

**Feeding the late and moderately preterm infant: A position paper of the
ESPGHAN Committee on Nutrition**

**Long Title: Feeding the late and moderately preterm infant: A position paper of the
European Society for Paediatric Gastroenterology, Hepatology and Nutrition
Committee on Nutrition**

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List of abbreviations

AGA: appropriate for gestational age; CoN: committee of nutrition; ELBW: extremely-low-birth weight; ESPGHAN: European Society for Paediatric Gastroenterology, Hepatology and Nutrition; ID: iron deficiency; IDA: iron-deficiency anaemia; IUGR: intrauterine growth retardation; LC-PUFA: long-chain polyunsaturated fatty acids; LMPT: late and moderately preterm; LPT: late preterm; MPT: moderately preterm; PCA: postconceptional age; PGR: postnatal growth restriction; REE: resting energy expenditure; SGA: small for gestational age; TEE: total energy expenditure; VLBW: very-low- birth weight

Abstract

Nutritional guidelines and requirements for late or moderately preterm (LMPT) infants are notably absent although they represent the largest population of preterm infants. The European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) Committee on Nutrition (CoN) performed a review of the literature with the aim to provide guidance on how to feed infants born LMPT, and identify gaps in the literature and research priorities.

Only limited data from controlled trials are available. Late preterm infants have unique, often unrecognized, vulnerabilities that predispose them to high rates of nutritionally related morbidity and hospital readmissions. They frequently have feeding difficulties that delay hospital discharge, and poorer rates of breastfeeding initiation and duration compared to term infants. This review also identified that moderately preterm infants frequently exhibit postnatal growth restriction.

The ESPGHAN CoN strongly endorses breast milk as the preferred method of feeding LMPT infants and also emphasizes that mothers of LMPT infants should receive qualified, extended lactation support, and frequent follow-up. Individualized feeding plans should be promoted. Hospital discharge should be delayed until LMPT infants have a safe discharge plan that takes into account local situation and resources.

In the LMPT population, the need for active nutritional support increases with lower gestational ages. There may be a role for enhanced nutritional support including the use of human milk fortifier, enriched formula, parenteral nutrition, and/or additional supplements, depending on factors such as gestational age, birth weight and significant co-morbidities. Further research is needed to assess the benefits (improved nutrient intakes) versus risks (interruption of breastfeeding) of providing nutrient-enrichment to the LMPT infant.

Key words: Breastfeeding, growth restriction, premature infants, recommendations

What is Known

- Late or moderately preterm infants represent the largest population of preterm infants.
- Late preterm infants frequently have feeding difficulties that delay hospital discharge, and poorer rates of breastfeeding initiation and duration compared to term infants.
- Moderately preterm infants frequently experience postnatal growth restriction.

What is New

- The European Society for Paediatric Gastroenterology, Hepatology and Nutrition Committee of Nutrition strongly endorses breastmilk as the preferred method of feeding and emphasizes that mothers should receive qualified and extended lactation support.
- The need for active nutritional support increases with lower gestational ages but research is needed to assess the benefits versus risks of providing nutrient-enrichment in these infants.

List of abbreviations

AGA: appropriate for gestational age; CoN: committee of nutrition; ELBW: extremely-low-birth weight; ESPGHAN: European Society for Paediatric Gastroenterology, Hepatology and Nutrition; ID: iron deficiency; IDA: iron-deficiency anaemia; IUGR: intrauterine growth retardation; LC-PUFA: long-chain polyunsaturated fatty acids; LMPT: late and moderately preterm; LPT: late preterm; MPT: moderately preterm; PCA: postconceptional age; PGR: postnatal growth restriction; REE: resting energy expenditure; SGA: small for gestational age; TEE: total energy expenditure; VLBW: very-low- birth weight

Introduction

In recent years, much attention has been focused on enhancing the nutritional support of very preterm infants to improve both survival and longer term outcomes. Significant efforts have been made to improve the provision of adequate nutrition during their in-hospital course stay and during the first months of life. In the preterm population weighing less than 1800 g, nutritional requirements have been reviewed (1). Similarly, nutritional requirements for term-born infants during the early months of life have also been re-evaluated to more closely match the nutritional intakes of breastfed term infants (2).

Nutritional requirement guidelines for late and moderately preterm (LMPT) infants are notably absent despite them representing the largest population of preterm infants. Feeding regimens designed specifically to meet the nutritional requirements of LMPT infants have not been established and need consideration. Therefore, the aim of this ESPGHAN committee of nutrition (CoN) position paper is to critically review the available evidence on the role of nutrition in infants born LMPT, to provide guidance on how best to feed these infants, and identify gaps in the literature and research priorities.

Definitions and scope of manuscript

Despite widespread agreement in defining preterm birth, there is less uniformity in defining different subgroups. The common subgroup terminologies used are very preterm (less than 32 weeks) and extremely preterm (less than 28 weeks). In contrast, a variety of terms have been used to describe preterm infants born at a number of different intervals between 32 and 36 weeks' gestation ("late preterm," "near term," "marginally preterm," "moderately preterm," "minimally preterm," "mildly preterm", and "larger preterm"). An expert panel at a workshop convened by the National Institute of Child Health and Human Development (NICHD) of the National Institutes of Health (NIH) in July 2005 recommended that births between 34 completed weeks (34 0/7 weeks) and less than 37 completed weeks (36 6/7 weeks) of gestation be referred to as "late preterm" (3). Specifically, this discourages the use of the phrase "near term" which may suggest that the infant is almost term, whereas the phrase "late preterm" emphasizes that these infants are at risk of immaturity-related medical complications (3). Although there has been no such consensus for a classification of birth between 32 completed weeks (32 0/7 weeks) and less than 34 completed weeks (33 6/7 weeks), "moderately preterm" is now commonly used.

The term "low birth weight" is a widely accepted definition for newborns with a birth weight below 2500 g. However, use of this term does not discriminate those infants with a low birth weight due to prematurity from those born small for gestational age (SGA) or in-utero growth restricted (IUGR) at term. SGA/IUGR infants may not have achieved full in utero growth potential often because of a complex range of genetic, epigenetic, maternal and environmental factors and present increased risks for specific short term and long term morbidities. The most frequent cause of IUGR is placental insufficiency, which impacts foetal growth and many physiological and development processes (4). It is tempting to extrapolate these observations to preterm infants as they, too, are almost always born LBW.

However, many preterm infants have normal or relatively normal growth prior to birth, meaning the optimal nutritional management may differ between a LBW infant born preterm and a LBW infant born at term who is IUGR.

The definitions of LMPT indicated above have been used throughout this report.

Methods

A systematic literature search was conducted up to April 13th 2018. For each outcome of interest relating to the nutrition of LMPT infants, searches were conducted in the databases Medline (via PubMed) and the Cochrane Library for relevant publications in English, including original papers, systematic reviews and meta-analyses - see Appendix 1. Specific features relating to late preterm (LPT) or moderately preterm (MPT) infants have been reviewed and reported separately when possible. Recommendations were formulated and discussed in a total of 3 face-to-face meetings which were held in Geneva, Rotterdam, and Zagreb. Between meetings CoN members interacted by iterative e-mails. All disagreements were resolved by discussion until a full consensus was reached for every statement. Similarly to the rules provided by ESPGHAN for Guidelines (http://www.espghan.org/fileadmin/user_upload/Society_Papers/ESPGHAN_-_Overview_ESPGHAN_Publications_January_2018.pdf), final agreement for each conclusion and recommendation was assessed anonymously using a web-based questionnaire enabling a list of arguments for and against each conclusion and recommendation. This possibility also allowed members to suggest new conclusions and/or recommendations to be submitted to the panel. One round of questionnaires was sufficient to reach consensus of >85% for all conclusions and recommendations.

Background

Epidemiology and common morbidities of LMPT infants

The incidence of preterm birth in different countries varies widely (5) as does that of LMPT infants with a rate less than 4% in Scandinavia and up to 10% in Korea (6-9). Interestingly, when moderate- and late-preterm are combined, the LMPT population represents more than 80% of all preterm births and consume about two thirds of all hospital expenditures related to prematurity (10, 11).

While serious morbidities are rare, LMPT infants have a 2 to 10 fold increased incidence of mild to moderate morbidities compared to term infants including hypothermia, respiratory distress, jaundice, and infection. These infants are also prone to develop nutritionally related neonatal morbidities such as hypoglycaemia, poor feeding, dehydration and malnutrition in the early neonatal period (12-18). Several studies have shown that LMPT infants are 2 to 3 times more likely to be readmitted after initial hospital discharge due to multiple factors including jaundice, sepsis and feeding difficulties (17, 19-21).

Hypoglycaemia

Our systematic literature search identified 6 studies on hypoglycaemia rates in the LMPT population. The incidence of early hypoglycaemia (within the first 12 hours of life) was 3 to 4 times greater in the LPT infants as in the term infants, with 1/3 experiencing recurrent episodes of hypoglycaemia (22). The rate of hypoglycaemia ranged from 16 to 34% and was associated with lower GAs (9, 22, 23), the risk being further increased in infants born at 34 weeks compared to those born at 35 to 36 weeks of gestation (9, 24). In a large retrospective cohort study from Australia, including 735 LMPT infants, the rate of hypoglycaemia was similar to the rates found in LPT infants: 22% in the LMPT appropriate for gestational age (AGA) infants, increasing to 32% in the LMPT small for gestational age (SGA) infants (25). This rate is higher than the 13% observed in MPT infants from a multicentre observational study in France which included infants with GA as low as 30 weeks (26). Interestingly, in a randomized controlled trial that aimed to determine the efficacy of a proactive feeding regimen in reducing hospital length of stay in MPT born small for gestational age (SGA) infants (27), one-third of the group receiving standard care (60 mL/kg/d of human milk at day 1 followed by a gradual increase to 170 mL/kg/d by day 9) developed hypoglycaemia compared to none in the proactive feeding group (100 mL/kg/d of human milk on day 1, followed by 130 mL/kg/d on day 2, 165 mL/kg/d on day 3, and 200 mL/kg/d from day 4). This significant reduction in the incidence of hypoglycaemia by a proactive regimen in a risk subgroup of LMPT (i.e., MLT born SGA) suggests that enhanced feeding support may reduce the risk of hypoglycaemia in LMPT infants.

Taken together, these studies show that LMPT infants are at high risk of hypoglycaemia, and this is due to numerous factors including immature gluconeogenesis, lower hepatic glycogen reserves, and a weaker peripheral counter-regulatory ketogenic response due to inadequate lipolysis exacerbated by low adipose tissue stores and inadequate milk intake (24). However, in part, hypoglycaemia may simply be due to a lack of early feeds including delayed initiation or use of low volumes, and/or a lack of PN when early feeding is not initiated (24, 28). The findings of the randomized controlled trial cited above strongly support the hypothesis that LMPT infants should not be treated as term infants, but deserve specific nutritional care, including proactive nutritional support for the prevention of hypoglycaemia.

Postnatal growth restriction

Postnatal growth restriction (PGR) has been identified as a major problem reflecting suboptimal nutrition of very preterm infants. Five studies assessed growth of LPT infants. In a population-based cohort of all births in 2004 in Brazil LPT infants were at increased risk of being underweight (i.e., weight-for-age z-scores below -2) and stunted (i.e., length-for-age z-scores below -2) at 12 and 24 months of age compared to term infants (adjusted OR: 2.57 [95% CI, 1.27-5.23] and 2.35 [95% CI, 1.49-3.70], and 3.36 [95% CI, 1.56-7.23] and 2.30 [95% CI, 1.40-3.77], respectively) (29). In a large cohort of 7866 US infants, LPT infants had a significant increased risk of having a weight-for-age z score of -2 or less at 6 months (adjusted OR, 3.48 [95% CI, 2.17-5.72]) and 12 months (2.22 [1.07-4.61]) but not at 18 months (30). In contrast, 108 LPT infants in a large cohort of 2465 children born in Beijing,

China, exhibited complete catch-up in weight, length and ponderal index by 1 year of age (31). In another study from China, the difference in weight and length of LPT infants compared to term infants decreased significantly with age during the first year of life ($p < 0.001$) but only weight demonstrated complete catch-up at 12 months corrected age (32). Finally, 1107 LPT infants from a large observational cohort in the United Kingdom exhibited a lower weight (-0.2 kg (-0.5 to 0.0) and -0.3 kg (-0.6 to -0.1), respectively) and height (-0.8 cm (-1.1 to -0.4) and -0.8 cm (-1.3 to -0.4), respectively) at 3 and 5 years compared to their term counterparts (33), yet exhibited a similar risk of being overweight at 3 and 5 years as their term counterparts. It is clear that growth patterns of LPT infants in these countries differ, suggesting that population context and perhaps nutritional practices have the potential to modify outcomes of LPT infants during the first years of life. Whether or not poor early growth of LPT infants is linked to inadequate early nutrition remains to be determined.

Five studies report growth in MPT premature infants, two during hospitalization, and two during the first 4 years of life. In a study performed in 15 NICUs in the United States, only 2% of the MPT infants achieved growth rates approximating those in-utero (15 g/kg/d) during neonatal hospitalization (34). The average decrease of weight z-score from birth to discharge was 0.67 (95% CI: -1.98 , 0.22), with large variations across neonatal units, ranging from 0.45 to 0.93 . A significant association existed between low protein and energy intake and reduced growth velocity. Continued use of supplemental gavage feeding at 35 weeks GA (i.e., intermittent enteral nutrition) was associated with a higher net growth velocity, than subjects not receiving any gavage supplement (7.0 ± 4.6 vs 5.0 ± 5.8 g/kg/d, $p < 0.001$), suggesting that the end of gavage feeding may reflect variation in recognition rather than the attainment of mature feeding, and that gavage feeding may be discontinued sooner than desirable to enable optimal growth (34). In a French study, premature infants born either very preterm (i.e., 30-31 weeks of gestation) or MPT had a 24% chance of having a weight below the 10th percentile at 36 weeks postconceptional age (PCA) (26).

In a large community-based cohort of 1123 MPT infants born in the Netherlands, MPT infants were shorter and weighed less at each assessment during the first 4 years of life than their term-born counterparts (35). At 4 years of age the preterm boys were 0.15 SD lighter ($p=0.09$) and 0.3 SD ($p=0.01$) shorter and the preterm girls were 0.25 SD lighter ($p=0.01$) and 0.2 SD ($p=0.04$) shorter. At 7 years of life, a subgroup of 234 of these infants remained slightly shorter and lighter than reference values (-0.12 SD and -0.21 SD respectively) (36). Being SGA at birth was identified as a strong predictor of final weight and height for both symmetrical (i.e., head circumference is in proportion to weight and length) and asymmetrical (i.e., only weight and length are reduced) growth restricted preterm-born infants (37). Of note, those born large for gestational age (i.e., birth weight >90 th percentile) demonstrated well balanced growth in height, weight, and head circumference during infancy but an accelerated weight gain during subsequent years leading to a BMI similar to that of LGA term babies (38).

In a longitudinal population-based study in Japan including 1,414 LPT and 25,556 term infants, the incidence of short stature (height <-2 SD for their age) was 2.9% in the LPT

infants, which was significantly higher than in the term infants (1.4%). This study also showed that short stature was more common in LPT SGA infants (9.4%) compared to LPT AGA infants (2.1%) (39).

Finally, the 147 MPT infants of a large observational cohort from the United Kingdom exhibited a lower weight (−0.8 kg (−1.2 to −0.4) and −1.2 kg (−1.7 to −0.7), respectively) and height (−0.9 cm (−1.9 to 0.0) and −1.3 cm (−2.3 to −0.3), respectively) at 3 and 5 years compared to their term counterparts (33). Contrarily to what was observed in LPT who exhibited a similar risk of being overweight than their term counterparts, MPT exhibited a lower risk of overweight at 3 and 5 years. Overall, these studies in LMPT infants show that they are at risk of being shorter and lighter during childhood than their term counterparts, but also have a lower risk of being overweight.

Altered body composition

Our systematic search identified 3 studies assessing early body composition of LMPT using reliable methods. In the first study, predominantly breastfed healthy MPT infants at term postconceptional age were significantly lighter than full-term newborns, but had a similar proportion of body fat and subcutaneous fat when assessed by magnetic resonance imaging (40). The total body water using the doubly labelled water methodology was also similar between the 2 groups confirming similar body composition (40).

In a cohort study published in several manuscripts, body composition of the LPT infants was assessed by air displacement plethysmography. In a first set of data on a limited number of patients (n=49), the LPT infants had a similar fat content at 3 months corrected age than term infants aged 3 months, despite a transient higher percentage of fat at term corrected age and at 1 month corrected age (41). This transient increase in adiposity, which may simply come from the comparison of a newborn infant with one who is several weeks old, was confirmed by a second set of data of 216 LPT infants (42). Among the factors studied, intrauterine growth was not significantly associated with postnatal body composition changes, but more human milk feeding appeared to be associated with increased fat-free mass deposition (43, 44).

Finally, the third study assessed body composition using air displacement plethysmography in a group of 25 LMPT infants at expected term. The LMPT infants had a similar weight but a lower fat free mass and a higher fat mass than term infants matched for body weight and gestational age (45).

These observations suggest that LMPT infants may have a transient excess of fat at expected term when compared to term infants measured at birth, although the clinical relevance of this finding remains to be studied.

Feeding and eating difficulties

Feeding difficulties are the primary reason for prolonged hospital admission of LPT infants and up to 3/4 of LPT infants require feeding support (46). These feeding difficulties are

related to gestational age being more frequent in infants born at 34 weeks compared to those born at 35-36 weeks of gestation (30% vs. 9%) (9). This is related to immaturity of multiple physiological processes including cardiorespiratory instability, metabolic disturbances, immaturity of state regulation, uncoordinated suck, swallow, breathe organization, and decreased oromotor tone (46, 47). Furthermore, the risk of feeding difficulties may also be increased by maternal conditions (e.g.; obesity, multiple births, pregnancy-induced hypertension, infections) causing or associated with preterm delivery (46). Successful feeding is sometimes not sustained after discharge and this may result in readmission, and this may be due to being discharged home before problems with latch and milk transfer have been resolved. Parental education and timely outpatient follow-up by a provider knowledgeable in breastfeeding seem crucial in the proper management of breastfeeding for these mother–infant dyads (48).

In a post-discharge parental survey of 571 LPT infants, symptoms compatible with oromotor dysfunction (17%) and avoidant feeding behaviour (29%) were frequently reported at 3 months of age (49). The most commonly reported form of oromotor dysfunction was choking and the most common avoidant feeding behaviour was spitting. The rates of oromotor dysfunction and avoidant feeding behaviour decreased over time to reach 4% and 12% at 1 year respectively. The only difference between LPT infants who were admitted to the NICU and those admitted to the term nursery was that those admitted to the NICU were twice as likely to require hospitalization or specialty care before 3 months (16% vs 8%; $P = .009$).

Increased risk of eating difficulties at 2 years of age has been recently documented in a large population-based cohort of 1130 LMPT and 1255 term born controls (50). Infants born LMPT were at increased risk of oral motor (RR: 1.62; 95% CI: 1.06, 2.47) and picky eating problems (RR: 1.53; 95% CI: 1.03, 2.25) at 2 years corrected age but these observations were mediated by other neurobehavioral sequelae in this population. Whether or not LMPT infants are at risks of long term feeding disorders requires further study.

Neonatal nutrition and long term cardiovascular and metabolic outcomes of LMPT infants

It remains uncertain whether the transient altered body composition observed in LMPT infants at term persists into later life, and if so, whether this may be mediated by early nutrition. Up until 3 months of age, fat mass accretion of LPT infants is not associated with early perturbation of glucose homeostasis (42). A population-based study from Sweden showed that children born LMPT are significantly leaner at 5 years than those born at term (51). This longitudinal study showed a transient larger waist circumference at 2 years in the LMPT group which was not apparent later (51). Compared to healthy control children born at term, a group of appropriate for gestational age LMPT children exhibited lower weight at 3.5y, smaller height at both 3.5y and 7y, similar skinfold thicknesses at 3.5y and similar fat mass and % fat at 7y (52). Lean mass assessed by dual X-ray absorptiometry was however reduced at 7 years compared to the controls in absolute value but not when adjusted for height (52).

In a population-based cohort study, which included 329 495 Swedish men born in 1973 to 1981, the adjusted odd ratios (95% confidence intervals [CIs]) for high systolic BP (≥ 140 mm Hg) was 1.25 (1.19 to 1.30) in preterms born between 33 to 36 weeks of gestation (53). Compared to very preterm infants, the risk observed in LMPT infants is lower, but still significantly higher than in term infants. Furthermore, one large prospective study performed in New Zealand, which included 311 adults born MPT and 147 adults born at term, showed that moderate prematurity was associated with increased systolic blood pressure by 3.5 mmHg at age 30 (95% CI 0.9-6.1 mmHg, $p=0.009$). Overall the risk of hypertension was significantly increased in preterm vs. term born adults (20% vs 10% respectively; $p=0.01$) (54). Finally, a case-control study with a limited number of patients (22 adults born MPT vs. 14 adults born at term) but using a detailed measure of blood pressure (i.e., 24-hour ambulatory blood pressure monitoring) showed that mean 24-hour arterial pressure and both nocturnal and daytime diastolic blood pressure were significantly increased in adults born MPT (55).

Insulin resistance or glucose intolerance in very preterm patients may develop during childhood, but is more commonly observed in adulthood (56). In a large cohort study, response to a standard 75 g oral glucose tolerance test demonstrated that young adults born LMPT have decreased insulin sensitivity compared to adults born at term (54). Decreased insulin sensitivity was further confirmed in a nested study using hyperglycaemic clamps, the gold standard method for assessment of insulin sensitivity (57). These adults (at 34 to 38 years) born preterm had greater abdominal adiposity, increased truncal fat and higher android to gynoid fat ratio compared to those born at term (58). Furthermore, they exhibited a compensatory increased first-phase insulin secretion, but similar disposition index, indicating an appropriate insulin secretion (57).

Whether or not cord lipoprotein profiles at birth or during the first month of life in LPT infants translates into long term effects is not known (59, 60). In the New Zealand study described previously, young adults born LMPT did have altered blood lipid and early morning cortisol levels at age 30 (54), and those followed to 34-38 years exhibited a less favourable lipid profile, including lower HDL-C concentrations and greater total cholesterol to HDL-C ratio (58)

A few studies have assessed bone development and the risk of bone disease in LMPT infants by the use of dual-energy X-ray absorptiometry. At 1 year corrected age, a minimal difference of less than 1% of the bone mineral density (BMD) of the lumbar spine was found in LMPT infants compared to infants born full term (32). At 7 years, bone mineral content (BMC) was reduced in LMPT infants compared to the controls in absolute value but not when adjusted for height (52). At 31 years of age birth weight, independent of gestational age, was positively associated with lumbar spine BMC, area, and areal BMD (61). However, these associations disappeared when adjusted for adult height, indicating that LMPT infants have appropriate bone development in adulthood (61).

These limited data suggest that the cardiovascular and metabolic risk profiles in LMPT are similar to features observed in very preterm infants. Our review highlights the lack of data on

the effects of nutrition during hospitalization or after discharge on later metabolic risks and emphasize that further studies are needed to determine the long-term impact of early nutrition.

Neonatal nutrition and long term neurological outcomes of LMPT infants

While multiple studies have focused on the neuro-development of very preterm infants, there is increasing evidence that LMPT infants are also at increased risk of impaired neuro-development. A systematic review shows that LPT infants are at increased risk of adverse developmental outcomes and academic difficulties up to 7 years of age in comparison to term infants (62). Whether or not developmental delay of LMPT infants is affected by early nutrition remains unclear. It is likely that several nutritional factors, combined or independently, may affect development of LMPT infants

Since large changes in plasma sodium concentrations have been found to be associated with later adverse development of very preterm infants (63), it is reassuring that data from a large observational study showed that term and LPT infants with neonatal dehydration were not at risk of abnormal neurologic examinations or neurologic diagnoses at five years of age (64).

A study performed in 225 LPT infants born in Northern Ireland showed no significant association between growth and cognitive, motor, or language skills assessed by the Bayley Scales of Infant and Toddler Development, Third Edition (65). In contrast, short stature during the first 7 years of life was associated with poorer motor, IQ, and attention scores and was associated with increased risks of impaired motor skills and low IQ in a group of 234 MPT children (36). Lower weight at 1 and 4 years was associated with lower IQ scores, whereas accelerated weight gain between age 4 and 7 years was associated with poorer motor, IQ, and attention scores (36). A large cohort of 1130 LMPT infants has been studied at 2 years corrected age by using questionnaires assessing the risk of neurosensory and cognitive impairment (66). Compared to the 1255 term-born infants, the LMPT infants had twice the risk for neurodevelopmental disability at 2 years of age with the vast majority of identified impairments in the cognitive domain. Not receiving breast milk at discharge was identified as an independent risk factor for cognitive impairment (66). Together with similar studies performed in very preterm infants these studies suggest that long term neurological outcomes of LMPT infants may be modified by breastfeeding and early nutrition.

Current nutritional practices

Benchmarking or comparative studies often show that care of preterm infants, including nutritional practices varies greatly among countries and centres. The LPT infant presents a nutritional challenge to healthcare providers starting immediately following birth when deciding where the appropriate level of care should be provided. Triage of the LPT may vary among hospitals; some infants may be cared for on the postnatal ward, whereas others are admitted to a newborn nursery or neonatal intensive care unit.

A survey of admission practices for LPT infants in England showed that the median (range) birth weight and gestational age limits for direct postnatal ward admission were 35 (34–37)

weeks and 2 (1.5-2.5) kg respectively (67). This survey also highlighted that besides the large variation of admission criteria among units, these criteria vary according to the type of neonatal units. In a large prospective population-based study comprising births in four UK maternity centres, 64% of the LPT infants were never admitted to a neonatal unit (14, 18) although most (83%) of those who stayed on the postnatal wards still required some kind of medical input (18). LPT infants have significantly more medical problems and are more likely to require specific medical support including intravenous infusions than term infants (26.7% vs. 5.3%; OR: 6.48; 95% CI: 2.27–22.91; $P = .0007$) (23), resulting in a significantly longer duration of hospital stay compared to term infants (68) (16) (18). Furthermore, resource utilization including total parenteral nutrition/intravenous support (53% vs 17% vs 3%) and length of stay (14 ± 22 days vs 4 ± 4.7 days vs 2.6 ± 3.9 days) is significantly higher ($P < 0.001$) in MPT infants vs LPT and term infants (9).

Striking variations in nutritional practices for LMPT infants have been documented (69). NICU admission of LMPT infants has been shown to have a positive effect on breastfeeding continuation in some settings (70), a negative effect in some settings (71), and no effect in other settings (72, 73). In a very large study including 138 359 term and preterm infants in the United States, the incidence of breast feeding after 4 months was 48% vs 44% in LPT infants admitted vs. those not-admitted in the NICU and 49% vs 35% in MPT infants (70). This suggests that treating LPT infants as healthy term babies may serve as a disadvantage to this group and that different settings require different solutions. Early rooming-in and breastfeeding support is generally encouraged and adequate care and support should be provided.

Parenteral nutrition support

Within the group of LMPT, those born at a lower gestational age are more likely to receive parenteral nutrition/intravenous support than those born at a higher gestational age (9, 74, 75). The need for central venous access remains a controversial issue in the nutritional care of LMPT infants. In a recent survey including 25 different centres in France, 56% of them had a written protocol stating that parenteral nutrition should be started on the first day of life for MPT infants. (26). In practice 61% of the MPT infants received a central line during hospitalisation (26).

In another observational study, the use of peripherally inserted central catheters in MPT infants improved nutrition delivery and postnatal growth in 187 infants born between 32 and 34 6/7 week gestation (76). Energy and protein intakes were 16% and 36 % higher ($p < 0.001$) in the group with central line.

The use of central lines in MPT infants allows delivery of parenteral nutrition with high osmolarity, and thus facilitates adequate nutrient intakes, which in turn may help prevent postnatal growth restriction. On the other hand, use of central lines is associated with risks including sepsis and thrombosis, it is time consuming, and it requires expertise and admission in units with appropriate resources.

Enteral nutrition support

Enteral nutrition support varies from unit to unit. In a retrospective review of medical records of 647 preterm infants from 6 different NICUs including LMPT infants, the median time to the first feed offered was one day and the median duration of tube feeding was 12 days but with a very large interquartile range (77). Gestational age, birthweight, medical conditions and centre were strong predictors of the time to attain full oral feeding (77).

Whether or not combining breastfeeding with supplementary formula feeds to improve growth is beneficial or not in LPT infants remains a matter of debate. Indeed, in the LPT population, those who received regular supplementary formula feeds may experience a longer delay before initiation of breastfeeding, and may have longer hospital stay than infants exclusively breast fed from birth without any evidence of higher weight gain (78).

Observational studies performed in MPT infants show that the average time of initiation of enteral feeding, the advancement of feeding volume, and the rate of human milk fortification varies greatly. On average breastmilk fortification was provided to 65 % of MPT infants studied in France (26). Likewise, there is a range in the type of formula prescribed at discharge for these infants. A study performed in 10 NICUs in the United States showed that being discharged on a post discharge formula varied from 4% to 72% (69). Due to challenges in establishing successful breastfeeding, formula milk may be used in up to 80% of MPT infants (75). Interestingly, the MPT infants with lowest GAs, received higher nutrient intakes per kg, reflecting a greater use of PN and pro-active nutritional support. (75).

In the randomized controlled study by Zecca et al, assessing the efficacy of a proactive feeding regimen in reducing hospital length of stay in MPT infants born small for gestational age (27), the infants assigned to the proactive feeding regimen (n=31) received significantly less intravenous fluids (2.8% vs 33.3%; P = .0013), had less weight loss and significantly faster regain of birth weight, while feeding intolerance and faecal calprotectin levels did not differ compared to the controls. As previously described, the proactive group also had a highly significant lower incidence of hypoglycaemia (33.3% vs. 0%, p=0.0002), and they were discharged significantly earlier (11.9 ± 4.7 days vs. 9.8 ± 3.1 days, p=0.029) (27). This well designed study shows that providing efficient enteral support, may improve weight gain, reduce the need for intravenous fluid and dramatically lower the risk of hypoglycaemia.

These findings support the idea that LMPT infants require specific nutritional regimens.

Breastfeeding support

Policy statements and practice guidelines support breastfeeding in the LPT population (79). LPT gestation may have a negative effect on mothers' psychological profiles in the puerperium, where levels of anxiety, depression, and psychological distress correlate negatively with early lactation success (80). Mothers of LPT infants recognize that breastfeeding is a bonding experience for themselves and their infants (81, 82). They do report however that their breastfeeding experiences include challenges with latching and milk supply, inadequate lactation support from providers after discharge and a feeling of failure.

Although breastfeeding initiation in LPT infants has increased over the past decades (73), establishing breastfeeding in these infants is frequently more problematic than in term infants and as a consequence they are less likely to be breastfed and less likely to breastfeed for a long duration (18, 83-87). Because of their immaturity, LPT infants may be sleepier, have less stamina and more difficulty with latch, suck, and swallow. They are more often separated from their mother, who might also have a medical condition affecting the success of breastfeeding (88). Finally, LPT infants are more likely to be born after with? caesarean-section, which may adversely affect the onset of lactation and the success of breastfeeding (89).

In a large population-based study performed in four large maternity centres in the UK, LPT infants appeared less likely to receive any breast milk during initial hospitalization than term infants or MPT infants (18). These recent data confirm earlier data showing that breastfeeding initiation among LPT infants is around 59% to 75%, which is lower than that observed in term infants (46).

Several reasons and factors including marital status, maternal age, race/ethnicity, education, parity, Women, Infants and Children Program participation, NICU admission, and smoking status have been found to be associated with successful breastfeeding of LPT infants (73). Interestingly, the rate of initiation of breastfeeding of LMPT infants has been described to be lower than that of very preterm infants with the lowest rates for LMPT infants not admitted to a NICU (55.3 vs 70.2 %). (70). However, NICU admission may also disrupt the establishment of breastfeeding because of the inability to initiate breastfeeding within one hour after birth, separation from their mother, and by the use of infant formula.

Limited data are available for assessing the duration of breastfeeding in the LMPT population. Breastfeeding tends to decrease over the postpartum period, and rates may be less than that for either term or earlier preterm infants at several weeks postpartum (46, 90). In the UK population-based study described above, the chance of receiving breast milk at discharge was 18% lower for the LPT infants and 26 % lower for the MPT infants compared to the term infants. The chance of being exclusively breastfed at discharge was also significantly lower (40% and 34 % respectively vs. 65%) (46). These data demonstrate the shorter duration of breastfeeding in the LMPT population, and suggest that breastfeeding may only continue for a few days or weeks in many infants. It has been suggested that the higher breastfeeding rates among very preterm as compared to LPT infants may be the result of extra vigilance, breastfeeding support, and importance placed on breast milk feeds in the NICU.

Interestingly, a study of breastfeeding patterns after hospital discharge showed that the proportion of feeds at the breast increased steadily over the first 4 weeks and that infants who received breast milk exclusively during the first week of life were significantly more likely to be primarily fed directly at the breast at one month (91). Perceived inadequate milk supply and nursing difficulties were among the reasons cited by the mothers for discontinuing breastfeeding their LPT infant after discharge (72). Duration of successful breastfeeding tends to be strongly associated with maternal confidence, (92) and breastfeeding support should be provided to address these concerns.

The PROBIT cluster randomized trial clearly demonstrated that breastfeeding promotion increases the duration and degree of breastfeeding and also decreases the risk of gastrointestinal tract infection and atopic eczema in the first year of babies born with a birth weight above 2500 g (93). A systematic review confirms that interventions supporting breastfeeding are associated with an increase in the rates of any and exclusively breastfeeding (94). The effect of interventions to promote breastfeeding in the late preterm infant has recently been reviewed (95). Inpatient care practices such as kangaroo mother care or rooming-in (90, 96), early skin-to-skin care (97), and cup feeding (98, 99) may improve breastfeeding establishment and duration whereas others such as expressing breastmilk (96), use of pacifier or nipple shields (90), or use of infant formula (78, 97) are some of the common practices that may negatively impact mother's establishment of exclusive breastfeeding of LMPT infants.

Breastfeeding education provided by nurses, peer counselors and lactation consultants contribute to earlier initiation of breastfeeding after birth and a higher likelihood of longer breastfeeding after discharge (95). A structured psycho-educative intervention up to 3 months for parents of preterm infants reduced postpartum depression and extended the period of breastfeeding (100). Because a high level of in-hospital support is associated with increased exclusive breastfeeding (97), the WHO- Baby-Friendly Hospital Initiative strongly emphasizes the need for supportive practices during hospitalization to promote breastfeeding (101). However, LPT versus term infants are less likely to be exclusively breastfed and data suggest that hospital supportive practices may be paradoxically less frequent among LPT infants than in term infants (97). For example, LPT infants experience less skin-to-skin contact with their mother in the first hour of life, and they benefit less from rooming-in and/or withholding of a pacifier (97). After discharge from hospital, receiving sufficient help with breastfeeding is also associated with improved breastfeeding in LPT infants (102). Evidence-based recommendations for appropriate discharge timing and post-discharge follow-up for LPT infants have been proposed to prevent neonatal morbidity and readmission (103). The Academy of Breastfeeding Medicine issued guidelines to promote and sustain breastfeeding in the LPT infant (104).

Estimation of nutritional requirements

It is generally accepted that the goal for the nutrition of the preterm infant is to supply nutrients such that the rate of growth and body composition would be equivalent to that of a normal foetus of the same postmenstrual age, without producing metabolic stress. Clinical studies have shown that enteral and parenteral nutrient intakes for very preterm infants that are closer to those estimated to produce growth rates that approximate that of the foetus, reduce the cumulative energy and protein deficits and promote postnatal growth, optimal body composition at discharge and perhaps even neurodevelopmental outcomes (1, 105, 106). The 2010 ESPGHAN guidelines for the enteral nutrient supply for preterm infants propose advisable ranges for nutrient intakes for stable-growing preterm infants from 1000 g up to a weight of approximately 1800 g (1). Indeed, most data that are available have been obtained for this weight range, which tends to correspond to ~50% of the MPT infants but does not correspond to many LPT infants.

Nutrient requirements of very preterm infants are estimated by considering intrauterine accretion rates, organ development, factorial estimates of requirements, nutrient interactions and supplemental feeding studies. Nutritional requirements of normal birth weight term infants are based on the average intake and nutrient content of breast milk. Nutrient requirements per kg body weight of LMPT infants are likely somewhere between those of very preterm infants and term infants. The exact nutrient requirements of LMPT infants are however not known. It is likely that the nutrient requirements of LPT infants will be higher than those of term infants but may be provided by un-supplemented breast milk, especially if the infant is capable of upregulating feeding volumes to cover needs. However, the nutrient requirements of MPT infants are likely to be closer to those of very preterm infants and the most immature MPT infants and those with a birth weight < 1800 g will need supplements in addition to breast milk to comply the 2010 ESPGHAN recommendations (1).

Resting energy expenditure (REE) is approximately 45 kcal/kg/d in very preterm infants and 50 kcal/kg/d in less preterm infants. Additional energy expenditure for occasional thermal stress and physical activity (movement, crying) increases from 15 in very preterm infants to 20 kcal/kg/d in less preterm infants. During gestation, fat mass deposition as a proportion of weight gain increases from 12% at 28 weeks GA to 20 % at term and reaches 40% in breast fed term infants (107). Foetal energy deposition per g of weight gain also increases from 1.8 kcal/g at 28 weeks GA to 2.3 kcal/g at term and represents 3.8 kcal/g in breastfed term infants. Therefore, energy requirements vary only slightly across all preterm groups. One study, which specifically assessed total energy expenditure (TEE) in MPT infants at corrected term age, showed that TEE was on average 75 kcal/kg/d and 23% higher than that of term infants (40). In another study using indirect calorimetry, REE in SGA MPT infants was significantly higher than that of AGA MPT infants (108). These studies provide evidence that energy requirements of MPT infants is higher than that of term infants, and that those born SGA have significantly higher energy needs than those born AGA. Overall, the higher TEE/kg body weight in MPT infants can be explained by a higher growth rate. Postnatally, energy intake per kg body weight is linearly associated with weight gain during the first 28 days of life in LMPT infants (109).

Foetal weight gain decreases dramatically during the last trimester of gestation from 18 – 20 g/kg/d at 28 weeks GA to 10 g/kg/d in term infants (110, 111). Protein accretion, and therefore requirement related to body weight, decreases progressively according to gestational age during the last trimester of gestation up to the values estimated for term infants. There is no study assessing protein requirements in LMPT infants.

Among other nutritional factors that affect early infant development or visual acuity, long-chain polyunsaturated fatty acids (LCPUFAs) have been recognized to be particularly important in the very preterm population (112). Very little is known about the importance of these fatty acids in the LMPT population. At birth, a significant correlation exists between gestational age and circulating docosahexaenoic acid (DHA) and arachidonic acid (AA) levels. In turn, a 30% lower DHA level is observed in MPT infants compared to term infants (113). One study performed in Taiwan aimed to specifically assess the effects of a 6 month postnatal intervention on visual acuity and cognitive development in MPT infants (i.e., 30-37

weeks GA) (114). This study suggests possible benefits on neurodevelopment at one year of a formula supplementation with both docosahexaenoic acid (DHA) and arachidonic acid (AA). DHA and AA requirements in LMPT are likely to be higher than term infants but there is insufficient data to recommend precise intakes.

Because of shorter duration of pregnancy and lower birthweights, LMPT infants have lower iron stores at birth than term infants (115), particularly those born SGA or from a diabetic mother (116). In the latter study, the LPT infants with serum ferritin concentrations below 75 ng/mL exhibited abnormal auditory neural maturation within the first 48 hours of life (116). In contrast, other LMPT infants may have higher iron stores during their first weeks of life because of delayed cord clamping or cord milking (117). Several studies have described that LMPT infants are at risk of early iron deficiency (ID) and iron-deficiency anaemia (IDA). In a case control study performed in Turkey, the mean ferritin and haemoglobin concentrations of LPT infants were statistically lower than those of term infants at 2 months of age but not at 4 months (118). In a cohort study in Brazil, LPT infants had a decline in haemoglobin concentration but similar ferritin concentrations as term infants at the same postconceptional age of 1 month (119). In a prospective longitudinal study performed in Greece, formula-fed LMPT infants exhibited progressive decline of blood ferritin concentration during the first year of life to reach a mean value \pm SD of 20 ± 9 ng/mL at 12 months of age, with lower values more commonly observed in the children of lower gestational ages (120). In a prospective cohort of 161 Dutch infants born LMPT, ID was present in 21% and IDA in 8.5% of the infants at age 4 months. In another observational study performed in the Netherlands, ID and IDA were found to be common and present in 38.2% and 30.9% of the LMPT infants aged 6 weeks who did not receive iron supplementation on a routine basis (121). The rate of ID decreased with increased postnatal age to 18.9% at 4 months and 5% at 6 months (122). The risk for ID was significantly associated with lower birth weight, a shorter duration of formula feeding, more weight gain in the first 6 months of life and lower ferritin concentrations at the age of 1 week (122). There is evidence from a Swedish randomized controlled trial performed in a mixed group of LMPT infants and SGA term infants that iron supplementation reduces the risk of ID at 6 months (123) and 1 year but not at 3.5 years (124). Iron supplementation independently lowered systolic blood pressure at age 7 (125), reduced the risk of behavioural problems at 3.5 and 7 years of age (126, 127) but did not alter auditory brainstem response (128). This study, however, did not observe different effects of iron supplementation in LMPT infants as compared to small for gestational age term infants.

Nutritional stores of essential nutrients of newborn infants depend on transplacental transfer and are related to gestational age as illustrated above for LC-PUFAs and iron. The nutritional requirements of LMPT for calcium, phosphorus, vitamins and trace elements are likely to be higher than those for term infants but there are insufficient data to recommend precise intake since our systematic review did not identify observational nor randomized controlled trials assessing the nutritional needs of LMPT infants for those nutrients except vitamin D. A vitamin D intake of 800 to 1000 IU/d (and not per kilogram) during hospitalization has been recommended by the ESPGHAN committee on Nutrition for the very preterm infants (1). A study performed in Korea showed that in both MPT and LPT infants the incidence of vitamin

D deficiency was very high and that half of the infants had severe deficiency defined by a circulating 25 hydroxyvitamin D below 10 ng/mL (129). In this study, the risk of vitamin D deficiency was not associated with lower gestational age but was associated with twin pregnancy and seasonal variation. Another study performed in LPT infants demonstrated that even in a sunny country like Greece, the circulating levels of 25 hydroxyvitamin D is low during the first three month of life (130). This suggests that vitamin D supplementation is also required from birth in LMPT infants. A study performed in Canada showed that the chance of receiving vitamin supplementation after discharge is lower in the LPT population than in preterm infants born before 34 weeks of gestation (131). Targeting LPT infants could improve vitamin D intake in these infants who are at high risk of vitamin deficiency. Further studies are nevertheless needed to confirm whether higher vitamin D intakes (i.e., 800 to 1000 IU/d) are needed or if 400 IU/d is sufficient.

Conclusions

- Compared to term infants, LPT infants require specific management because they have unique, often unrecognized, medical vulnerabilities that predispose them to high rates of morbidity and hospital readmissions.
- LPT infants frequently have lower rates of breastfeeding initiation, take longer to establish breastfeeding, and have shorter breastfeeding duration than term infants. Breastfeeding support through maternal education, kangaroo care, rooming-in, skin to skin care and post-discharge support, is associated with improved breastfeeding initiation and duration in LPT infants.
- Similar to very preterm infants, lack of breastfeeding at discharge in LMPT infants is associated with worse cognitive and behavioral outcomes.
- MPT infants are prone to develop postnatal growth restriction and transient altered body composition. Children and young adults born LMPT have a higher risk of lower weight and height during childhood, insulin resistance, glucose intolerance and high blood pressure than those born at term, but there is a lack of data on the effects of early nutrition during hospitalization or after discharge on these outcomes.
- LMPT infants are at high risk of hypoglycemia. The use of proactive nutritional support for high risk infants is effective in preventing hypoglycemia.

- There is a lack of data for determining precise nutritional requirements in LMPT infants. In the LMPT population, the need for active nutritional support is strongly correlated with gestational age. There are insufficient data to make precise recommendations for the use of parenteral nutrition, human milk fortifier, preterm formula or nutritional supplements. A subgroup of MPT infants may benefit from more active enteral and parenteral nutrition support to promote growth, even though the long term benefits of such an approach have not been evaluated.

Recommendations

Based on the above conclusions and considering current practice, the ESPGHAN CoN makes the following recommendations:

- Hospitals should have their own policies to prevent and treat the known complications associated with LMPT birth, particularly early hypoglycemia. Early rooming-in is encouraged and pro-active nutritional care and support should be provided.
- Breastfeeding for LMPT infants is strongly endorsed. Mothers of LMPT preterm infants should receive qualified, extended lactation support, and frequent follow-up.
- Health care providers should remain vigilant for evidence of poor breast milk transfer and infant problems related to poor intake. Individualized feeding plans should be promoted and should include special considerations to compensate for immature feeding skills and difficulties in establishing lactation and breastfeeding.
- Individual discharge plans should be developed in every hospital taking into account local situation and resources. Delayed hospital discharge should be considered if the LMPT infant does not fulfill the requirements of a safe discharge plan.
- LMPT infants with birthweight less than 1800 g should receive enteral nutrient supply as previously described by the ESPGHAN CoN (1).

- The use of human milk fortifier, enriched formula and/or additional supplements, and parenteral nutrition may be appropriate for some LMPT infants taking into account factors such as gestational age, birth weight and significant co-morbidities.
- LMPT infants are at risk of iron deficiency which may impair neurodevelopment. LMPT infants weighing less than 2500 g at birth should receive 1 to 2 mg/kg/d of iron up to 6 months age. LMPT infants weighing less than 2000 g should receive 2 to 3 mg/kg/d of iron at least up to 6 months.
- LMPT infants require a daily vitamin D supplement of at least 400 IU/d throughout early childhood.

Research gaps

- Further research is needed to better understand how breastfeeding rates can be improved in LMPT infants.
- Current nutritional practices provided to LMPT infants may result in transient undernutrition but its magnitude and consequences are not well known. Research on the effects of early nutrition on long-term outcomes (e.g. neurological, developmental, metabolic and cardiovascular) of LMPT infants is required
- Benefits (growth, improved development) versus risks (interruption of breastfeeding, complications associated with parenteral nutrition, cardiovascular and metabolic outcomes) of providing nutrient-enriched feeds to the LMPT infant are not well determined. Research in this area is strongly encouraged as they represent the largest group of preterm infants.
- Further research is needed to determine whether nutritional requirements are mainly dependent on gestational age or birth weight in preterm infants.

Appendix 1

The searches were limited to human studies. Literature search terms included firstly those related to the definition of the population studied, restricting the search to words in the title or abstract of the manuscript (Late preterm infant[TIAB] OR Late preterm infants[TIAB] OR Late preterm newborn[TIAB] OR Late preterm newborns[TIAB] OR moderately preterm infants[TIAB] OR moderately preterm infant[TIAB] OR moderately preterm newborn[TIAB] OR moderately preterm newborns[TIAB] OR marginally preterm infant[TIAB] OR marginally preterm infants[TIAB] OR marginally preterm newborn[TIAB] OR marginally preterm newborns[TIAB] OR Larger preterm infant [TIAB] OR Larger preterm infants [TIAB] OR near term infant [TIAB] OR near-term infant [TIAB] OR near term infants [TIAB] OR near-term infants [TIAB]). These were combined, as appropriate, with MeSH terms and keywords relating to nutrition, breastfeeding, and growth (growth OR nutrition OR breastfeeding OR breastmilk OR nutrient OR nutrients OR lipid OR lipids OR protein OR proteins OR enteral nutrition OR parenteral nutrition OR glucose OR iron OR minerals OR calcium OR phosphorus OR zinc OR sodium OR potassium OR trace elements OR vitamin OR vitamins). Among the 498 manuscripts retrieved, 54 were selected for this review based on the reading of titles and abstracts. Furthermore, the reference list from all relevant articles was also searched to complete this review.

Disclaimer

ESPGHAN is not responsible for the practices of physicians and provides guidelines and position papers as indicators of best practice only. Diagnosis and treatment is at the discretion of physicians.

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