Evidence-Based Updates on the First Week of Exclusive Breastfeeding Among Infants ≥35 Weeks

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The nutritional and immunologic properties of human milk, along with clear evidence of dose-dependent optimal health outcomes for both mothers and infants, provide a compelling rationale to support exclusive breastfeeding. US women increasingly intend to breastfeed exclusively for 6 months. Because establishing lactation can be challenging, exclusivity is often compromised in hopes of preventing feeding-related neonatal complications, potentially affecting the continuation and duration of breastfeeding. Risk factors for impaired lactogenesis are identifiable and common. Clinicians must be able to recognize normative patterns of exclusive breastfeeding in the first week while proactively identifying potential challenges. In this review, we provide new evidence from the past 10 years on the following topics relevant to exclusive breastfeeding: milk production and transfer, neonatal weight and output assessment, management of glucose and bilirubin, immune development and the microbiome, supplementation, and health system factors. We focus on the early days of exclusive breastfeeding in healthy newborns ≥35 weeks’ gestation managed in the routine postpartum unit. With this evidence-based clinical review, we provide detailed guidance in identifying medical indications for early supplementation and can inform best practices for both birthing facilities and providers.

Exclusive breastfeeding significantly improves maternal and child health. Although US pediatricians’ recommendations are increasingly aligned with American Academy of Pediatrics (AAP) policies, their optimism about the potential for breastfeeding success has declined.1 To maintain familiarity with the benefits of breastfeeding and the skills necessary to promote this positive health intervention, providers caring for neonates and/or new mothers need updated evidence-based information and tools to assess and manage breastfeeding.

In this review, we provide new evidence from the past 10 years on the following topics relevant to exclusive breastfeeding: milk production and transfer, neonatal weight and output assessment, glucose stabilization, hyperbilirubinemia, immune development and the microbiome, supplementation, and health system interventions. We focus on the early days of exclusive breastfeeding in healthy newborns ≥35 weeks’ gestation managed in the routine postpartum unit.2–6 Tables 1 through 3 and Fig 1 provide summaries based on evidence and authors’ recommendations to provide concise abstract

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Drs Feldman-Winter, Kellams, and Stuebe conceptualized and designed the review of the literature, conducted the literature review and analysis, drafted the initial manuscript, and reviewed and revised the manuscript. Dr Peter-Wohl made substantial contributions to the acquisition of data and to the analysis and interpretation of data, drafted the article, and revised it critically for important intellectual content; Dr Taylor made substantial contributions to conception and design and made critical revisions; Drs Lee and Terrell made substantial contributions to the design and to the acquisition of data and made critical revisions for important intellectual content; Drs Meek and Noble and Ms Maynor made substantial contributions to the conception, design, and analysis and interpretation of data and revised the article critically for important intellectual content; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

and clear bullets on optimal management. The search strategy and tables of evidence for milk production and transfer, neonatal weight and output assessment, management of glucose, and hyperbilirubinemia are summarized in the Supplemental Information.

**MILK PRODUCTION AND TRANSFER**

Three stages of milk production, lactogenesis I to III, are defined on the basis of volume and composition of milk. For volume, Fig 2 shows estimated daily milk production. In relation to composition, human milk changes dramatically over the first week of lactation. Colostrum, which is produced during the initial stage of lactation (lactogenesis I) in the first days after birth, contains more protein than mature milk. This highly dense early milk has a high concentration of immunoglobulins, activated macrophages, lymphocytes, neutrophils, and growth factors with essential roles in development of gut-associated lymphoid tissue. As milk volume increases (lactogenesis II), sodium concentration and the sodium/potassium ratio decline rapidly with increased secretory activity of the lactocytes and closure of tight cellular junctions. Production of fat-rich, higher-calorie mature milk typically occurs by ~10 days post partum (lactogenesis III).

Most, but not all, women experience lactogenesis II, referred to as “milk coming in,” by 72 hours post partum. In the Infant Feeding Practices Survey II, 19% of multiparous women and 35% of primiparous women reported milk coming in on day 4 or later. Reasons for delayed lactogenesis II include primiparity, cesarean delivery, and BMI > 27. Conditions associated with obesity, such as advanced maternal age (possibly related to reduced fertility associated with obesity-variant polycystic ovarian syndrome) and excessive gestational weight gain, may also lead to a delay. Delayed lactogenesis II is associated with neonatal weight loss >10%.

Occasionally, a woman does not experience lactogenesis II and only produces small volumes of milk (prevalence 5%–8%). The differential diagnosis includes breast pathology, previous breast surgery (with damage to ducts or augmentation for hypoglandular breasts), developmental anomalies of the breast tissue, hormonal disruptions (such as retained placental fragments and pituitary insufficiency, including Sheehan’s syndrome, hypothyroidism, polycystic ovarian syndrome, or theca-lutein ovarian cysts), and toxins (such as excessive tobacco exposure). Occasionally, strategies described

<table>
<thead>
<tr>
<th>Schedule for observed feeding by trained health professional (physician, midwife, or a physician-supervised, breastfeeding-trained health care provider) to evaluate breastfeeding effectiveness</th>
<th>Inpatient</th>
<th>Hospital Discharge</th>
<th>Outpatient</th>
</tr>
</thead>
<tbody>
<tr>
<td>• At least once every 8–12 h during the hospitalization</td>
<td>• At least once within 8 h before hospital discharge</td>
<td>• Within 24–48 h of hospital discharge for mother-infant pairs with: ○ Infants &lt;37 wk gestation</td>
<td>• Within 48–72 h of discharge for all other breastfed infants</td>
</tr>
<tr>
<td>Key components of breastfeeding assessment and documentation</td>
<td>• Risk factors for breastfeeding problems (Table 2)</td>
<td>• Evidence of milk transfer such as audible milk swallowing, level of maternal comfort while feeding, satisfaction of infant after a feed, and softening of breasts after feeding compared with before feeding (softening is difficult to assess before lactogenesis II)</td>
<td>• Mother: nipple pain, nipple trauma, compression, engorgement, and mastitis require thorough assessment and management</td>
</tr>
<tr>
<td>○ Latch (including maternal comfort)</td>
<td>○ With equivocal physical findings, obtain pre- and postfeeding weights on an accurate (&lt;5 g) infant scale</td>
<td>○ Infants with greater-than-expected wt loss (&gt;75th percentile on NEWT curve)</td>
<td>• Infant: infants with wt loss ≥7% of birth wt at 5–6 d after birth should be monitored every 24–48 h in the outpatient setting until wt gain is well established</td>
</tr>
<tr>
<td>○ Milk transfer</td>
<td>○ Infants ≤48 h of age at discharge</td>
<td>○ Infants with risk factors for hyperbilirubinemia</td>
<td>• Mothers with persistent breastfeeding problems should be assessed for a latch problem</td>
</tr>
<tr>
<td>○ Clinical jaundice</td>
<td>○ Urine output and notation of uric acid crystals if present</td>
<td>○ With equivocal physical findings, obtain pre- and postfeeding weights on an accurate (&lt;5 g) infant scale</td>
<td>○ Infants with risk factors for hyperbilirubinemia</td>
</tr>
<tr>
<td>○ Urine output and notation of uric acid crystals if present</td>
<td>○ Stool output, color, and transition</td>
<td>○ With equivocal physical findings, obtain pre- and postfeeding weights on an accurate (&lt;5 g) infant scale</td>
<td>○ Infants with risk factors for hyperbilirubinemia</td>
</tr>
<tr>
<td>○ Stool output, color, and transition</td>
<td>○ Before discharge, infant’s wt and percentage wt loss should be documented by using NEWT (<a href="https://www.newbornweight.org">https://www.newbornweight.org</a>)</td>
<td>○ With equivocal physical findings, obtain pre- and postfeeding weights on an accurate (&lt;5 g) infant scale</td>
<td>○ Infants with risk factors for hyperbilirubinemia</td>
</tr>
<tr>
<td>Clinical pearls</td>
<td>○ Before discharge, infant’s wt and percentage wt loss should be documented by using NEWT (<a href="https://www.newbornweight.org">https://www.newbornweight.org</a>)</td>
<td>○ With equivocal physical findings, obtain pre- and postfeeding weights on an accurate (&lt;5 g) infant scale</td>
<td>○ Infants with risk factors for hyperbilirubinemia</td>
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TABLE 2  Mother, Infant, and Systems-Level Risk Factors for Breastfeeding Difficulties

<table>
<thead>
<tr>
<th>Risk Factors for Breastfeeding Difficulties</th>
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<tbody>
<tr>
<td>Prenatal</td>
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<tr>
<td>Past medical history</td>
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<tr>
<td>Maternal obesity (BMI ≥ 30)</td>
</tr>
<tr>
<td>Significant medical problems (eg, thyroid disease, diabetes or insulin resistance, cystic fibrosis, polycystic ovarian syndrome)</td>
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<tr>
<td>Extremes of maternal age (eg, adolescent mother or older than 40 y)</td>
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<tr>
<td>Any previous breast surgery, including cosmetic procedures (important to ask, not always obvious on examination)</td>
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<tr>
<td>Previous breast abscess</td>
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<tr>
<td>Lack of noticeable breast enlargement or tenderness during puberty or pregnancy</td>
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<tr>
<td>Past gynecology history</td>
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<tr>
<td>History of infertility</td>
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<tr>
<td>Conception by assisted reproductive technology</td>
</tr>
<tr>
<td>Past obstetrics history</td>
</tr>
<tr>
<td>Primiparity</td>
</tr>
<tr>
<td>History of previous breastfeeding problems, early breastfeeding cessation, or breastfed infant with slow wt gain</td>
</tr>
<tr>
<td>Postpartum plans</td>
</tr>
<tr>
<td>Intention to both breastfeed and bottle-feed or formula feed at &lt;6 wk</td>
</tr>
<tr>
<td>Intention to use pacifiers or dummies and/or artificial nipples or teats at &lt;6 wk</td>
</tr>
<tr>
<td>Early intention or necessity to return to school or work</td>
</tr>
<tr>
<td>Intended use of hormonal contraceptives before breastfeeding is well established (6 wk)</td>
</tr>
<tr>
<td>Medications</td>
</tr>
<tr>
<td>Inadequate counseling on maternal medication safety in lactation</td>
</tr>
<tr>
<td>Social history</td>
</tr>
<tr>
<td>Psychosocial problems (eg, depression, anxiety, lack of social support for breastfeeding)</td>
</tr>
<tr>
<td>Physical examination findings</td>
</tr>
<tr>
<td>Variation in breast appearance (marked asymmetry, hypoplastic, tubular)</td>
</tr>
<tr>
<td>Flat, inverted, or large nipples</td>
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<tr>
<td>Intrapartum</td>
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<tr>
<td>Prolonged labor</td>
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<tr>
<td>Long induction or augmentation of labor</td>
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<tr>
<td>Use of medications during labor (benzodiazepines, morphine, or others) that can cause drowsiness in the newborn</td>
</tr>
<tr>
<td>Peripartum complications (eg, maternal hyperglycemia in labor, postpartum hemorrhage, hypertensive disorders of pregnancy, infection)</td>
</tr>
<tr>
<td>Infant initial assessment</td>
</tr>
<tr>
<td>Low birth wt, small for gestational age, or premature birth (&lt;37 wk)</td>
</tr>
<tr>
<td>Early-term birth (37 + 0/7–38 + 6/7 wk)</td>
</tr>
<tr>
<td>Multiples</td>
</tr>
<tr>
<td>Oral anatomic abnormalities (eg, cleft lip or palate, macroglossia, micrognathia, tight frenulum or ankyloglossia)</td>
</tr>
<tr>
<td>Medical problems (eg, hypoglycemia, infection, jaundice, respiratory distress, birth trauma, birth asphyxia)</td>
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<tr>
<td>Neurologic problems (eg, genetic syndromes, hypertonia, hypotonia)</td>
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<tr>
<td>Early postnatal care</td>
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<tr>
<td>Mother signs and symptoms</td>
</tr>
<tr>
<td>Perceived inadequate milk supply</td>
</tr>
<tr>
<td>Sore nipples or evidence of nipple compression with feedings</td>
</tr>
<tr>
<td>Failure of secretory activation or lactogenesis stage II (milk did not noticeably come in by 72 h post partum); this may be difficult to evaluate if the mother and infant are discharged from the hospital in the first 24–48 h post partum</td>
</tr>
<tr>
<td>Mother unable to hand express colostrum</td>
</tr>
<tr>
<td>Need for breastfeeding aids or appliances (such as nipple shields, breast pumps, or supplemental nursing systems) at the time of hospital discharge</td>
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<tr>
<td>Use of breast milk substitutes during hospital stay</td>
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<tr>
<td>Use of opiate pain medications</td>
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<tr>
<td>Infant signs and symptoms</td>
</tr>
<tr>
<td>Persistently sleepy infant</td>
</tr>
<tr>
<td>Difficulty in latching on to 1 or both breasts</td>
</tr>
<tr>
<td>Ineffective or unsustained suckling</td>
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here to improve milk production and transfer are not effective, and long-term supplementation with either donor milk or infant formula is medically necessary.

Milk expression is safely and effectively achieved by both manual and mechanical methods and can be used to maintain milk supply in the event of separation from the infant. Hand expression also facilitates milk transfer for the infant learning to breastfeed; both latch and an effective suckling pattern are key. Among mothers of term infants who were feeding poorly, those randomly assigned to hand expression versus electric pumps were more likely to still be breastfeeding at 2 months (96.1% vs 72.7%; P = .02). Infrequent or inadequate signaling due to ineffective or infrequent breastfeeding or milk expression may trigger the autocrine-paracrine mechanisms of halting milk production and dismantling the mammary gland architecture. Milk removal, either via direct breastfeeding or expression, is essential for continuation of milk production.

Some women experience engagement with lactogenesis II. There is limited evidence regarding the optimal management of engagement. However, because severe engagement can impede infant removal of milk, breastfeeding mothers should learn hand expression and reverse pressure softening, which is positive pressure to the central subareolar region, before discharge from maternity care. If a mother is unable to hand express or her infant is unable to latch, she may require a breast massage and/or use of an electric breast pump.

The components of a comprehensive breastfeeding assessment are described in Table 1. It is important to note that a mother's pumped milk volume may be an
TABLE 2 Continued

<table>
<thead>
<tr>
<th>Risk Factors for Breastfeeding Difficulties</th>
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<tbody>
<tr>
<td>Excessive infant wt loss (&gt;7%–10% of birth wt in the first 48 h or &gt;75th percentile for age and mode of delivery on NEWT curves)</td>
</tr>
<tr>
<td>Supplementation with breast milk substitutes</td>
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<tr>
<td>Early pacifier use</td>
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<tr>
<td>Signs of infant dehydration: Lack of bowel movements</td>
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<tr>
<td>Urate crystals in diaper</td>
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<tr>
<td>Dry mucous membranes</td>
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<tr>
<td>Loss of skin turgor</td>
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<tr>
<td>Sunken eyes</td>
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<tr>
<td>Depressed anterior fontanelle</td>
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<tr>
<td>Thready radial pulse</td>
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<tr>
<td>Cold extremities</td>
</tr>
<tr>
<td>Health system: Mother-infant separation</td>
</tr>
<tr>
<td>Nonadherence to BFHI-based maternity practices</td>
</tr>
<tr>
<td>Hospital discharge before effective breastfeeding established</td>
</tr>
<tr>
<td>Discharge from the hospital at &lt;48 h of age</td>
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inaccurate estimate of milk transfer because transfer also depends on the infant’s capabilities. Associated risk factors for suboptimal milk transfer are listed in Table 2.

Painful latching deserves special attention as a contributor to low milk transfer, impaired milk transfer, and early cessation of breastfeeding. In an ultrasound study in which breastfeeding mothers with nipple pain were compared with those without, nipple pain was associated with abnormal infant tongue movement, restricted nipple expansion, and lower rates of milk transfer. In a retrospective audit of an Australian breastfeeding center, 36% of visits were for nipple pain. A US study revealed that nipple pain and trauma were among the most frequently cited reasons for early weaning. In a study of >1600 women with singleton births, ~10% had nipple pain that persisted at postpartum day 7; 72% was attributed to inappropriate positioning and latching, 23% to tongue-tie in the infant, and 4% to oversupply. Women who received treatment recovered within 1 to 2 weeks, and 6-week exclusive breastfeeding rates were no different from those of mothers without nipple pain. Although high-quality randomized controlled trials (RCTs) are needed, frenotomy has been shown to reduce maternal nipple pain in infants with congenital ankyloglossia. There is no evidence that any one topical treatment is superior; the mainstay of management for nipple pain and fissuring is assistance with positioning and latching.

TABLE 3 Risk Factors for Hypoglycemia

<table>
<thead>
<tr>
<th>Risk Factors</th>
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<tbody>
<tr>
<td>Large for gestational age</td>
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<tr>
<td>Small for gestational age</td>
</tr>
<tr>
<td>Infant of a mother with diabetes (including gestational diabetes)</td>
</tr>
<tr>
<td>Premature (&lt;37 wk) or postmature delivery (&gt;41 wk 6 d)</td>
</tr>
<tr>
<td>Symptoms of hypoglycemia (jitteriness, cyanosis, seizures, apneic episodes, tachynea, weak or high-pitched cry, flappiness or lethargy, poor feeding, and eye-rolling)</td>
</tr>
<tr>
<td>Family history of congenital errors in metabolism that may be associated with hypoglycemia</td>
</tr>
<tr>
<td>Congenital syndromes (eg, Beckwith-Wiedemann syndrome), abnormal physical features (eg, midline facial malformations, microphallus) that may be associated with hypoglycemia</td>
</tr>
<tr>
<td>Perinatal stress (asphyxia)</td>
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</table>


NEONATAL WEIGHT AND OUTPUT ASSESSMENT

Healthy newborns experience physiologic weight loss after birth, which, in the exclusively breastfed infant, typically plateaus as the mother’s milk transitions from lactogenesis I to lactogenesis II. The addition of infant formula, either as a supplement or in the form of exclusive formula feeding, is associated with rapid weight gain. This nonphysiologic weight trajectory is associated with childhood obesity. Exclusive direct breastfeeding is inversely associated with the velocity of weight gain throughout the first year of life.

In one prospective cohort study of >300 newborns, weight gain >100 g during the first week after birth was independently associated with overweight status at age 2 (adjusted odds ratio [aOR] 2.3; 95% confidence interval [CI] 1.1 to 4.8). Early infant weight loss should be evaluated in the context of the clinical status of the infant and the mother. Nomograms for newborn weight have been developed by using data from >100 000 healthy, exclusively breastfed infants in California. Individual infant weights can be plotted against these nomograms by using the Newborn Early Weight Tool (NEWT) (https://www.newbornweight.org). Weight loss trajectory over time, combined with clinical information, provides a robust
context for evidence-based decision-making. Weight loss in the >75th percentile on NEWT nomograms for mode of delivery and infant age should prompt a thorough evaluation.

A term newborn’s weight is 75% water, compared with 60% for an adult. Urine output is usually low in the first 1 to 2 days after birth, after which a physiologic diuresis and loss of up to 7% to 10% of birth weight occurs. Insufficient milk production and/or transfer in the exclusively breastfed newborn can contribute to excessive weight loss in the first few days of life. Low milk supply, often exacerbated by poor feeding or difficulty in suckling, correlates with elevated milk sodium levels.

Exclusively breastfed infants, especially those born via cesarean delivery, are at increased risk for greater weight loss, dehydration, and hypernatremia. In a systematic review of hypernatremia among breastfed infants, significant risk factors included weight loss >10%, cesarean delivery, primiparity, breast anomalies, reported breastfeeding problems, excessive prepregnancy maternal weight, delayed first breastfeeding, lack of previous

FIGURE 1
Supplementation decision algorithm.

FIGURE 2
Milk volume estimated by breast milk transfer over the first 6 days in vaginal and cesarean births.

breastfeeding experience, and low maternal education. Prevention strategies included daily weights coupled with lactation support during the first 4 to 5 days after birth.

Early weight loss nomograms for exclusively breastfed newborns can help identify those infants at risk for hypernatremic dehydration (HD).**54,55** A rare condition characterized by lethargy, restlessness, hyperreflexia, spasticity, hyperthermia, and seizures, with an estimated incidence of 20 to 70 per 100,000 births among primiparous mothers.**56** Use of charts for weight loss with SD scores specifically to detect HD, combined with a policy of weight checks on days 2, 4, and 7 of life, had high sensitivity (97%) and specificity (98.5%) to detect HD.**47** However, given the low incidence of HD, the positive predictive value (PPV) of repeated weight checks alone was only 4.4%.**56**

Importantly, elimination patterns during the first 2 days of life are neither sensitive nor specific as measures of infant intake.**49** Infants may be voiding and stooling despite insufficient intake or, more commonly, have decreased voiding and stooling compared with exclusively formula-fed infants despite adequate intake. In a cohort study of 313 infants, the frequency of urination and stooling was significantly decreased among exclusively breastfed infants compared with exclusively formula-fed infants during the first 3 days of life then rose and significantly surpassed that of exclusively formula-fed infants by day 6 of life.**49** Another prospective cohort study of 280 mother-infant pairs examined elimination patterns in relation to excessive weight loss (>10%) between 72 and 96 hours after birth.**48** The strongest association with weight loss >10% was with <4 stools after 72 hours or maternal perception of delayed lactogenesis II.

Although term and late-preterm infants generally pass meconium within 48 hours (76%–83% in a study of 198 infants), delayed passage of meconium can be a marker for insufficient milk intake.**57** Correlations between infants’ intake and elimination are more reliable after the first 3 days (lactogenesis II).

**GLUCOSE STABILIZATION**

To prepare for transitional energy needs, the third-trimester fetus stores glycogen, manufactures catecholamines, and deposits brown fat. Healthy newborns use these stores to maintain thermoregulation and meet their energy needs through metabolism of brown fat and the release of counterregulatory hormones such as glucagon, epinephrine, cortisol, and growth hormone. Combined with declining insulin secretion, these hormones mobilize glucose and alternative fuels, such as lactate and ketone bodies, to support organ functions.**58,59**

Because oral intake is not the main energy source for healthy term neonates in the first days after birth, physiologic volumes of colostrum (16 kcal/oz) are sufficient to meet metabolic demands. As glucose stores are depleted, coinciding with the transition from colostrum to mature milk, newborns transition from a catabolic state to reliance on enteral feeds, with approximately half of the caloric content derived from fat.**60**

After placental detachment, neonatal glucose levels reach a physiologic nadir in the first hours after birth and then typically rise to adult levels a few days later. The threshold for neonatal glucose that is associated with neurotoxicity is unclear; a 2008 National Institutes of Health workshop concluded that “there is no evidence-based study to identify any specific plasma glucose concentration (or range of glucose values) to define pathologic hypoglycemia.”**61** In one cohort study, treatment of asymptomatic newborn hypoglycemia to maintain blood glucose levels >47 mg/dL had no effect on cognitive performance at 2 years; however, at 4.5 years, there were dose-dependent concerns regarding visual motor and executive function, with the highest risk in children exposed to severe (<36 mg/dL), and recurrent (≥3 episodes) hypoglycemia.**62,63**

In the first hours after birth, healthy term neonates compensate for relatively low glucose levels by decreasing insulin production and increasing glycolysis, gluconeogenesis, and ketone production. Among at-risk newborns, early skin-to-skin care plus early feeding and blood glucose assessment at 90 minutes supports glucose homeostasis and is associated with decreased risk of hypoglycemia and NICU admission.**64** In a Cochrane review, early skin-to-skin contact increased glucose levels by 10.49 (95% CI 8.39 to 12.59) mg/dL or 0.6 (0.5 to 0.7) mmol/L.**65** Conversely, practices that separate the mother and infant and delay the first feeding increase hypoglycemia risk.

Glucose monitoring is recommended for infants with risk factors (Table 3) and for any infant who exhibits symptoms of hypoglycemia.**66** Because operational thresholds for treating hypoglycemia and target glucose levels are not defined, clinical recommendations vary. Infants who require early or more frequent feedings should be supported to breastfeed and/or receive expressed milk. Authors of multiple studies confirm the benefits of using glucose gel rather than formula as an initial treatment of low glucose levels, and this practice has become increasingly commonplace.**67–73** Some institutions use pasteurized donor human milk (PDHM) as a treatment of hypoglycemia; however, there are, as yet, no published studies describing...
outcomes of this practice. The option of antenatal milk expression for lower-risk women with preexisting or gestational diabetes may also be considered because this technique may preserve exclusive breastfeeding without adversely affecting perinatal outcomes. Infants requiring intravenous glucose should breastfeed, when able, during the therapy.

Persistent or late-onset hypoglycemia (>48 hours after birth) can occur in the setting of congenital endocrine disorders or, more commonly, perinatal stress due to birth asphyxia, intrauterine growth restriction, maternal preeclampsia, or persistent problems establishing breastfeeding. Infants with these risk factors may be more vulnerable to insufficient feeding, so skilled assessment is essential.

**HYPERBILIRUBINEMIA**

Management of hyperbilirubinemia in the exclusively breastfed newborn depends on whether the excess in bilirubin is pathologic or physiologic. Neonatal bilirubin levels rise after birth because of physiologic immaturity of glucuronyl transferase, which is exaggerated with each decreasing week of gestational age. Exclusively breastfed infants have higher serum bilirubin levels than formula-fed infants, possibly because of differences in fluid intake and bilirubin excretion and increased enterohepatic resorption of bilirubin. Some individuals may also have a genetic predisposition to higher bilirubin levels. Bilirubin is an antioxidant, and it has been hypothesized that moderate increases in bilirubin levels may be protective for the transition to extrauterine life.

In contrast, pathologic hyperbilirubinemia resulting from insufficient breastfeeding, sometimes referred to as breastfeeding jaundice, is better defined as suboptimal intake jaundice. In the United States and Canada, it is recommended that all neonates undergo bilirubin risk screening at least once before hospital discharge. The Academy of Breastfeeding Medicine and the AAP advise the use of Bhutani curves to assess risk and need for treatment of hyperbilirubinemia; clinical tools are available on mobile device applications. This approach has led to a decrease in severe pathologic hyperbilirubinemia; however, concerns for overtreatment and the potential harm of phototherapy have arisen recently. Using subthreshold bilirubin levels to initiate phototherapy as a mechanism to prevent readmission is not recommended because this approach increases length of stay and results in many infants receiving unnecessary treatment to reduce each case of readmission.

Breastfed infants with hyperbilirubinemia require assessment of milk production and transfer, feeding frequency, and neonatal weight loss. If there is pathologic hyperbilirubinemia, and infant intake at the breast is insufficient, exclusive breastfeeding should be continued while the infant receives phototherapy. Although supplementation with infant formula may decrease the bilirubin level and risk of readmission for phototherapy, it will also interfere with the establishment and continuation of breastfeeding. If intake at the breast is insufficient and supplementation is medically necessary, expressed maternal milk is preferred. Despite the current lack of data on its benefits in reducing hyperbilirubinemia in term infants, the use of PDHM to preserve exclusive human-milk feeding is increasing.

Phototherapy for neonatal jaundice and concerns about insufficient milk can be anxiety provoking for parents, even in a supportive environment, and can be disruptive to successful breastfeeding. Practices to minimize mother-infant separation, including providing phototherapy in the same room and maintaining safe skin-to-skin care with the infant’s mother, also promote exclusive breastfeeding.

**IMMUNE DEVELOPMENT AND THE MICROBIOME**

Early colostrum and exclusive breastfeeding establish an optimal and intact immune system. Unlike infant formula, human milk has a dynamic composition of both macro- and micronutrients that varies within a feed, diurnally, and over the course of lactation. Protective proteins abound in human milk, including lactoferrin, secretory immunoglobulin A, transforming growth factor-β, and α-lactalbumin. These factors promote development of the infant’s immune system. Additionally, lactoferrin has unique antibacterial properties important in the prevention of sepsis. Unique nonnutritive oligosaccharides that are specific to the mother-infant pair’s shared environment and exposures prevent binding of pathogenic bacteria and promote a healthy microbiome in the gut. Differences in immune cell distributions based on neonatal diet can be detected through 6 months of age, with natural killer cells most significantly affected.

During vaginal birth, the newborn’s intestine and mucosal surfaces are colonized with maternal microbes that act synergistically with bioactive factors in mother’s milk to establish a robust lymphoid follicle replete with a healthy balance of T helper cells. Surgical delivery is associated with aberrant colonization, which may lead to differences in the mother’s milk microbiome only partially restored by vaginal secretions. Formula supplementation may effect the most change in the newborn’s microbiome and immune development. These basic science
findings are supported by clinical studies.

Given the multiple mechanisms through which exclusive human milk impacts gut development, formula supplementation should always be avoided when the mother’s own milk is available. Although an exploratory study of early limited supplementation with extensively hydrolyzed formula followed by a return to exclusive breastfeeding did not reveal differences in the developing microbiome ($N = 15$), a longitudinal study among infants exclusively breastfeeding at 3 months ($N = 579$) revealed alterations in the microbiome among infants exposed to formula as neonates ($n = 179$). Just as antimicrobial stewardship requires appropriate use of antibiotics, supplementation stewardship requires judicious use of formula when medically indicated.

**SUPPLEMENTATION**

A systematic review of healthy, term, breastfed newborns revealed no benefit from routine supplementation with foods or fluids in the early postpartum period. These findings are consistent with consensus recommendations for exclusive breastfeeding for the first 6 months, followed by continued breastfeeding with the addition of complementary foods until at least 12 months of age. Early introduction of supplemental formula is associated with a greater than twofold increase in risk of early cessation of breastfeeding even when controlling for confounding variables. Among almost 1500 women in the Infant Feeding Practices Study II, only early exclusive breastfeeding remained significant for achieving intended breastfeeding duration (aOR 2.3; 95% CI 1.8 to 3.1) after adjustment for relevant hospital practices. This finding may be due in part to the supply and demand nature of milk production and the role of suckling, oxytocin release, and milk removal in establishing lactation.

If supplemental feeds are medically indicated, they should be accompanied by manual or mechanical milk expression, recognizing that direct breastfeeding usually provides more complete milk removal. In a pilot RCT ($N = 40$), early limited formula supplementation for infants with $\leq 5\%$ weight loss increased exclusive breastfeeding at 3 months post partum. In a subsequent larger study ($N = 164$), early limited supplementation did not affect overall breastfeeding at 1 or 6 months but slightly increased rates of formula use at 1 month (36.7% vs 22.4%; $P = .08$), decreased breastfeeding at 12 months (30% vs 48%; risk difference $-18\%$ [CI $-34\%$ to $-3\%$]), and shortened the time to breastfeeding cessation (hazard ratio 0.65; 95% CI 0.43 to 0.97).

Because evidence continues to accrue that supplementation in the first days after birth has major health risks, judicious use of supplementation is a critical goal, with a return to exclusivity whenever possible. If supplementation is indicated (Fig 1), options in order of preference are (1) expressed milk from the infant’s own mother, (2) PDHM, and (3) commercial infant formulas. The potential risks and benefits of these options should be considered in the context of the infant’s age, the volume required, and the impact on the establishment of breastfeeding.

Methods of supplemental feeding include spoon or cup feeds, supplemental nursing systems, syringe feeds, and paced bottle feeds. Methods should be tailored to staff training and family preferences. Among late-preterm newborns, there is evidence that some may be more susceptible to feeding problems when supplemented via a bottle; in an RCT in which the 2 methods were compared, cup feeding was associated with a longer duration of exclusive breastfeeding compared with bottle-feeding. Among term newborns, the manner in which supplementation is delivered, whether a bottle or alternative devices, has no apparent impact on continuation of breastfeeding. If the supplement is the mother’s own expressed milk, avoidance of bottles and nipples may preserve a longer duration of breastfeeding, especially among late-preterm newborns.

To ensure milk removal, which is key to establishing a milk supply, a mother should be assisted to express milk each time her infant is supplemented, even if the infant is also “practicing” at the breast. “Hands on” pumping, combining breast massage with pumping, has been shown to increase milk production in mothers of preterm infants who are hospitalized.

**HEALTH SYSTEM INTERVENTIONS: THE BABY-FRIENDLY HOSPITAL INITIATIVE**

Physiologic early infant feeding is facilitated by keeping mothers close to their infants, beginning with skin-to-skin care immediately after birth and continuing with 24-hour rooming-in and feeding on cue. These are core practices of the recently updated World Health Organization’s Ten Steps to Successful Breastfeeding of the Baby-Friendly Hospital Initiative (BFHI). Feeding on cue or “responsive feeding” is associated with more frequent breastfeeding throughout the day, more exclusive breastfeeding up to 6 months and beyond, and decreased likelihood of abnormal rapid weight gain in infancy.

Several major health organizations, including the US Preventive Services Task Force and the Agency for Healthcare Research and Quality, have generated systematic reviews and quality improvement (QI) reports.
that demonstrate the positive impact of the BFHI on breastfeeding outcomes.\textsuperscript{10,13,14} Implementation of maternity care practices aligned with any component of the BFHI is associated with improved in-hospital and postdischarge breastfeeding rates.\textsuperscript{11,13,126} Best Fed Beginnings increased exclusive breastfeeding initiation from 39\% to 61\% ($t = 9.72; P < .001$) at 89 hospitals over 2 years.\textsuperscript{127} The Community and Hospitals Advancing Maternity Care Practices initiative reported that the BFHI helped to reduce racial disparities in breastfeeding in southern US states.\textsuperscript{128}

Since the initial implementation of the BFHI, safety concerns have emerged, including case reports of inadvertent bed-sharing, suffocation, falls, and increased risk of neonatal jaundice.\textsuperscript{3,129} In this context, the World Health Organization conducted an extensive evidence-based review.\textsuperscript{7,130} Key differences in the revised Ten Steps include highlighting the Code of Marketing of Breastmilk Substitutes, the need to collect ongoing data, a focus on safety and surveillance (especially as it relates to skin-to-skin care and rooming-in), and acknowledgment that there is insufficient evidence to limit pacifiers and other artificial nipples.

Step 10 of the BFHI requires a direct connection between the delivery hospital and the community for ongoing support. Referral for outpatient support as well as provision of contact information for those who can manage breastfeeding problems is paramount.

**LIMITATIONS AND IMPLICATIONS FOR FUTURE RESEARCH**

Given the importance of exclusive breastfeeding for maternal and child health, both intent and initiation are increasing. However, maternal conditions linked with delayed lactogenesis, such as advanced maternal age, obesity, and fertility treatment, are increasingly common. Priority research areas to help families meet their breastfeeding goals include accurate identification of women with risk factors for delay or absence of lactogenesis, more sensitive methods of identifying at-risk newborns, and exploration of the implications of early limited formula supplementation on infant outcomes such as ontogeny of the immune system and the microbiome, maternal self-efficacy, and continued breastfeeding.

**CONCLUSIONS**

Health care professionals’ support is critical for families to meet their infant feeding goals and achieve optimal health outcomes. All physicians who care for new mothers and infants need skills to evaluate early breastfeeding, perform maternal and infant risk stratification, understand the range of potential interventions in the context of the risk/benefit ratio of supplementation, and ensure appropriate follow-up.

Most mothers can produce adequate colostrum and mature milk, and most newborns are able to breastfeed exclusively. Nevertheless, conditions that require medical supplementation are common and important to recognize. The decision to supplement with infant formula requires thoughtful analysis of the risks and benefits, with consideration of the family’s informed choice. Early-term and late-preterm newborns are at a higher risk of complications. Therefore, more careful monitoring, detailed assessments, and case-based interventions are warranted. Further research is needed to identify the best methods to support exclusive breastfeeding in high-risk populations.

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**ABBREVIATIONS**

AAP: American Academy of Pediatrics  
aOR: adjusted odds ratio  
BFHI: Baby-Friendly Hospital Initiative  
CI: confidence interval  
HD: hypernatremic dehydration  
NEWT: Newborn Early Weight Tool  
PDHM: pasteurized donor human milk  
PPV: positive predictive value  
QI: quality improvement  
RCT: randomized controlled trial

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