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Nutrition in late preterm infants

Sharin Asadi, Frank H. Bloomfield, and Jane E Harding [*]

Liggins Institute, University of Auckland, Auckland, New Zealand

A R T I C L E I N F O

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A B S T R A C T

Late preterm infants comprise the majority of preterm infants, yet there are few data to support best nutritional practice for these infants. Breastmilk is considered the best choice of enteral feeding for late preterm infants. However, supplementation of breastmilk may be indicated to promote optimal growth. Preterm formulas can be used for supplementation of breastmilk or as a breastmilk substitute but there is little evidence for their use in the late preterm infant. Feeding difficulties are common and some infants require intravenous nutritional support soon after birth. Others require tube feeding until full sucking feeds are established. Future research should focus on whether nutritional support of late preterm babies pending exclusive breastfeeding influences growth, body composition and long-term outcomes of late preterm infants and, if so, how nutritional interventions can optimise these outcomes.

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Introduction

Late preterm infants are defined as infants born between 34 completed weeks and 36 weeks and 6 days of gestation.[1] The rate of late preterm birth rose 20% from 1990 to 2006 in the United States[2] and, in 2002, 74% of singleton preterm births in the United States were late preterm births.[3] Although these infants may be born at a similar size to term infants, they are less mature and experience increased mortality and morbidity.[1]

Feeding difficulties in late preterm infants

In late preterm infants, poor feeding is one of the main reasons for inadequate weight gain after birth. Immaturity of the gastrointestinal tract,[1] feeding difficulties due to immaturity of sucking movements, low breastmilk supply,[4] and lack of hepatic glycogen stores[5] all contribute to difficulty in meeting the nutritional requirements of the late preterm infant, especially in the first few days after birth.

The generally accepted goal of postnatal nutrition of all preterm infants is to achieve a growth rate similar to intrauterine growth at the same gestational age[6] and to reach developmental outcomes similar to infants born at term.[7] However, there are few data on which to base recommendations for nutrition of late preterm infants to achieve these goals.

What to feed

Breastmilk

Mother's breastmilk is the best choice for enteral feeding but when it is unavailable donor milk is often used. In situations where neither is available, formula can be used.[8] The advantages of using breastmilk include: stimulating the release of endocrine and metabolic regulatory factors such as gastrin, enteroglucagon, motilin, neurotensin, gastro-inhibiting

* Corresponding author at: Liggins Institute, University of Auckland, Private Bag 92019, Auckland 1142, New Zealand.
E-mail address: j.harding@auckland.ac.nz (J.E. Harding).

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peptide, and pancreatic polypeptide in the infant; stimulating the growth of Bifidobacteriae and Lactobacilli in the gut; supplying essential fatty acids which are important in retinal and neurologic development; lowering the risk of sepsis and necrotising enterocolitis; improving feeding tolerance; and faster achievement of full enteral feeding.[9,10]

Late preterm infants may face many challenges to receiving adequate breastmilk. Their poor feeding skills coupled with their sleepiness which limits their feeding opportunities may lead to inadequate nutrition.[11] Late preterm infants commonly have a weak suck and early fatigue in sucking, so the mother may receive false signals of early satiety when intake is in fact inadequate.[11] Moreover, the risk of delayed breastmilk production is higher among mothers of late preterm infants, compared to mothers of term infants.[11] To assist with breastfeeding, skin-to-skin contact by placing the infant on mother's chest is helpful, since mothers who experience skin-to-skin contact are more likely to breastfeed their infants and the breastfeeding duration is longer among their infants.[12] Mothers should be encouraged to express milk after each breastfeeding attempt and/or 8−10 times per day for the first two weeks or until the infant has acheieved full breastfeeding.[11]

Breastmilk supplements

Supplementation of mother's breastmilk may be indicated in infants with excessive weight loss, low metabolic reserve, poor feeding, or significant jaundice as a result of low intake.[13] The best supplement is the mother's own breastmilk which has been previously expressed, but when mother's own milk is not available, donor milk or formula are alternative choices. As the nutritional requirements of some preterm infants cannot be met solely with breastmilk, using human milk fortifier may increase growth in breastfed late preterm infants.[13] The best time for receiving the supplement is during breastfeeding.This may not be possible for mothers who feed their infants directly from the breast. However, they may choose to express their breastmilk and give some fortified milk to their infant via cup or tube.[13] Moreover, fortification is also important in infants given donor breastmilk, which contains lower amount of nutrients than mothers' own milk.[14] Some authors consider that fortification is not required in healthy late preterm infants who are more than 1800 g, as they may be able to achieve sufficient protein and calorie intake by consulming a greater volume of milk.[13]

Some authors recommend the initiation of fortification for all preterm infants who weigh <1800 g.[15] Fortifiers can be in liquid or powder form, can be based on human milk or cow's milk, and can include hydrolysed or intact proteins (whey and casein). Most commercially available fortifiers contain different amounts of protein, carbohydrates, calcium, phosphate, vitamins and minerals.[16] A Cochrane review in 2016 concluded that multi-nutrient fortification can increase the growth rate of preterm infants during their hospital stay.[17]

There are two methods for fortification: standard fortification and individualised fortification. The standard method is the addition of fortifier according to the manufacturer's instructions based on assumptions about human milk composition. As macronutrients content, particularly protein, of milk differs between mothers and even between different expression sessions within the same mother, this standardised approach may not be optimal for reaching each infant's nutritional targets. Individualised fortification methods are an alternative to overcome this problem. Targeted fortification and adjustable fortification are two methods of individualised fortification. Targeted fortification involves periodic analysis of the macronutrient content of the milk (e.g. twice per week[18]) and adding fortifiers to reach the target amounts of nutrients for each infant. However, there are no clear data on the relationship between day-to-day variation of macronutrients as a result of measurement frequencies and preterm infants' growth and neurodevelopment.[18] On the other hand, adjustable fortification is based on periodic measurement of an infant's blood urea nitrogen and adjusting protein intake according to the infant's metabolic response.[16,19] The effectiveness of targeted and standard fortification has been compared in a clinical trial in preterm infants born less than 30 weeks of gestation.[20] There was no significant difference between the two groups in weight gain velocity and fat mass percentage. In addition, targeted fortification is labour intensive and time-consuming. As a result, targeted fortification is not superior to standard fortification.[20] One compromise approach is to use the standard method for human milk fortification and then move to individualised fortification if the infant's growth is insufficient.[15] In this approach, individualised fortification can be done either as target fortification or adjustable fortification, depending on the facilities and staff experience.[15]

Formula

The risk of having insufficient milk supply due to delayed production is higher among mothers of late preterm infants, compared to mothers of term infants.[11] Although breastmilk is considered the best choice of feeding in preterm infants, in situations when neither breastmilk nor donor milk are available, formula can be used.[8] In preterm and low birth weight infants, use of formula, either in the form of sole diet or as a supplement to maternal breastmilk results in increased rate of weight gain, linear growth and head growth. However, the risk of developing necrotising enterocolitis is also increased.[21] There is no evidence of effects on overall mortality or long-term growth and neurodevelopment, but data are limited for these outcomes.[21]

Due to different nutritional needs of preterm infants, specific preterm formulas are available that contain more energy and protein than term formulas, and the content of minerals and vitamins are also greater.[22] In preterm formulas, whey compromises the majority of protein complexes and medium chain fatty acids account for approximately 40% of the fat content.[23] Some authors recommended using preterm formula for all preterm infants until they reach term corrected age.[24] For volume intolerant infants, more energy dense formulas are also available that have more energy in the same amount of fluid.[22]

Parenteral nutrition

When all the nutritional requirements of late preterm infants cannot be met through enteral feeding, particularly if feed intolerance is prolonged or enteral feeding must be withheld for any reason, parenteral feeding can be helpful.[25] Parenteral nutrition initiation and advancement should proceed as quickly as tolerated.[26] However, parenteral nutrition can also allow for slow initiation and slow advancement of enteral nutrition in infants who have poor tolerance of enteral feeding.[9,27]

Parenteral nutrition is made of an aqueous solution that contains glucose, lipid emulsions, amino acids, electrolytes, minerals and vitamins. It can be used as an individualised or standardised prescription. The individualised prescription is based on each infant's nutritional requirements, whereas the standardised prescription uses fixed amounts of nutrients. There are also concentrated standardised parenteral nutrition preparations which offer the same amount of nutrients in a lower volume, which are helpful when fluid restriction is needed.[9]

Recommendations regarding energy intake are based on both growth and basal energy expenditure. The European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) recommends energy intake of 110–135 kcal/kg/day for a healthy growing infant.[7] To reach a normal growth rate, adequate protein intake is also required. However, there is a lack of data on optimal protein intake for all preterm infants,[7] and the amount of protein required decreases as gestational age increases. The recommended amount is 2.5–3.5 g/kg/day in infants between 32–37 weeks of gestation and 1.5–2.0 g/kg/day for term infants.[27] For all preterm infants, some authors recommend an initial protein intake of at least 2.0–2.5 g/kg/day and a gradual increase of this amount,[28] while others recommend an initial dose of 1–3 g/kg/day and advancement to meet needs, without the gradual increase.[29] For late preterm infants, it has been recommended that amino acid infusion is started on the first day at 2.5–3.0 g/kg/day,[27] although both policy and practice vary widely between neonatal units.[28]

Lipids are an important source of energy and essential fatty acids. For preterm infants receiving parenteral nutrition, most authors recommend the initiation of intravenous lipids in the first 2 days,[28] starting at 2–3 g/kg/day with slow advancement to 3.0–3.5 g/kg/day over 2–3 days.[27]

As glucose can be directly utilised by the brain, it is the most important component of parenteral nutrition for meeting energy requirements. Some authors recommend starting glucose infusions for all preterm infants at a rate of 4–6 mg/kg/min and increasing gradually to 12–15 mg/kg/min as the best method for prevention of hyperglycaemia.[30,28] Moreover, the preterm infant needs both fat soluble and water soluble vitamins. As soon as the parenteral nutrition has started, water-soluble vitamins should be added. Fat-soluble vitamins should be administered as soon as lipid is added to the parenteral nutrition.[31]

Post-discharge nutrition

The ESPGHAN recommendation for post-discharge nutrition in preterm infants is that infants with an appropriate weight for postconceptional age should be breastfed, and infants with a subnormal weight for postconceptional age should receive supplemented breastmilk.[7] If infants are formula-fed, those with an appropriate weight-for-age should receive standard formula which provides adequate long-chain polyunsaturated fatty acids, while infants with subnormal weight should receive post-discharge formula with higher content of protein, minerals and long-chain polyunsaturated fatty acids until 40 weeks and up to as long as 52 weeks' postconceptional age. However, in order to prevent overfeeding or underfeeding, all infants should have their growth monitored regularly.[32] Growth monitoring should be based on regular measurements of length, weight and head circumference.[32]

A Cochrane review on the effect of nutrient-enriched formula versus standard formula for preterm infants following hospital discharge found inconsistent evidence of effects on growth of preterm infants up to 18 months post-term.[33] However, all of the included studies recruited smaller preterm infants (<1800 g), and there are no specific data to inform appropriate post-discharge feeding of late preterm infants.

ESPGHAN recommend that iron supplementation of 2–3 mg/kg/day should start at 2–6 weeks of age in preterm infants and should continue until 6–12 months of age, depending on the infant's diet.[7] Iron can be provided as medicinal iron or through iron-fortified complementary food. However, both standard preterm infant formulas and standard term infant formulas can provide enough iron.[34] As a result, supplementation is only required until the infant is receiving iron-fortified formula or begins eating complementary food containing sufficient iron.[35]

A systematic review on definition, diagnosis, treatment and prevention of nutritional rickets in children recommended that all infants from birth to 12 months of age should receive 400 IU/day of vitamin D supplements, independent of their mode of feeding.[36]

How to feed

Tube placement

Enteral feeding delivery can be through gastric or trans-pyloric routes. When possible, gastric routes should be preferred, as they are more similar to the physiological routes and easier to apply. However, the trans-pyloric route is useful for situations related to gastric emptying problems, such as gastric outlet obstruction.[37] Another important factor in site selection is the duration of time that the feeding will be needed. For short-term access, nasoenteric or nasogastric tubes are recommended. However, it is not recommended to use them for more than 3 months.[37]

Continuous vs bolus

Enteral feeding can be provided as either continuous or bolus feeding. Bolus feeding has some drawbacks, as it has been shown to result in increased pulmonary resistance[38] and fluctuations in cerebral blood flow.[39] On the other hand, bolus feeding is more similar to physiological feeding in term infants, inducing the same hormone surges, such as secretion of gastrin, gastric inhibitory peptide, and entroglucagon, that can help in gastrointestinal tract maturation and protein accretion.[40,41] The cyclic hormone release of the gastrointestinal tract will be altered by continuous feeding.[42] Another

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downside of continuous feeding is the loss of nutrients such as fat and calcium, due to adherence to the tube delivery system.[43] However, continuous feeding is cheaper than intermittent feeding, and results in fewer prescription errors[44] and better glycaemic stability.[42] The results of studies which compare these two methods are conflicting, but some authors recommend the use of continuous feeding for infants weighing <1250 g and infants who are haemodynamically unstable. In stable infants intermittent feeding may be more appropriate.[45] There is no study on the effect of continuous or intermittent feeding in late preterm infants.

Transition to sucking feeds

Although it is generally assumed that once a preterm infant reaches term-equivalent age their nutritive feeding skills will match those of a term born infant, a number of studies have shown that the sucking pattern of preterm infants at term-equivalent age is less coordinated and less efficient than that of term-born infants.[46,47] Greater degrees of morbidity and the presence of a feeding tube can extend the transition time to exclusive oral feeding,[4] whereas demand or semi-demand feeding and non-nutritive sucking during tube feeds can shorten the transition time to exclusive oral feeding.[4] Once feeding at the breast, late preterm infants are at risk of under-consumption of breastmilk. Using breast pumps and nipple shields can help with increasing milk intake in these babies.[48]

Effect of smell and taste on feeding

When infants are tube fed, they will not experience the smell and taste of the milk they are fed.[49] Exposure to milk odour with a pacifier in preterm infants with nasogastric tubes in situ has been shown to increase non-nutritive sucking.[50] Moreover, milk odour exposure prior to breastfeeding will increase the amount of milk consumed by the baby.[51] A randomised controlled trial in preterm infants born <29 weeks' gestation showed that regular exposure to smell and taste of milk before each feed may improve feed tolerance and weight gain and decreased time to full enteral feeding.[52] This may suggest that smell and taste may enhance the cephalic phase response of digestion and hence improve feed absorption and metabolism.[52]

Another experimental study on preterm infants born between 28 and 34 weeks gestation showed that exposure to breast milk odour during gavage feeding decreased both time

Table 1 – Level of evidence for cited recommendations.

Recommendation	Source	Level of evidence[57]
Skin-to-skin contact to assist with breastfeeding.	Systematic review	1
Express breastmilk after each breastfeeding attempt and/or 8–10 times per day for the first two weeks or until the infant has achieved full breastfeeding.	Systematic review	1
Mother's own breastmilk is the best supplement but when not available, donor milk or formula are alternative choices.	Expert opinion	5
The best time for receiving supplements is during breastfeeding.	Expert opinion	5
Fortification is important in infants given donor breastmilk.	Systematic review	1
Fortification should be started for all preterm infants <1800 g.	Expert opinion	5
Targeted fortification is not superior to standard fortification.	Randomised clinical trial	2
Use standard human milk fortification and move to individualised fortification if growth is insufficient.	Expert opinion	5
Use preterm formula for all preterm infants until they reach term corrected age.	Expert opinion	5
Parenteral nutrition initiation and advancement should proceed as quickly as tolerated.	Expert opinion	5
Slow initiation and slow advancement of enteral nutrition in infants with poor tolerance of enteral feeding.	Narrative review	5
Recommended energy intake in parenteral nutrition.	Expert opinion	5
Recommended amount of protein in parenteral nutrition.	Expert opinion	5
Recommended amount of lipids in parenteral nutrition.	Expert opinion	5
Recommended amount of glucose in parenteral nutrition.	Expert opinion	5
Recommended amount of vitamins in parenteral nutrition.	Expert opinion	5
Post-discharge nutrition in preterm infants should be breastfeeding, but those with a subnormal weight for postconceptional age should receive supplements.	Expert opinion	5
Post-discharge formula for infants with subnormal weight.	Review of randomised clinical trial	2
To prevent overfeeding or underfeeding, all infants should have their growth monitored regularly.	Review of randomised clinical trial	2
Growth monitoring should be based on regular measurements of length, weight and head circumference.	Review of randomised clinical trial	2
Iron supplementation.	Expert opinion	5
Vitamin D supplementation.	Systematic review	1
Tube placement for enteral tube feeding.	Expert opinion	5
Continuous vs bolus enteral feeding.	Systematic review	1
Demand or semi-demand feeding and non-nutritive sucking to shorten the transition time to exclusive oral feeding.	Narrative review	5
Use breast pumps and nipple shields to help increase milk intake in late preterm infants.	Expert opinion	5

to oral feeding and length of hospitalisation.[53] In this study, infants were exposed to milk odour at the same time as gavage feeding three times a day until they reached full enteral feeding. The weight gain differences between the two groups were not significant, but the intervention group reached full enteral feeding three days earlier than the control group infants. Moreover, intervention group infants were discharged from hospital approximately four days sooner than the control group.[53] There are no trials of the effect of smell and taste on late preterm infants to help determine whether these babies may benefit from these interventions.

Future research focus

The generally accepted goal for postnatal growth is to achieve the same growth rate as intrauterine growth. However, it has not yet been established whether reaching this growth rate in terms of weight gain is healthy or not, since it may result in accumulation of fat rather than lean tissue.[9]

As the exact nutritional requirements of late preterm infants have not yet been established, most recommendations are based on fetal and term infant requirements. Currently, clinical judgement is the basis of decision making around how to provide optimal nutrition for late preterm infants, including whether they should receive formula or fortifiers.[35] Most of the recommendations for nutrition in late preterm infants are derived from expert opinions (Table 1).

Moreover, growth assessment in infants commonly is only based on anthropometric data, and body composition often is not assessed. Late preterm infants have different body composition than term born infants. Although late preterm infants are generally lighter and shorter than term infants at the time of birth, they have a higher fat percentage than term infants at term corrected age.[54–56] However, there are no clear data on how to encourage changes in body composition toward gaining more lean mass rather than fat mass. Furthermore, there are no clear data on the relationship between nutritional interventions and neurodevelopmental and long-term health outcomes of late preterm infants. These issues need to be the focus of high quality active research to optimise not only short-term weight gain, but also longterm health and development of late preterm infants.

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