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Nutritional policies for late preterm and early term infants - can we do better?

Mariana Muelbert, **Jane E. Harding**, and **Frank H. Bloomfield***

Liggins Institute, University of Auckland, Auckland, New Zealand

SUMMARY

Late preterm (LP) and early term (ET) infants can be considered the “great dissemblers”: they resemble healthy full-term infants in appearance, but their immaturity places them at increased risk of poor short- and long-term outcomes. Nutritional requirements are greater than for full-term babies, but there are few good data on the nutritional requirements for LP and ET babies, leading to substantial variation in practice. Recent data indicate that rapid growth may be beneficial for neurocognitive function but not for body composition and later metabolic health. Breastfeeding the LP or ET infant can be challenging, and mothers of these infants may need additional support to breastfeed successfully. Future research should investigate nutritional requirements of LP and ET infants for optimal growth, addressing both short- and long-term outcomes and the potential trade-off between neurocognitive and metabolic benefits.

Keywords

Late preterm; Early term; Nutrition; Infant growth; Breastfeeding

1. Trends in late preterm and early term birth

Late preterm (LP) and early term (ET) are defined as births at 34^{+0} to 36^{+6} and at 37^{+0} to 38^{+6} weeks gestation, respectively [1]. Whereas the definition of preterm birth as birth before 37 weeks gestation is widely accepted [2], the definition of term birth as birth between 37 and 42 completed weeks gestation has been questioned given that maternal, neonatal and childhood outcomes vary considerably across this range. Recent recommendations are that births between 37^{+0} and 38^{+6} be designated “early term,” births between 39^{+0} and 40^{+6} as “full term” and births after 41^{+0} as “late term” births [3]. These definitions take into account the continuum of fetal maturation and that infant mortality rates and adverse health outcomes are lowest for births occurring at full term [4].

*Corresponding author. Address: Liggins Institute, The University of Auckland, Private Bag 92019, Auckland 1142, New Zealand. Tel.: +64 9 923 6107 ext 86107. f.bloomfield@auckland.ac.nz (F.H. Bloomfield).

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LP birth accounts for ~75% of all preterm births [5]. In the USA, there has been an estimated 25% increase in late preterm births between 1990 and 2006 [1]; by 2016, LP births accounted for 7%, and ETB 25%, of all live births, equating to more than 275,000 and one million babies, respectively [6]. Similar trends have been observed in Australia, where between 2001 and 2009 planned births (labour induction or pre-labour caesarean delivery) have increased by 40% at <37 weeks gestation and by 52.5% at 38 weeks gestation [7].

Many factors have contributed to the increasing incidence of LP and ET birth, including increasing use of assisted reproductive technologies, higher rates of multiple births, and increasing use of obstetric interventions [7].

2. Outcomes following LP and ET birth

Although LP and ET babies are apparently “well” when compared to more preterm babies, they can be thought of as “the great dissemblers:” they often look like full-term babies and so are treated as such, although in fact they have a degree of immaturity that places them at higher risk of many clinical problems, and these outcomes are inversely correlated with gestational age [1,8–10]. Compared to term-born peers, LP and ET infants are at increased risk for requiring special education (adjusted odds ratio (aOR); 95% confidence interval (CI): 1.16; 1.12–1.20; and 1.53; 1.43–1.63, respectively) [10] and LP have twice the risk for neurodevelopmental disability (relative risk (RR): 2.19; 95% CI: 1.27–3.75) [11].

LP infants also are more likely to be obese by 3–5 years of age [12] and, as young adults, are more likely to require prescriptions for hypertension and diabetes [13,14], translating into increased risk of mortality from cardiovascular and endocrine disorders in those both LP and ET [15,16].

Faster growth following LP birth is associated with better childhood [17] and adult neurocognitive functioning [18]; intriguingly, however, there may be a trade-off with greater risk of childhood overweight/obesity [17]. These data suggest that nutrition and growth may be just as important for the LP and ET baby as for the extremely preterm baby.

3. Challenges for nutrition of LP and ET babies

Providing adequate nutritional support for LP and ET infants presents challenges different from those for the extremely preterm baby. First, location of care in a newborn nursery or postnatal ward varies [19,20], and may impact upon practice and outcome. In the Late And Moderately preterm Birth Study (LAMBS) in the UK, 35% of LP infants received all or part of their neonatal care in a neonatal intensive care unit (NICU) [5]. Of those receiving care in a postnatal ward, almost 84% required a non-routine review, 60% of which were due to unexpected concerns. Of LP neonates admitted to the postnatal ward in the UK, 10% required hospital re-admission from home, suggesting that some of the complications seen in LP and ET infants may not be identified during the short period of admission to postnatal wards [19].

Further, there are significant variations in management of moderate and LP infants, mostly related to respiratory support, fluids, and nutrition [5,20]. A survey of clinicians in Australia

and New Zealand found wide variation in approach to the initial nutritional support of LP babies while waiting for mother's own milk (MOM) to meet the baby's needs [21]. In an hypothetical scenario of an LP neonate born with appropriate weight-for-gestational-age, 53% of respondents, while waiting for sufficient MOM to meet the infant's needs, would initiate nutritional support with 10% dextrose, with most of the remainder commencing infant formula. Of those providing 10% dextrose, almost 50% would continue 10% dextrose as the only additional nutritional support for three or more days while waiting for MOM [21]. This variation in practice may reflect the lack of high-quality evidence around optimal nutrition support in the LP population and the long-term outcomes of common complications of LP and ET birth, such as neonatal hypoglycaemia.

4. Hypoglycaemia

Hypoglycaemia, or its perceived risk, is one of the commonest reasons for additional nutritional support in LP infants. At birth, the constant supply of glucose from the maternal circulation ceases abruptly. The fall in blood glucose concentration triggers a reduction in insulin secretion and increased secretion of counter-regulatory hormones such as glucagon, catecholamines, and cortisol, which initiate the endogenous synthesis of glucose from glycogenolysis and gluconeogenesis. This physiological sequence is a normal and transitional adaptation to postnatal life, and blood glucose concentration usually stabilises by 72 h of life, rising steadily to a normal range of >3.9 mmol/L [22]. Disruption of this pathway leads to hypoglycaemia [23].

Transitional neonatal hypoglycaemia is influenced by many factors such as birth weight, gestational age, body stores, presence of metabolic conditions and maternal health during gestation [24]. It is pertinent to note that 50% of hepatic glycogen stores, a key source of glucose in the immediate newborn period, are deposited between 36 and 40 weeks gestation.

The overall incidence of hypoglycaemia (defined as <2.5 mmol/L) in a population- based cohort was 19% [25]. However, among LP infants and ET infants at risk of developing hypoglycaemia (e.g. because of maternal gestational diabetes), 50% developed blood glucose concentrations <2.6°mmol/L in the first 48 h after birth [26]. Infants who are exclusively breastfed tend to have lower blood glucose concentrations during the first days after birth compared with infants fed formula [27].

It is important to note that there is a lack of consensus on the definition and management of hypoglycaemia, again reflecting the limited evidence available to determine the safest approach [23,24]. The American Academy of Pediatrics (AAP) suggests blood glucose thresholds for treatment of asymptomatic hypoglycaemia in infants at risk, including LP infants, of <1.4 mmol/L in the first 4 h after birth, <1.9 mmol/L from 4 to 24 h after birth, and a threshold of <2.2 mmol/L for symptomatic infants, with a target blood glucose concentration of > 2.5 mmol/L for all infants requiring treatment [28]. The British Association of Perinatal Medicine recommend blood glucose thresholds for treatment of asymptomatic term infants of <1.0 mmol/L, or two measurements <2.0 mmol/L, or <2.5 mmol/L in symptomatic infants [29]. By contrast, the World Health Organization recommends maintaining blood glucose concentrations >2.6 mmol/L in all asymptomatic

infants, while the US Pediatric Endocrine Society recommends >2.8 mmol/L in the first 48 h after birth and >3.3 mmol/L thereafter [30,31]. Differences in thresholds for diagnosis and treatment will markedly affect the reported incidence of neonatal hypoglycaemia, potentially under- or over-estimating the risk in a population [23], and there is no evidence about whether thresholds or treatments should be different for LP and ET infants from those for full-term infants.

The first line of treatment for hypoglycaemia is usually feeding, preferably with breast milk. Breast milk produced in the first days after birth has a lower carbohydrate content than formula. However, there is also some evidence that breastfeeding may have a more sustained effect on blood glucose concentrations in hypoglycaemic babies than formula feeding [23]. A randomised controlled trial (RCT) has shown that treatment of hypoglycaemia in LP and ET infants with oral dextrose gel is effective in restoring blood glucose concentrations, reducing separation of mother and baby for treatment of hypoglycaemia (RR: 0.54; 0.31–0.93) and reducing the likelihood of formula feeding at 2 weeks of age (RR: 0.34; 0.13–0.90) when compared to treatment with placebo [26]. Thus, dextrose gel and breastfeeding are preferable to formula feeding and provide a safe and non-invasive treatment for hypoglycaemia. If hypoglycaemia is profound or recurrent, then admission to a neonatal unit and provision of intravenous glucose may be required.

Based upon use of dextrose gel for treatment of hypoglycaemia, attention has turned to the potential for use of dextrose gel for preventing neonatal hypoglycaemia in babies at risk, including LP babies. An initial dosage RCT has reported that this approach is promising, with any dose of prophylactic oral dextrose gel reducing the risk of neonatal hypoglycaemia compared with placebo (RR: 0.76; 0.62–0.94) [32]. A larger trial is now in progress to assess effects on NICU admission [33].

5. Hypernatraemia

Neonatal dehydration leading to hypernatraemia can affect healthy term neonates but is more common in preterm infants due to their higher water content, lower fat tissue stores and a more permeable skin. Hypernatraemia is mainly associated with excessive weight loss (>10% of birth weight) and feeding difficulties [34] and is estimated to occur in two to 58 cases per 100,000 live births each year [34]. It is often asymptomatic; however, apnoea, bradycardia, lethargy or irritability and convulsions can occur, resulting in permanent injury. Management involves rehydration therapy, either enterally with provision of breast milk if available or infant formula, or, in some cases, intravenous infusion of fluids [34]. Prevention centres around monitoring of postnatal weight loss and of breastfeeding efficacy [34].

6. Hyperbilirubinaemia

Exclusively breast-fed infants have higher concentrations of total serum bilirubin (TSB) than formula-fed infants, even when consuming adequate volumes of breast milk [35]. Substances in breast milk - including steroids, fatty acids, cytokines, β-glucuronidase and the epidermal growth factor - result in elevated TSB through increased enterohepatic reabsorption of bilirubin, decreased bilirubin excretion, or through inhibition of uridine

diphosphate glucuronosyltransferase 1A1 [36], the sole enzyme responsible for the glucuronidation of bilirubin. This can lead to breast-milk jaundice, which is two to four times more common in LP than in term babies because of hepatic immaturity and feeding difficulties [37]. Poor milk intake can also result in dehydration leading to late onset neonatal jaundice, also referred to as inadequate breastfeeding jaundice [35]. Promotion and support of successful breastfeeding is a key element for prevention of severe neonatal jaundice [35].

7. Energy and nutrient requirements of LP and ET babies

Nutritional support in LP and ET babies needs to be sufficient to avoid short-term complications of inadequate nutrition, adequate to support optimal brain development, yet not promoting excessive growth that may predispose the infant to increased adiposity even by term-equivalent age [38].

Nutritional support for preterm infants often is targeted at supporting growth equivalent to intrauterine growth trajectories. However, there is inevitable weight loss after birth due to loss of extracellular fluid, and growth charts derived from cross-sectional data from infants born at different gestational ages are unlikely to represent optimal postnatal growth of preterm infants. Furthermore, preterm neonates are, as a population, relatively growth-restricted compared with their gestational-age matched in-utero peers who go on to be born at term [39]. Longitudinal preterm growth charts recently have been published, but the sample size is small [40].

Most nutrition guidelines provide recommendations for more preterm (<32 weeks) or very low birth weight neonates (<1500 g) but few provide nutritional recommendations for LP and ET babies [41]. The increased numbers of LP and ET births suggests that new research should focus on best nutrition practices among this growing population.

Guidelines from the European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) recommend that total energy intake for preterm infants should be 110–135 kcal/kg/d [42], regardless of gestational age. This recommendation takes into account that resting energy expenditure does not vary with gestational age and is ~45 kcal/kg/d; that requirements for new tissues are ~4.5–4.9 kcal/kg and for fat and protein deposition are 1.55–1.6 and 5.5–7.75 kcal/g, respectively; and that an optimal intrauterine weight gain of 17 g/kg/d will require 76–83 kcal/kg/d of energy intake for preterm babies [42]. However, more recent guidelines based upon fetal growth, fetal accretion rates and intestinal absorption estimate that, for LP and ET babies, fetal growth should be between 13 and 11 g/kg/d respectively; energy intake 127 and 115 kcal/kg/d and protein intake 3.1 and 2.5 g/kg/d respectively [41].

These lower recommendations for LP babies are consistent with the findings of an RCT in five European countries which compared different protein concentrations in term infant formula [43]. Term babies were randomised to receive either low protein formula (1.25 and 2.05 g/100 mL in initial and follow-on formula, respectively) or high protein formula (1.6 and 3.2 g/100 mL in initial and follow-on formula, respectively) during the first year.

Breastfed children served as reference group. Babies randomised to higher protein content formula had higher weight at the age of two years [43], increased risk for excessive body fat in the second year that lasted until school age [44], and a greater than two-fold increased risk of obesity by 6 years of age (OR: 2.43; 95% CI: 1.12–5.27) compared to the low protein content group [45]. These findings suggest that excessive protein intake in early life can cause increased adiposity in childhood among term-born children and raise the question of whether this also may explain the increased body fat at term-corrected age in LP infants [38], although it must be emphasised that, to date, there are only observational data in LP babies.

Breast milk may not provide sufficient micronutrients and vitamins for LP infants. The AAP recommends multivitamin and iron supplements for all preterm infants until receiving a diverse complementary diet [46]. Additional phosphate and calcium also may be required [41]. Breast-milk fortifiers can be added to breast milk to provide adequate intake of minerals but are recommended for use only in very low birth weight or very preterm babies with the AAP recommending that fortification of breast milk is only required for babies with birth weights <1500 g [46].

8. Breastfeeding in LP and ET babies

The Academy of Breastfeeding Medicine suggests that to support breastfeeding of LP infants, there should be early initiation of breastfeeding (within the first hour where possible) and, should mothers and babies be separated, stimulation of milk production through regular expressing and frequent skin-to-skin contact or ‘kangaroo cuddles’ [47]. This approach also improves mother-infant bonding, exclusive breastfeeding rates, and it reduces costs of care [47]. Breastfeeding LP infants successfully can be challenging as they are less alert, have poorer coordination of sucking-swallowing-breathing reflexes and have delayed maturation of the autonomic system that can predispose to cardiorespiratory instability [48]. Expressed breast milk may need to be given by gavage, cup, bottle, syringes, or finger-feeding [47]. Cup feeding may improve breastfeeding rates up to six months among LP babies when compared to bottle-feeding, but compliance is problematic as it may increase feeding time [47] and require greater attention to possible adverse effects (choking, vomiting) that may be concerning for parents. Retrospective cohort data from the Pregnancy Risk Assessment Monitoring System (PRAMS) in the USA found that LP babies are less likely to be initially breastfed and to be breastfed for 10 weeks or longer compared with full-term infants [49]. Other data suggest that this also is true for ET infants in the USA, who are significantly less likely than full-term infants to be breastfed one month postpartum (OR: 0.77; 95% CI: 0.600.99) [50]. These data suggest that improved evidence on how best to support successful breastfeeding in LP and ET babies is needed.

9. Breastfeeding support for mothers of LP and ET babies

Mothers who birth preterm are more likely to experience factors that may impact upon lactation, including separation from their infant, medical conditions that may have contributed to the early birth such as diabetes and pre-eclampsia, multiple births, and birth via caesarean section [47]. Various breastfeeding assessment tools are available, although

few have undergone adequate assessment and testing, with the Early Feeding Skills Assessment and the Bristol Breastfeeding Assessment Tool probably the most robust [51]; “lactation technology,” such as nipple shields and hospital-grade breast pumps, may also facilitate breastfeeding LP and ET babies [47].

10. Transition from enteral nutrition via tube feeds to oral feeds

For many LP babies, a brief requirement for gastric tube feeding is not uncommon. A retrospective review of 647 moderate- to late-preterm infants in six New Zealand NICUs between 2005 and 2011 reported that gestational age, birth weight, days of parenteral nutrition support, and clinical condition were significantly associated with time to start oral feeds and time required to attain full oral feeding [52]. In this study, on average LP infants had their first oral feed attempt in the first two days after birth, reaching full oral feeds by the eighth day. Local practice impacted upon timing and the authors suggested that the lack of specialised services to support feeding may have contributed to differences in transition time [52].

11. Role of smell and taste stimulation

Late preterm and ET infants receiving tube-feeds may miss out on exposure to olfactory and flavour stimulation because tube feeds bypass the nasal and oral cavities where these sensory perceptions mostly occur [53]. Smell and taste of food initiate a sequence of pre-absorptive physiological responses that are triggered by the brain, preparing the body to digest, absorb and metabolise food before food is ingested. Evidence from a pilot randomised trial in very preterm babies (<29 weeks gestation) indicated that exposure to taste and smell of milk before each feed may reduce time to full enteral feeds and improve weight gain, but sample size was small [54]. An ongoing RCT is investigating the role of smell and taste prior to tube feedings on time to full sucking feeds and body composition [55]. Results should shed light on whether this simple intervention to support early nutrition of LP babies is of benefit.

12. Breast-milk substitutes

When MOM is not available, the WHO recommends donor human milk (DHM) as the preferred alternative [56]. There are few data on the benefits of DHM in LP and ET infants, although in more preterm infants DHM has been associated with a positive impact on any breastfeeding on discharge [57] and a lower incidence of necrotising enterocolitis when compared to formula feeding [58]. However, growth is recognised to be slower in DHM-fed infants, and most recommendations are that DHM should be fortified to provide adequate nutrition [58]. MOM remains preferable to DHM and effort should be focused on supporting lactation and breastfeeding in mothers, where this is possible [59].

When neither MOM nor DHM are available, then a variety of artificial formulas are available with differences in energy, protein, and mineral content intended to mimic the nutritional content of human milk. Standard term formulas typically provide 68 kcal/100 mL of energy and 1.4—1.7 g/100 mL of protein in addition to calcium and phosphate, whereas preterm formulas are energy- and protein-enriched to provide typically 80 kcal/100 mL of

energy and 2.0–2.4 g/100 mL of protein. In term infants, this protein content results in greater infant weight gain and fat mass from 2 to 6 years of life [43,45]; whether this may also be the case in LP infants is not known.

The fat components of infant formulas are also different from those in human milk. Lipids in human milk are essentially milk fat globules of triglycerides enveloped by a three- layer emulsifier membrane (phospholipids, proteins and cholesterol), whereas infant formulas have lipids with different molecule size and emulsifier membrane architecture. Palmitate in infant formula is low in the sn-2 stereoisomer compared with breast milk, which is high in this isomer. Novel infant formulas addressing fat structure [60] and the proportion of sn-2 palmitate [61] suggest that current infant formulas can be improved substantially, resulting in better tolerance, stool composition and, potentially, other outcomes such as bone health. Future research should address the effect of formulas that reflect more closely the composition of human milk on later growth, body composition, and neurodevelopment in LP and ET formula-fed infants.

13. Post-discharge formulas

For formula-fed infants, nutrient-enriched post-discharge (or “follow-on”) formulas are available which have higher energy density, increased protein concentrations and greater mineral and vitamin content compared with standard term formula. The evidence for the benefit from post-discharge formula in preterm babies is of moderate quality and inconsistent, and currently is insufficient to support their routine use [62,63], although there may be benefit for infants who have been identified as growing poorly on standard formula or who have ongoing mineral or vitamin deficiencies. However, there are no data to support their use in LP or ET infants.

14. Parenteral nutrition

Parenteral nutrition (PN) is usually considered when provision of nutrients via the enteral route is clinically contraindicated or will result in nutrient insufficiency. The composition of PN varies from intravenous infusion of carbohydrates (mostly dextrose) alone, combinations of dextrose and amino acids in addition to minerals and vitamins, and separate infusion of lipids. There is little evidence regarding whether PN is more beneficial than 10% dextrose in LP infants while waiting for maternal milk supply to meet demand and for full enteral feeds to be tolerated [64] but its use in LP infants appears to be rare [21]. Each day of parenteral support in LP infants has been reported to predict an increase in time to achieve full oral feeds of 2 h (hazard ratio: 0.92; 95% CI: 0.89–0.95) [52]. Although it has been reported that 27% of LP infants require intravenous infusions compared to 5% of term babies [65], very few LP and ET babies will receive parenteral nutrition support, with this usually reserved for babies with congenital malformations predicted to lead to delays in reaching full enteral feeds.

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Practice points

- The incidence of LP and ET birth has increased significantly in recent years, mostly due to increased obstetric intervention.
- LP and ET infants are at increased risk of developing short-term and long-term adverse outcomes.
- There is significant variation in nutrition support for the LP and ET infant.
- Nutrition of the LP/ET infant may be related to both short- and long-term outcomes.
- Maternal breast milk remains the optimal feed for LP and ET infants.
- Breastfeeding the LP/ET baby can be challenging, and increased support is needed.

Research directions

- Optimal nutritional support for LP and ET infants to support neurodevelopment and healthy body composition should be investigated in well-designed RCTs with appropriate sample sizes.
- The potential effect of smell and taste stimulation for tube-fed infants on time to full oral feeds, body composition, and breastfeeding rates should be assessed by RCTs.
- More detailed information on the composition of breast milk in mothers of LP and ET infants may improve understanding of the nutrient requirements of these babies.
- Further research into the potential benefits of novel infant formulas for those LP and ET infants for whom breast milk is unavailable should focus on longer-term outcomes such as development and body composition.