborns had additional health care utilization beyond an assigned study visit in the first 14 days.[98] Our sample size will therefore have adequate power to detect a 25% reduction in health care utilization. In NITTANY, mean scores for the Satisfaction with Maternal and Newborn Health Care Measure were 47.9 ± 7.1. Therefore, the ELF study will have adequate power to detect a 4-point difference (out of 55 possible) in satisfaction with quality of care.

D. ANALYTIC PLAN FOR MAJOR OUTCOMES

All primary statistical analyses will invoke the intent-to-treat paradigm; i.e., based on the randomized assignment to ELF or continued exclusive breastfeeding and regardless of actual treatment received, protocol violations, etc. A major study consideration is that many infants who are randomly assigned to exclusive breastfeeding at 18-72 hours will, in fact, actually receive formula at some point during the first week. In our pilot, about 50% of those who were initially randomly assigned to exclusive breastfeeding did receive formula

in the first week. This is consistent with national statistics, which show that about half of breastfed infants receive formula in the first week.[15] Our study hypothesizes that such unstructured formula use, which is common in the population as a whole and more common in babies with rapid early weight loss, may cause significantly worse breastfeeding outcomes than the carefully managed formula in the ELF intervention. The purpose of this trial is to compare the use of ELF with the current standard of care of recommending exclusive breastfeeding, with the recommendation followed by some and not by others. Therefore, analysis for most of our outcomes, including our primary outcome of breastfeeding duration at 6 months, will be intention-to-treat, which will inform the primary public health policy question of whether recommending against formula during the birth hospitalization improves breastfeeding duration.

We will use chi-square analysis to report the effect of ELF on our outcomes of breastfeeding at 6 and 12 months and breastfeeding without formula at 3 months. For each of the outcomes that assess the effect of ELF on breastfeeding duration, we will also attempt a Cox proportional hazards model. Using a Cox model adjusting for parity, race, ethnicity, income and delivery method, we will check for a lack of proportional hazards by including a time-varying interaction term in our predictor variables to identify any potential interaction between time and our primary predictor, use of ELF. We will then test the time-varying interaction terms and include them in the analysis to accommodate non-proportional hazards. We will use Student's t-test to assess the effect of ELF on the total volume of formula used in the first week and on maternal anxiety in the first week and the first month. We will also use multivariate linear regression to examine the effect of ELF on maternal anxiety after adjusting for parity, race, ethnicity, prior breastfeeding experience, income and method of delivery and to examine the effect of maternal anxiety on breastfeeding rates at 6 and 12 months adjusting for the same covariates.

Although most of our analyses will be conducted using an intention to treat approach, we will also conduct a limited as-treated cohort analysis to examine the effect of any type of formula use on health care utilization, because health care utilization may be more affected by whether or not any formula was used than by whether it was used on-protocol or off-protocol. Newborns should have at least one outpatient health care visit in the first month.[111] Therefore, for the outcome of health care utilization, we will use chi-square testing to examine the effect of ELF on whether or not ≥2 utilizations occurred. We will use Student's t-test to examine the effect of ELF on maternal satisfaction with quality of care.

Missing data: Loss to follow-up is an important concern for our study since mothers will be at a time of life with much change. We have learned how to maintain follow-up from our previous studies by using the following techniques: obtaining multiple phone numbers, obtaining the phone number of a contact who does not live with the participant, using a dedicated call-back number and multiple reminder calls. We have also found that our detailed assessment of breastfeeding information offers an opportunity to develop an emotional bond with participants that improves retention. To protect further against loss to follow-up for breastfeeding duration, we will obtain permission at enrollment to request medical records for babies with missing data to gain information on breastfeeding duration and formula use.

If there are participants for whom the primary outcome of breastfeeding duration remains unknown, we will compare rates of drop-out between the study arms and use a chi-square test to report whether follow-up is differential. We will also compare mothers with complete follow-up with mothers with incomplete follow-up using the validated Breastfeeding Attrition Prediction Tool to generate a likelihood of breastfeeding discontinuation,[112] and will use ANOVA to report whether mothers with missing follow-up had a higher *a priori* likelihood of breastfeeding discontinuation. For additional missing data not related to breastfeeding duration, we will use multiple imputation techniques to complete our analysis.

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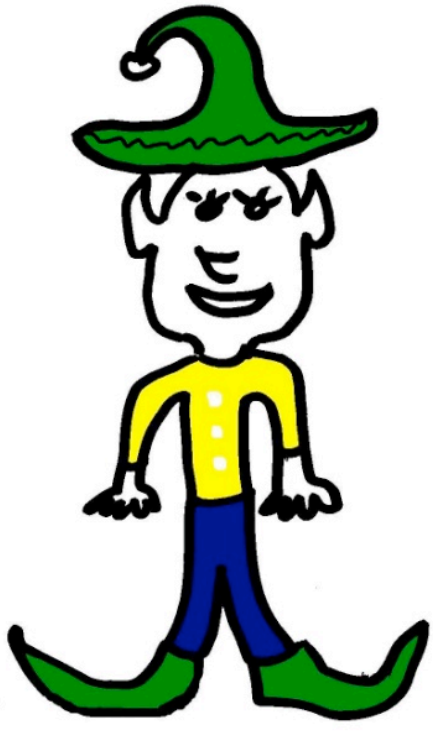
Appendix I

Breastfeeding Education for Mothers Enrolled in the Early Limited Formula (ELF) Study

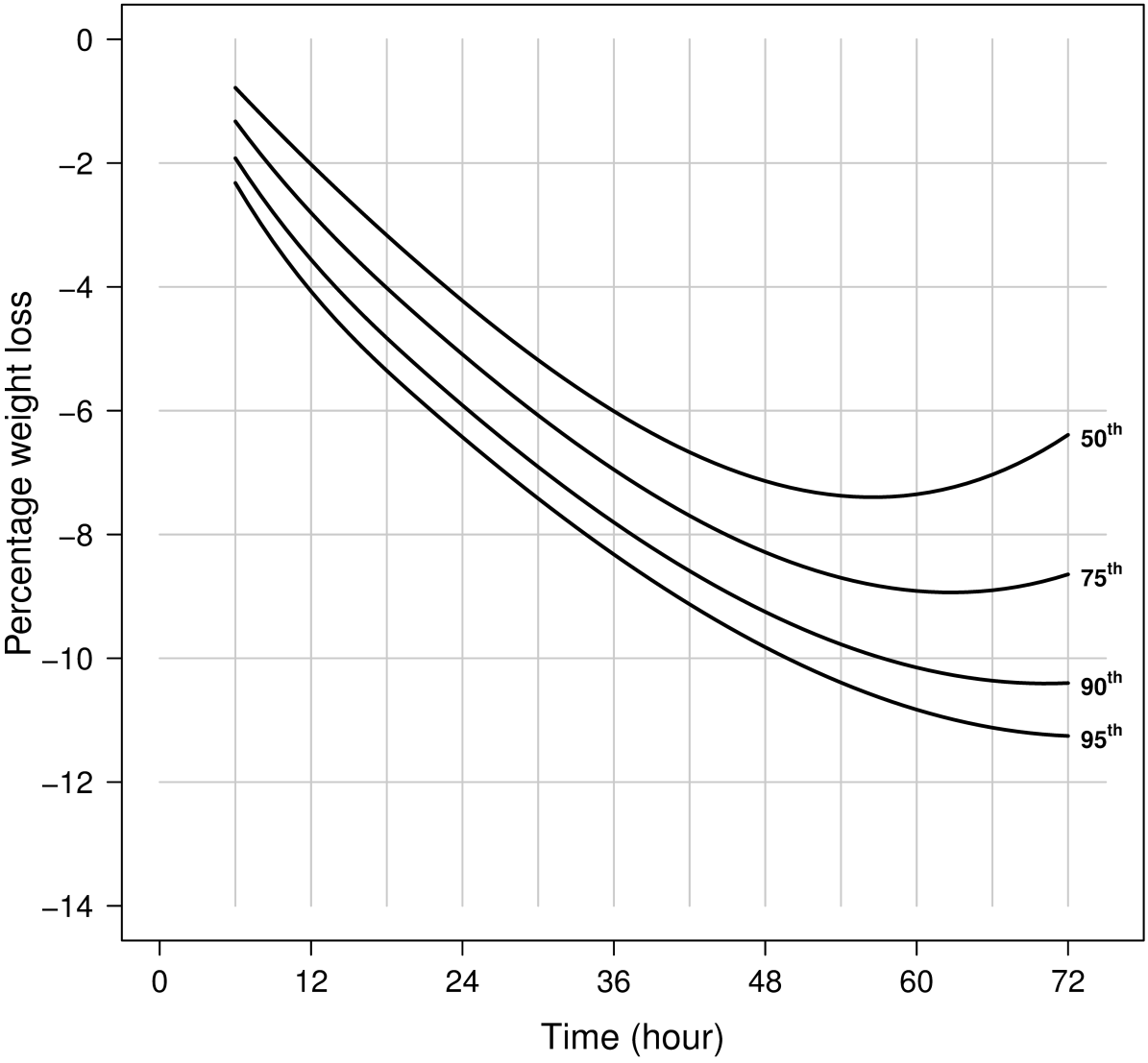
Thank you for enrolling in the Early Limited Formula (ELF) Study. Your participation will help us learn more about how to give each baby the best possible start with breastfeeding.

- Breastfeeding is a natural process, but getting started is not always easy. Here are some suggestions to help you on your way!
- For the first few weeks after birth, breastfeed 8-12 times in each 24 hours. This averages out to about one feeding every 2-3 hours, but sometimes newborns feed several times in a brief period and then sleep for a bit longer.
- Newborns will generally breastfeed for about 10-20 minutes per breast.
- Your newborn has important hunger signs. These include: opening his or her eyes, crying, sticking out his or her tongue and turning his or her head towards one side or from side to side. If it's been more than an hour since you fed your baby and you see these signs, consider feeding your baby.
- Make sure you are comfortable before you start to breastfeed. If you are sitting down, make sure you have support for your back and arms.
- Your baby should latch with a wide-open mouth, taking as much of your areola (deeply colored circle around your nipple) into his or her mouth as possible.
- If your baby is not interested in latching, try expressing a little bit of colostrum by hand and see if that helps with the latch
- In the beginning of breastfeeding, your breasts will make colostrum, a yellowish/orange liquid that has very important vitamins for your baby. When your baby is 2-5 days old, you will begin production of large volumes of mature breast milk.
- Before mature milk production begins, babies lose some weight each day.
- Before you make mature milk, your baby will urinate and stool only a few times per day. Once your mature milk comes, your baby should urinate and stool about 8 times per day.



Appendix IIa

Estimated percentile curves of percent weight loss by time after birth for vaginal deliveries



Appendix IIb.

Estimated percentile curves of percent weight loss by time after birth for Cesarean deliveries