BMJ Paediatrics Open

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Journal:	*BMJ Paediatrics Open*
Manuscript ID	bmjpo-2021-001153
Article Type:	Original research
Date Submitted by the Author:	03-May-2021
Complete List of Authors:	Abdul Hamid, Haslina; University of Nottingham, Population and Lifespan Sciences, School of Medicine; Universiti Kebangsaan Malaysia, Dietetic Programme, Faculty of Health Sciences Szatkowski, Lisa; University of Nottingham, Population and Lifespan Sciences, School of Medicine Budge, Helen; University of Nottingham, Population and Lifespan Sciences, School of Medicine Cheah, Fook-Choe; Universiti Kebangsaan Malaysia, Department of Paediatrics, Faculty of Medicine Ojha, Shalini; University of Nottingham, Population and Lifespan Sciences, School of Medicine; University Hospitals of Derby and Burton NHS Foundation Trust, Neonatal Unit
Keywords:	Neonatology, Growth

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Nutrition and growth of preterm infants in the UK and Malaysia: prospective observational study

Haslina Binti Abdul Hamid[1,2], Lisa Szatkowski[1], Helen Budge[1], Fook Choe Cheah[3], Shalini Ojha[1,4]

Corresponding author: Shalini Ojha

Room 4117, Medical School Building, Royal Derby Hospital, Derby, DE23 3DT.

Email: shalini.ojha@nottingham.ac.uk

Telephone: +44 1332 724691

Haslina Binti Abdul Hamid

[1]Population and Lifespan Sciences, School of Medicine, University of Nottingham, UK

[2]Dietetic Programme, Faculty of Health Sciences, Universiti Kebangsaan Malaysia, 50300 Kuala Lumpur

Lisa Szatkowski

[1]Population and Lifespan Sciences, School of Medicine, University of Nottingham, UK

Helen Budge

[1]Population and Lifespan Sciences, School of Medicine, University of Nottingham, UK

Fook Choe Cheah

[3]Department of Paediatrics, Faculty of Medicine, Universiti Kebangsaan Malaysia, 56000 Kuala Lumpur

Shalini Ojha

[1]Population and Lifespan Sciences, School of Medicine, University of Nottingham, UK

[4]Neonatal Unit, University Hospitals of Derby and Burton, Derby, DE23 3DT

Word Count: 2485

Key words: infant, preterm, nutrition, growth

ABSTRACT

Objective To compare nutritional practices among preterm infants in neonatal units in Malaysia and the UK and assess the association with weight changes at discharge.

Design Prospective observational study of infants born <34 weeks gestational age (GA).

Setting Two neonatal units, one in Malaysia and one in the UK.

Methods Nutrition and growth data were collected from birth between May 2019 to March 2020 and compared between units. Factors associated with changes in weight-for-age Z-score (WAZ) at discharge were analysed.

Results From 100 infants included, median GA (IQR) was 31(30-33) and mean±SD birthweight was 1549±444g. Malaysian infants were smaller and had more morbidities. More of them received fortified breastmilk and parenteral nutrition with higher protein intake (mean±SD Malaysia: 3.0±0.5 vs UK: 2.7±0.6g/kg/d, p=0.004) in weeks 1-4 and had smaller cumulative protein deficits (mean±SD Malaysia: 11.4±6.1 vs UK: 15.4±8.0g/kg, p=0.006). More than half of the infants in both units had >-1.28 changes in WAZ at discharge (p=0.841). Length of stay was negatively associated with changes in WAZ in Malaysian infants (adjusted β of -0.01, p<0.001). In the UK unit, protein and protein energy ratio were positively associated with changes in WAZ (adjusted β of 0.36 and 0.34, p=0.004 and 0.027).

Conclusions There were differences in patient characteristics, nutritional practices and intakes. Weight changes among Malaysian infants were influenced by non-nutritional factors despite numerically sufficient intakes. In the UK, low protein intakes affected weight. Nutritional recommendations should take local demographics into consideration and optimising intakes should be prioritised.

Word count: 247

What is already known on this topic

1. There is a high rate of postnatal growth failure among preterm infants in neonatal units worldwide.

2. Varied nutritional practices such as parenteral nutrition and protein intakes are independent predictors of the growth outcomes of preterm infants at discharge.

What this study adds

1. Preterm infants' co-morbidities which possibly lead to longer hospital stay might be associated with growth failure at discharge.

2. Protein deficits are independently associated with growth failure at discharge.

3. Current nutrient recommendations should be modified to target infants of lower gestations and those at-risk of severe co-morbidities.

4. Demographic and nutritional practice differences affecting growth outcomes in preterm infants between the countries with upper- middle- and high-incomes

INTRODUCTION

Growth is one of the most important outcomes in determining the well-being of a preterm infant (1), and provision of optimal nutrition is a modifiable independent factor that could facilitate growth (2). Recommendations such as early initiation of parenteral nutrition (PN) and enteral nutrition (EN), shorter time in reaching full enteral feeding and the use of breast milk fortifier (BMF) may optimise growth outcomes in preterm infants (3). However, it is uncertain whether similar recommendations can be applied to different settings in which preterm infants are cared for. Factors such as clinical traditions and resource limitations in hospitals may influence the adoption of effective feeding practices (4). Internationally, nutritional recommendations (5,6) have been created and studied for preterm populations in the UK (7), USA (8) and other high-income settings (9). However, there is a paucity of studies in this area among low- and middle-income countries, despite the growing availability of neonatal intensive care in these settings. This study compares nutritional practices in a neonatal unit in Malaysia, as a lower income setting, with one in the UK. Secondly, the study investigates the association between the nutritional practices and postnatal growth in both units.

METHODS

The study was carried out in the neonatal units of the Royal Derby Hospital, UK and the Hospital Canselor Tuanku Muhriz, Malaysia, from May 2019 to March 2020. The UK unit is a Local Neonatal Unit (level II) (10) routinely caring for infants born at >25 weeks GA. More immature infants and those requiring surgical care are transferred to appropriate centres. The Malaysia unit is a tertiary neonatal unit (level IIIb) (11) which also provides surgical support on-site (except for cardiac surgery).

Infants <34 weeks' GA who were admitted to either unit were recruited consecutively and followed to discharge until the sample size of 50 was reached at

each site. Infants were included if admitted within 24 hours of birth, not transferred out for any part of their care and had length of stay of ≥ 14 days. Infants with major congenital anomalies, genetic abnormalities or missing records for ≥3 days were excluded. The number of infants included was determined based on the usual monthly admissions and length of stay at the respective units which was estimated to be from 30 to 50 infants. Therefore, collection of data from 50 infants from each unit (total of 100) was deemed to be feasible.

Anonymised data were extracted from paper or electronic medical records (accessed from BadgerNet (Client version 2.9.1.0) in the UK, and the Caring Hospital Enterprise System (C-HEtS) in Malaysia).

Baseline and feeding data

Infant and maternal characteristics including sex, GA at birth, maternal age, and parity as well as infants' clinical characteristics were collected prospectively. Daily nutritional intakes including parenteral nutrition (PN) and enteral nutrition (EN) were recorded. The nutritional content of EN and PN were calculated based on the manufacturers' literature while the composition of breast milk was based on current evidence (12). Nutrient deficits were calculated as the difference between actual intake and the intake recommended by ESPGHAN (2010) guidelines (5).

Growth measures

Fenton growth chart (13) was used as a reference for all growth assessments in both units in determining Z-scores. It was chosen for this study for its advantage of using more recent and larger sample of preterm infants' data from many countries which link to the WHO growth data. In this study, only weight and head circumference (HC) measurements were assessed, as length is not routinely measured in the UK unit.

The marker for growth used in this study is the change in weight-for-age Z-scores (WAZ) from birth to discharge which was determined by subtracting the WAZ at birth from the WAZ at discharge. This was used due to the better sensitivity of weight than HC measurements in determining short term growth and Z-score as the best system for presentation and evaluation of anthropometric data (14) especially in indicating change over time. Postnatal growth failure was defined as a decrease in WAZ between birth and discharge of ≥ 1.28 as used in previous studies (15,16). SGA was defined as birth weight < 10th centile for birth weight (17).

Statistical analysis

All statistical analyses were performed using STATA 16.0 (Stata Corp. College Station, TX). Descriptive statistics were used to summarise the demographic and clinical characteristics of infants and their mothers. Infants' EN, PN and combined intakes in weeks 1-4 and weeks 5-8 and the cumulative deficits accrued in this period were analysed. Growth outcomes and other variables collected at discharge were also compared.

Univariable analyses were used to explore factors that predicted changes in WAZ separately for each unit. In the exploratory analysis, variables with missing data such as intakes on weeks 5-8 for infants who were discharged before this period were excluded. Rare clinical conditions where fewer than 10 babies experienced that outcome were also excluded. Variables which were statistically significant at the 5% significance level in the univariable analysis and considered clinically important, were entered into a multivariable model. Likelihood ratio tests were used to build a final parsimonious multivariable model. Correlation between variables was assessed using the variance inflation factor (VIF) with a VIF of less than 5 taken to indicate no substantial correlation (18).

Regulatory approvals

Ethical approval was obtained from the Health Research Authority (HRA) and Health and Care Research Wales (HCRW) Approval (United Kingdom) [IRAS project ID: 258817, Protocol number: 19012] and Research Ethics Committee, National University of Malaysia, UKM (Malaysia) [JEP-2019-325]. No parental consent was sought as this was an observational study using routinely recorded clinical data.

Patient and Public Involvement

Patients or the public were not involved in the design, conduct, reporting or distribution plans of our study.

RESULTS

In this study, infants in Malaysia and the UK units were of similar GA, but Malaysian infants were lighter and had a lower WAZ and length-for-age Z-scores at birth although the HC Z-scores were not different (Table 1). There were more SGA infants in Malaysia (12/50; 24%) compared to the UK unit (3/50; 6%) (p=0.039). In Malaysia unit, there were fewer multiple births, more morbidities, mothers were older and had had more previous births (Table 1).

Enteral feeding

Milk feeding was started on median day of life (DOL) of 2 (p=0.833) in both units. Full milk feeds (defined as 150 ml/kg/day EN with no PN) was reached on median (IQR) DOL 9 (7-12) in Malaysia and DOL 8 (7-10) in the UK, p=0.400 (Table 2).

More infants in Malaysia received any mother's own milk (MOM) during admission (Malaysia: 98% vs UK: 76%, p=0.001) and more infants in the UK received formula

milk (Malaysia: 80% vs. UK: 94%, p=0.037). Among infants who were fed their MOM, 86% infants had BMF added on median (IQR) DOL 11 (8-16) in Malaysia when they were receiving a median (IQR) milk volume of 154 (149-164) ml/kg/d while 26% infants had BMF added on median (IQR) DOL 15 (10-20) at median (IQR) milk volume of 157 (132-167) ml/kg/d, p=0.655 in the UK. At discharge, 52% infants were exclusively breast milk-fed in Malaysia compared to 32% in the UK (p=0.043) (Table 2).

Parenteral feeding

40 (80%) infants received PN in Malaysia compared to 19 (38%) in the UK. PN was started on a median DOL 2 in both units (p=0.414) but was given for longer in Malaysia than in the UK (median (IQR) days of PN in Malaysia: 9 (6-14) vs. UK: 6 (5-8), p=0.031 (Table 2).

Nutritional intakes

There was no difference in energy intakes in weeks 1-4 between the two units (p=0.238). However, Malaysian infants received more protein (Malaysia: 3.0±0.5 g/kg/d vs UK: 2.7±0.6 g/kg/d, p=0.004) and had smaller cumulative energy and protein deficits over this period, than the UK infants (Malaysia (energy): 191.6±129.8 vs UK: 254.5±152.0 kcal/kg, p=0.028 and Malaysia (protein):11.4±6.1 vs UK: 15.4±8.0g/kg, p=0.006). Protein energy ratio (PER) was also higher in the Malaysia unit (Malaysia: 3.03±0.31 g/100kcal/d vs. UK: 2.61±0.48 g/100kcal/d, p<0.001) (Table 2).

For those infants who remained in the hospital in weeks 5-8 of life (Malaysia: n=28, UK: n=23), better energy intakes were shown in both units although energy deficits in the UK cohort persisted. No difference in protein intakes was found between units but cumulative protein deficits in Malaysian infants improved while the magnitude of

the deficit worsened in UK infants (Malaysia: 8.7±11.8 g/kg vs UK: 24.5 ±25.6 g/kg, p=0.005).

Postnatal growth

There were no differences in growth outcomes at discharge between infants from the two units (Table 3). WAZ declined by ≥1.28 in 52% and 54% of infants in Malaysia and the UK, respectively. The mean±SD change in WAZ between birth and discharge was similar between the two cohorts (Malaysia: -1.31±0.57; UK: -1.33 ±0.58; p=0.975) (Table 3).

Factors associated with change in WAZ from birth to discharge

In Malaysia, in univariable analyses, birthweight, HC and length at birth, GA at birth, being very/extremely preterm/low birthweight, length of stay, diagnosis of IVH and CLD, the use of IV fluid, PN, duration of PN, and DOL to reach full feed and first BMF use, were associated with changes in WAZ at discharge. After adjustment, the final multivariable regression model showed that length of stay was the only predictor that remained significant, showing negative changes in WAZ with longer hospital stay (adjusted β of -0.01, p<0.001, adjusted R^2 of 0.35) (Table 4).

In the UK, birthweight Z-score, mother's age, length of stay, protein intake in weeks 1-4, PER in weeks 1-4 and DOL reaching full enteral feeds, were significant in univariable models and remained so in the multivariable model (adjusted R^2 of 0.62). Of these variables, protein intakes and PER weeks 1-4 showed positive association with growth at discharge, indicating improved changes in WAZ with higher intakes of protein and PER in weeks 1-4 (Table 4).

DISCUSSION

The study found that more Malaysian infants received breast milk as compared to UK infants. This is consistent with each countries' national reports (19,20) that record a higher rate of breastfeeding among Malaysian infants. The higher rate of breastmilk feeding among Malaysian infants is possibly related to older maternal age and higher parity among mothers, as shown in many studies (21,22). The Malaysian unit has an established accreditation as Baby Friendly Hospital (BFH) (23) which is favourably related to the high rate of initiation and continuation of breastfeeding (24,25). The UK unit has achieved stage 1 of BFI accreditation and is building towards a stage 2 (26).

More Malaysian infants received PN which could be related to more SGA infants and higher rates of co-morbidities in this level IIIb unit where clinicians are more likely to give PN to enhance nutrition. Infants in the UK unit were larger and less unwell and hence more likely to establish enteral feeding and avoid initial or prolonged need for PN. Furthermore, more BMF use and higher use of protein supplementation were also practiced in Malaysia unit, while BMF was used more selectively in the UK unit. These distinctions in practice possibly explain the differences in nutrient intakes where Malaysian infants had higher protein intakes, lower cumulative deficits and earlier recovery of deficits.

Despite the differences in intakes, weight changes were similar in both units. Hospital stay was shown to be the only predictor for WAZ changes at discharge for Malaysian infants. This may be ~~as~~ due to smaller infants with greater burden of illnesses have longer stay and sub-optimal growth (27,28). In addition, more aggressive nutritional practices are practiced in Malaysia unit, enabling faster weight gain among clinically stable infants. This is to encourage earlier discharge due to limited space and resources in the unit, while sicker infants stay longer.

However, hospital stay accounted for only 35% of variation in changes in WAZ in this cohort. The remaining unexplained variation could be a combination of several other underlying factors. For example, this study shows that Malaysian infants were generally lighter and shorter than infants in the UK. This could be attributed to genetic influence (29) and generally higher rates of LBW in Malaysian infants as previously reported (30). However, there is a possibility that these differences are not entirely genetic and factors such as maternal and in-utero undernutrition underlie the smaller size at birth especially as there was no difference observed in HC between the two units (31).

In the UK unit, protein intakes and PER, which accounted for the largest variation in changes in WAZ, have also been shown to affect postnatal growth in previous studies (9,32). Even though formula milk offers higher protein intakes than unfortified breast milk (33,34), MOM is the optimal food for preterm infants and can be fortified when needed. Nearly half of the infants in this cohort received a mix of formula milk (2.0-2.6g protein/100ml) and unfortified breast milk (1.3-1.9 g protein/100ml). However, as a group, they did not achieve the recommended intake at 3.5 g/kg/d. Previous studies show that protein intakes aimed at >3.5-3.8 g/kg/d led to decreased cumulative deficits and better growth (35,36). Fortifying breast milk in more infants would increase protein intake although this would also involve using a cow's milk product and interfere with the exclusive breast milk feeding at least in some infants.

Despite notable differences in intake, there were no differences in the short-term growth at discharge between the units. The differences in infant characteristics, possibly co-morbidities may explain this. Therefore, with this data, it would be pertinent to re-evaluate if the current nutritional recommendations (5) used should

be similarly applied for all preterm infants considering the heterogeneity in intrauterine growth and co-morbidities that might affect growth. Besides, pushing for more aggressive nutrition to achieve target weights should be considered with caution, as 'optimal growth' outcome should also include longer-term growth and the neurodevelopmental and metabolic outcomes in later life. Studies show that preterm infants fed mainly breast milk have slower weight gain but show better neurodevelopmental outcomes (37,38).

The strengths of this study are that it is a two-centre cohort study with detailed daily actual nutritional intake and weekly growth data collected prospectively. However, the study is limited to a small number of infants and a larger sample size is needed to further evaluate reasons for growth failure. Maternal details including nutritional status and antenatal care should also be considered as these are vital determinants of fetal nutrition and infants' outcomes (39). Also, the predominant use of breastmilk, especially in Malaysian cohort, means that intakes were analysed by using the best available estimates (12) and may not reflect the true nutritional composition of the milk received.

CONCLUSION

Current nutritional practices often do not meet recommended intakes in preterm infants. Early use of PN and EN with fortified breast milk may improve nutrient intakes. More efforts are needed to produce evidence-based nutritional intake recommendations for settings that care for a large number of smaller or sicker infants. Follow-up in later life is then needed to determine if meeting recommended nutritional targets produces better quality growth and neurodevelopmental outcomes in those born preterm.

Acknowledgements We would like to acknowledge the support of all the staff at Royal Derby Hospital and Hospital Canselor Tuanku Muhriz neonatal units for their assistance during the data collection process of this study. We also would like to acknowledge Janine Abramson and Coral Smith who assisted in the electronic data collection in the UK unit, Drs Cho Cho Latt and Tian-Lee Tan for the data collection in Malaysia unit.

Contributors HAH, SO, LS, HB and FCC conceptualised and designed the study and reviewed and revised the manuscript. HAH performed the data collection in the UK unit, completed the data analysis and drafted the initial manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Funding HAH is supported by a PhD scholarship from the Ministry of Higher Education Malaysia and Universiti Kebangsaan Malaysia (UKM).

Competing interests None declared.

Patient consent Not required.

Provenance and peer review Yes

References

1. Young A, Andrews ET, Ashton JJ, Pearson F, Beattie RM, Johnson MJ. Generating longitudinal growth charts from preterm infants fed to current recommendations. Arch Dis Child - Fetal Neonatal Ed. 2020 Nov;105(6):646–51.

2. Stoltz Sjöström E, Öhlund I, Ahlsson F, Engström E, Fellman V, Hellström A, et al. Nutrient intakes independently affect growth in extremely preterm infants: Results from a population-based study. Acta Paediatr Int J Paediatr. 2013;102(11):1067–74.

3. Maas C, Poets CF, Franz AR. Avoiding postnatal undernutrition of vlbw infants during neonatal intensive care: Evidence and personal view in the absence of evidence. Arch Dis Child Fetal Neonatal Ed. 2015;100(1):F76–81.

4. de Waard M, Li Y, Zhu Y, Ayede AI, Berrington J, Bloomfield FH, et al. Time to Full Enteral Feeding for Very Low-Birth-Weight Infants Varies Markedly Among Hospitals Worldwide But May Not Be Associated With Incidence of Necrotizing

Enterocolitis: The NEOMUNE-NeoNutriNet Cohort Study. J Parenter Enter Nutr. 2018;

5. Agostoni C, Buonocore G, Carnielli VP, De Curtis M, Darmaun D, Decsi T, et al. Enteral nutrient supply for preterm infants: Commentary from the european society of paediatric gastroenterology, hepatology and nutrition committee on nutrition. J Pediatr Gastroenterol Nutr. 2010;50(1):85–91.

6. Koletzko B, Poindexter B, Uauy R. Nutrition of the preterm infant: Scientific Basis and Practical Guidelines. Basel: Karger; 2014.

7. Andrews ET, Ashton JJ, Pearson F, Mark Beattie R, Johnson MJ. Early postnatal growth failure in preterm infants is not inevitable. Arch Dis Child Fetal Neonatal Ed. 2018;10–2.

8. Horbar JD, Ehrenkranz RA, Badger GJ, Edwards EM, Morrow KA, Soll RF, et al. Weight Growth Velocity and Postnatal Growth Failure in Infants 501 to 1500 Grams: 2000-2013. Pediatrics. 2015;136(1):e84–92.

9. Cormack BE, Jiang Y, Harding JE, Crowther CA, Bloomfield FH. Relationships between Neonatal Nutrition and Growth to 36 Weeks' Corrected Age in ELBW Babies–Secondary Cohort Analysis from the Provide Trial. Nutrients. 2020 Mar 13;12(3):760.

10. British Association of Perinatal Medicine (BAPM) (2010). Service standards for hospitals providing neonatal care, 3rd edition. [Internet]. 2010. Available from: http://www.bapm.org/publications/documents/guidelines/BAPM_Standards_Final_Au g2010.pdf

11. Ministry of Health Malaysia. The Operational Policy for Paediatric Services. he Medical Services Development Section; 2012.

12. Gidrewicz DA, Fenton TR. A systematic review and meta-analysis of the nutrient content of preterm and term breast milk. BMC Pediatr. 2014 Aug 30;14:216.

13. Fenton T, Kim J. A systematic review and meta-analysis to revise the Fenton growth chart for preterm infants. BMC Pediatr. 2013;13:59.

14. Geneva: World Health Organization. Physical status: the use and interpretation of anthropometry. Report of a WHO Expert Committee. WHO Technical Report Series No. 854. 1995.

15. Lin Z, Green RS, Chen S, Wu H, Liu T, Li J, et al. Quantification of EUGR as a measure of the quality of nutritional care of premature infants. PLoS ONE. 2015;10(7):1–10.

16. Lee SM, Kim N, Namgung R, Park M, Park K, Jeon J. Prediction of Postnatal Growth Failure among Very Low Birth Weight Infants. Sci Rep. 2018;8(1):1–8.

17. Darmaun D, Lapillonne A, Simeoni U, Picaud J-C, Rozé J-C, Saliba E, et al. Parenteral nutrition for preterm infants: Issues and strategy. Arch Pediatr Organe Off Soc Francaise Pediatr. 2018 May;25(4):286–94.

18. Kim J. Multicollinearity and misleading statistical results. Korean J Anesthesiol. 2019 Dec 1;72(6):558–69.

19. Institute for Public Health. The National Health and Morbidity Survey (NHMS) 2016 [Internet]. Kuala Lampur: Institute for Public Health, National Institutes of Health, Ministry of Health Malaysia; 2016. Available from: http://iku.moh.gov.my/images/IKU/Document/REPORT/2016/NHMS2016ReportVolumeII-MaternalChildHealthFindingsv2.pdf

20. NHS Maternity Statistics, England 2017-18. Maternity and Breastfeeding [Internet]. Available from: https://www.england.nhs.uk/statistics/statistical-work-areas/maternity-and-breastfeeding/

21. Casey PH, Whiteside-Mansell L, Barrett K, Bradley RH, Gargus R. Impact of prenatal and/or postnatal growth problems in low birth weight preterm infants on school-age outcomes: an 8-year longitudinal evaluation. Pediatrics. 2006 Sep;118(3):1078–86.

22. Bonnet C, Blondel B, Piedvache A, Wilson E, Bonamy AE, Gortner L, et al. Low breastfeeding continuation to 6 months for very preterm infants: A E uropean multiregional cohort study. Matern Child Nutr [Internet]. 2019 Jan [cited 2021 Feb 15];15(1). Available from: https://onlinelibrary.wiley.com/doi/abs/10.1111/mcn.12657

23. Ministry of Health Malaysia. National Breastfeeding Policy 2005 [Internet]. 2005. Available from: http://nutrition.moh.gov.my/wp-content/uploads/penerbitan/poster/polisi%20penyusuan%20ibu.jpg

24. Spaeth A, Zemp E, Merten S, Dratva J. Baby-Friendly Hospital designation has a sustained impact on continued breastfeeding. Matern Child Nutr. 2018 Jan;14(1):e12497.

25. Broadfoot M, Britten J, Tappin DM, MacKenzie JM. The Baby Friendly Hospital Initiative and breast feeding rates in Scotland. Arch Dis Child Fetal Neonatal Ed. 2005 Mar;90(2):F114-116.

26. UNICEF UK. Accreditation [Internet]. 2019. Available from: https://www.unicef.org.uk/babyfriendly/accreditation/

27. Maier RF, Blondel B, Piedvache A, Misselwitz B, Petrou S, Van Reempts P, et al. Duration and Time Trends in Hospital Stay for Very Preterm Infants Differ Across European Regions*: Pediatr Crit Care Med. 2018 Dec;19(12):1153–61.

28. Zainal H, Dahlui M, Soelar SA, Su TT. Cost of preterm birth during initial hospitalization: A care provider's perspective. Isangula KG, editor. PLOS ONE. 2019 Jun 25;14(6):e0211997.

29. Chen ST. Growth chart based on longitudianal study of Malaysian children from birth to six years. Med J Malays. 1985 Jun;40(2).

30. United Nations Children's Fund (UNICEF), World Health Organization (WHO). UNICEF-WHO Low birthweight estimates: Levels and trends 2000–2015 [Internet]. Geneva: World Health Organization; 2019. Available from: https://apps.who.int/iris/bitstream/handle/10665/324783/WHO-NMH-NHD-19.21-eng.pdf?ua=1

31. Fleiss B, Wong F, Brownfoot F, Shearer IK, Baud O, Walker DW, et al. Knowledge Gaps and Emerging Research Areas in Intrauterine Growth Restriction-Associated Brain Injury. Front Endocrinol. 2019 Mar 29;10:188.

32. Fenton TR, Al-Wassia H, Premji SS, Sauve RS. Higher versus lower protein intake in formula-fed low birth weight infants. Cochrane Neonatal Group, editor. Cochrane Database Syst Rev [Internet]. 2020 Jun 23 [cited 2020 Oct 21]; Available from: http://doi.wiley.com/10.1002/14651858.CD003959.pub4

33. Schanler RJ, Shulman RJ, Lau C, Smith EO, Heitkemper MM. Feeding strategies for premature infants: randomized trial of gastrointestinal priming and tube-feeding method. Pediatrics. 1999 Feb;103(2):434–9.

34. Carlson SJ, Ziegler EE. Nutrient intakes and growth of very low birth weight infants. J Perinatol Off J Calif Perinat Assoc. 1998 Aug;18(4):252–8.

35. Senterre T, Rigo J. Reduction in postnatal cumulative nutritional deficit and improvement of growth in extremely preterm infants. Acta Paediatr Int J Paediatr. 2012;101(2):64–70.

36. Embleton NE, Pang N, Cooke RJ. Postnatal Malnutrition and Growth Retardation: An Inevitable Consequence of Current Recommendations in Preterm Infants? Pediatrics. 2001;107(2):270–3.

37. Rozé J-C, Darmaun D, Boquien C-Y, Flamant C, Picaud J-C, Savagner C, et al. The apparent breastfeeding paradox in very preterm infants: relationship between breast feeding, early weight gain and neurodevelopment based on results from two cohorts, EPIPAGE and LIFT. BMJ Open. 2012 Jan 1;2(2):e000834.

38. Vohr BR, Poindexter BB, Dusick AM, McKinley LT, Higgins RD, Langer JC, et al. Persistent beneficial effects of breast milk ingested in the neonatal intensive care unit on outcomes of extremely low birth weight infants at 30 months of age. Pediatrics. 2007 Oct;120(4):e953-959.

39. McCowan L, Roberts C, Dekker G, Taylor R, Chan E, Kenny L, et al. Risk factors for small-for-gestational-age infants by customised birthweight centiles: data from an international prospective cohort study: Risk factors for SGA infants by customised centiles. BJOG Int J Obstet Gynaecol. 2010 Dec;117(13):1599–607.

Tables

Table 1: Infant and maternal characteristics of infants born at <34 weeks' gestational age and cared for in a neonatal unit in Malaysia and one in the UK

Variables	Infants in the Malaysian unit n=50	Infants in the UK unit n=50	p-value
Female, n (%)	21 (42)	22 (44)	0.84
Gestational age at birth (weeks) median (IQR)	32 (29-32, 25-33)	31 (30-33, 26-33)	0.736
Birthweight (grams) mean (SD)	1448 (458)	1649 (409)	0.022
Birthweight-for-age z-score mean (SD)	-0.53 (0.93)	-0.10 (0.70)	0.009
Small for gestational age, n (%)	12 (24)	3 (6)	0.012
HC at birth (cm), mean (SD)	28 (2.68)	28.9 (2.35)	0.106
HC-for-age z-score at birth Mean (SD)	-0.26 (-0.98 to 0.59, -4.2 to 2.05)	0.06 (-0.57 to 0.59, -3.3 to 1.54)	0.310
Length at birth (cm) mean (SD)	38.4 (3.65)	41.9 (4.08)	<0.001
Length at birth-for-age z-score mean (SD)	-0.92 (1.05)	0.21(1.23)	<0.001
Singleton birth, n (%)	45 (90)	34 (68)	0.007
Mother's age (years) mean (SD)	32 (5)	29 (5)	0.009
Parity, median (IQR)	3 (1-4, 1-8)	0 (0-1, 0-6)	<0.001
Caesarean section, n (%)	37 (74)	32 (64)	0.280
Apgar score at 5 minutes, median (IQR)	9 (8-10, 3-10)	9 (9, 6-10)	0.844
Antenatal steroid use, n (%)	47 (94)	42 (84)	0.194
Received positive pressure ventilation, n (%)	21 (42)	27 (54)	0.230
Late onset sepsis (confirmed), n (%)	13 (26)	4(8)	<0.001
Necrotising enterocolitis (suspected), n (%)	6 (12)	3 (6)	0.243
Intraventricular haemorrhage, n (%)	36 (72)	2 (4)	<0.001
Retinopathy of prematurity, n (%)	4 (8)	1 (2)	0.181
Periventricular leukomalacia, n (%)	7 (14)	0	0.006
Chronic lung disease, n (%)	10 (20)	3 (6)	0.036
Patent ductus arteriosus, n (%)	16 (32)	6 (12)	0.014

HC, head circumference; IQR, inter-quartile range; SD, standard deviation

Table 2: Feeding practices and nutritional intakes in infants born at <34 weeks' gestational age and cared for in a neonatal unit in Malaysia and one in the UK

Variables, n (%)	Malaysian group n=50	UK group n=50	p-value
Received any breast milk	49 (98)	38 (76)	0.001
Any breast milk at discharge	46 (92)	25 (50)	<0.001
Exclusively breast milk feeding at discharge	26 (52)	16 (32)	0.043
Received infant formula milk	40 (80)	47 (94)	0.037
Energy proportion (%) from breast milk**	66.5 (40-83)	15.5 (2-82)	0.010
Energy proportion (%) from formula milk±	19.2 (2.2-52.3)	78.8 (12.7-93.9)	<0.001
Day of life at first enteral milk feed**	2 (1-3)	2 (1-2)	0.833
Day of life reaching 120 mL/kg/d feed**	4 (4-5)	5 (4-5)	0.044
Day of life reaching full enteral feed at 150 ml/kg/d**	9 (7-12)	8 (7-10)	0.400
Rate of feeding advancement to full feed**	13 (6-16)	16 (9-20)	0.390
Received breast milk fortifier	43 (86)	13 (26)	<0.001
Day of life at first breast milk fortifier received±	11 (8-16)	15 (10-20)	0.039
Received parenteral nutrition	40 (80)	19 (38)	<0.001
Day of life at first parenteral nutrition**	2 (1-2)	2 (1-2)	0.414
Duration of parenteral nutrition**	9 (6-14)	6 (5-8)	0.031
Energy intake, kcal/kg/d*			
Week 1-4	103 (13)	100 (11)	0.238
Week 5-8	110 (18)	115 (15)	0.363
Cumulative energy deficits/excess±, kcal/kg*			
Week 1-4	-191.6 (129.8)	-254.5 (152.0)	0.028
Week 5-8	93.2(237.4)	-93.8 (539.3)	0.105
Protein intake, g/kg/d*			
Week 1-4	3.0 (0.5)	2.7 (0.6)	0.004
Week 5-8	3.4 (0.7	3.0 (0.8)	0.088
Cumulative protein deficits/excess±, g/kg*			
Week 1-4	-11.4 (6.1)	-15.4 (8.0)	0.006
Week 5-8	-8.7 (11.8)	-24.5 (25.6)	0.005
Protein energy ratio, g/100 kcal/d*			
Week 1-4	2.82 (0.28)	2.61 (0.48)	0.008
Week 5-8	3.03 (0.31)	2.57 (0.38)	<0.001
Fat intake, g/kg/d*			
Week 1-4	4.8 (0.7)	4.8 (0.6)	0.627
Week 5-8	5.3 (1.0)	5.8 (0.7)	0.058
Carbohydrate intake, g/kg/d*			
Week 1-4	11.4 (1.9)	10.7(1.4)	0.020
Week 5-8	11.9 (2.0)	12.2(1.7)	0.607
Fluid intake, ml/kg/d*			
Week 1-4	137.1 (12.9)	138.8 (10.9)	0.491
Week 5-8	141.4 (22.4)	153.9 (13.9)	0.024

**Median (IQR); * Mean (SD); ±Negative value indicates deficits

Table 3: Postnatal growth measurements in infants born at <34 weeks' gestational age and cared for in a neonatal unit in Malaysia and one in the UK

Variables	Malaysia n=50	UK n=50	MD (95% CI)	p-value
Days to regain birth weight**	12 (11-14)	13 (10-16)	-0.08 (-0.14 to -0.01)	0.247
Weight (g) at discharge**	2060 (1890-2390)	2165 (2050-2380)	-0.001 (-0.001 to -0.0001)	0.221
Weight Z-score at discharge**	-1.65 (-2.3 to-1.0)	-1.3 (-1.8 to-0.80)	-0.25 (-0.32 to-0.19)	0.088
Changes in weight Z-score from birth to discharge*	-1.31 (0.57)	-1.33 (0.58)	0.01 (-0.22 to 0.23)	0.975
Infants with weight Z- score change ≥-1.28 from birth to discharge, n (%)	26 (52)	27 (54)	-	0.841
Head circumference at discharge, (cm)*	31.5 (1.61)	31.4 (1.39)	0.34(-0.29 to 0.98)	0.287
Head circumference Z-score at discharge**	-1.33 (-1.69 to -0.59)	-0.91 (-1.61 to -0.4)	-0.14 (-0.53 to 0.26)	0.383
Gestational age at discharge**	36.5 (35-38)	36 (35-37)	0.13 (0.08 to 0.17)	0.060
Length of stay (days) **	36 (22-55)	28.5 (20-52)	0.01 (-0.00 to 0.03)	0.157

** Median (IQR); * Mean (SD)

Table 4: Factors associated with the change in weight-for-age Z-score between birth and discharge

Factors	Malaysia		UK	
	Unadjusted β (95% CI), p-value	**Adjusted β (95% CI), p-value**	**Unadjusted β (95% CI), p-value**	**Adjusted β (95% CI), p-value**
Maternal and infant characteristics				
Mother's age (years)	-0.02 (-0.05 to 0.01), p=0.159		-0.04 (-0.07 to -0.02), p=0.003	-0.03 (-0.05 to -0.01) p=0.011
Birthweight-for-age Z-score	0.06 (-0.11 to 0.24), p= 0.482		-0.25 (-0.48 to -0.02), p=0.038	-0.29 (-0.45 to -0.13), p=0.001
Length of stay	-0.01(-0.02 to -0.01), p<0.001	-0.01 (-0.02 to -0.01), p<0.001	-0.01(-0.02 to 0.001), p=0.065	-0.01 (-0.02 to -0.005), p=0.001
Day of life reaching full enteral feed	-0.05 (-0.08 to -0.02), p=0.001		-0.08 (-0.14 to -0.02), p=0.013	-0.05 (-0.09 to -0.004), p=0.030
Nutritional intakes in weeks 1-4				
Protein intake, g/kg/d	-0.21(-0.51 to 0.10) p=0.178		0.47 (0.20 to 0.74), p=0.001	0.36 (0.12 to 0.59), p=0.004
Protein energy ratio, g/100kcal/d	-0.41(-0.98 to 0.16), p=0.158		0.48 (0.15 to 0.80), p=0.005	0.34 (0.04 to 0.65), p=0.027

Adjusted β values are displayed only for variables that are included in the final model of regression

BMJ Paediatrics Open

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Journal:	*BMJ Paediatrics Open*
Manuscript ID	bmjpo-2021-001153.R1
Article Type:	Original research
Date Submitted by the Author:	09-Jul-2021
Complete List of Authors:	Abdul Hamid, Haslina; University of Nottingham, Population and Lifespan Sciences, School of Medicine; Universiti Kebangsaan Malaysia, Dietetic Programme, Faculty of Health Sciences Szatkowski, Lisa; University of Nottingham, Population and Lifespan Sciences, School of Medicine Budge, Helen; University of Nottingham, Population and Lifespan Sciences, School of Medicine Cheah, Fook-Choe; Universiti Kebangsaan Malaysia, Department of Paediatrics, Faculty of Medicine Ojha, Shalini; University of Nottingham, Population and Lifespan Sciences, School of Medicine; University Hospitals of Derby and Burton NHS Foundation Trust, Neonatal Unit
Keywords:	Neonatology, Growth

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Nutritional practices and growth of preterm infants in two neonatal units in the UK and Malaysia: a prospective observational study

Haslina Binti Abdul Hamid[1,2], Lisa Szatkowski[1], Helen Budge[1], Fook Choe Cheah[3], Shalini Ojha[1,4]

Corresponding author: Shalini Ojha

Room 4117, Medical School Building, Royal Derby Hospital, Derby, DE23 3DT.

Email: shalini.ojha@nottingham.ac.uk

Telephone: +44 1332 724691

Haslina Binti Abdul Hamid

[1]Population and Lifespan Sciences, School of Medicine, University of Nottingham, UK

[2]Dietetic Programme, Faculty of Health Sciences, Universiti Kebangsaan Malaysia, 50300 Kuala Lumpur

Lisa Szatkowski

[1]Population and Lifespan Sciences, School of Medicine, University of Nottingham, UK

Helen Budge

[1]Population and Lifespan Sciences, School of Medicine, University of Nottingham, UK

Fook Choe Cheah

[3]Department of Paediatrics, Faculty of Medicine, Universiti Kebangsaan Malaysia, 56000 Kuala Lumpur

Shalini Ojha

[1]Population and Lifespan Sciences, School of Medicine, University of Nottingham, UK

[4]Neonatal Unit, University Hospitals of Derby and Burton, Derby, DE23 3DT

Word Count: 2485

Key words: infant, preterm, nutrition, growth

ABSTRACT

Objective To compare nutritional practices among preterm infants in neonatal units in Malaysia and the UK and assess the association with weight changes at discharge.

Design Prospective observational study of infants born <34 weeks gestational age (GA).

Setting Two neonatal units, one in Malaysia and one in the UK.

Methods Nutrition and growth data were collected from birth between May 2019 to March 2020 and compared between units. Factors associated with changes in weight-for-age Z-score (WAZ) at discharge were analysed.

Results From 100 infants included, median GA (IQR) was 31(30-33) and mean±SD birthweight was 1549±444g. Malaysian infants were smaller and had more morbidities. More of them received fortified breastmilk and parenteral nutrition with higher protein intake (mean±SD Malaysia: 3.0±0.5 vs UK: 2.7±0.6g/kg/d, p=0.004) in weeks 1-4 and had smaller cumulative protein deficits (mean±SD Malaysia: 11.4±6.1 vs UK: 15.4±8.0g/kg, p=0.006). More than half of the infants in both units had >-1.28 changes in WAZ at discharge (p=0.841). Length of stay was negatively associated with changes in WAZ in Malaysian infants (adjusted β of -0.01, p<0.001). In the UK unit, protein and protein energy ratio were positively associated with changes in WAZ (adjusted β of 0.36 and 0.34, p=0.004 and 0.027).

Conclusions There were differences in patient characteristics, nutritional practices and intakes. Weight changes among Malaysian infants were influenced by non-nutritional factors despite numerically sufficient intakes. In the UK, low protein intakes affected weight. Nutritional recommendations should take local demographics into consideration and optimising intakes should be prioritised.

Word count: 247

What is already known on this topic

1. There is a high rate of postnatal growth failure among preterm infants in neonatal units worldwide.
2. Varied nutritional practices such as parenteral nutrition and protein intakes are independent predictors of the growth outcomes of preterm infants at discharge.
3. Preterm infants' co-morbidities which possibly lead to longer hospital stay might be associated with growth failure at discharge.

What this study adds

1. Protein deficits are independently associated with growth failure at discharge.
2. Infants who are at-risk of severe co-morbidities need different targets for recommended nutrient intake.
3. Demographic and nutritional practice differences influencing the occurrence of postnatal growth failure in preterm infants between the countries with upper- middle- and high-incomes

INTRODUCTION

Growth is one of the most important outcomes in determining the well-being of a preterm infant (1), and provision of optimal nutrition is a modifiable independent factor that could facilitate growth (2). Recommendations such as early initiation of parenteral nutrition (PN) and enteral nutrition (EN), shorter time in reaching full enteral feeding and the use of breast milk fortifier (BMF) may optimise growth outcomes in preterm infants (3). However, it is uncertain whether similar recommendations can be applied to different settings in which preterm infants are cared for. Factors such as clinical traditions and resource limitations in hospitals may influence the adoption of effective feeding practices (4). Internationally, nutritional recommendations (5,6) have been created and studied for preterm populations in the UK (7), USA (8) and other high-income settings (9). However, there is a paucity of studies in this area among low- and middle-income countries, despite the growing availability of neonatal intensive care in these settings. This study compares nutritional practices in a neonatal unit in Malaysia, as a lower income setting, with one in the UK. Secondly, the study investigates the association between the nutritional practices and postnatal growth in both units.

METHODS

The study was carried out in the neonatal units of the Royal Derby Hospital, UK and the Hospital Canselor Tuanku Muhriz, Malaysia, from May 2019 to March 2020. The UK unit is a Local Neonatal Unit (level II) (10) routinely caring for infants born at >25 weeks GA. More immature infants and those requiring surgical care are transferred to appropriate centres. The Malaysia unit is a tertiary neonatal unit (level IIIb) (11) which also provides surgical support on-site (except for cardiac surgery). The two units have a similar number of preterm infant admissions (30-50 infants/month), number of beds and level of specific care in the unit. In RDH, the neonatal unit has 24 neonatal cots and caters to 6000-7000 birth per year, while in HCTM, its

neonatal unit has 26 cots and also caters to approximately 6000 birth per year. With an exception for not providing inhouse surgical support in the UK unit, both units provide similar types of care which comprises of care for the stable to intensive care infants. Both hospitals follow similar discharge criteria including weight of at least 1800g, not needing any additional medical support, and fully milk fed.

Infants <34 weeks' GA who were admitted to either unit were recruited consecutively and followed to discharge until the sample size of 50 was reached at each site. Infants were included if admitted within 24 hours of birth, not transferred out for any part of their care and had length of stay of ≥ 14 days. Infants with major congenital anomalies, genetic abnormalities or missing records for ≥3 days were excluded. The number of infants included was determined based on the usual monthly admissions and length of stay at the respective units which was estimated to be from 30 to 50 infants. Therefore, collection of data from 50 infants from each unit (total of 100) was deemed to be feasible within the time available for the study.

Anonymised data were extracted from paper or electronic medical records (accessed from BadgerNet (Client version 2.9.1.0) in the UK, and the Caring Hospital Enterprise System (C-HEtS) in Malaysia).

Baseline and feeding data

Infant and maternal characteristics including sex, GA at birth, maternal age, and parity as well as infants' clinical characteristics were collected prospectively. Daily nutritional intakes including parenteral nutrition (PN) and enteral nutrition (EN) were recorded. Volume of breast milk intakes were recorded only from bottle-feeding (expressed breast milk) as units do not routinely record before and after feeding weight for direct breastfeeding. The nutritional content of EN and PN were calculated based on the manufacturers' literature while the composition of breast

milk was based on current evidence (12). Nutrient deficits were calculated as the difference between actual intake and the minimum intake recommended by ESPGHAN (2010) guidelines (5).

Similar feeding protocols are used in both units. Generally, minimal enteral feeding (5-15ml/kg/d) is started within the first 24 hours. The units have guidelines on advancing feeds, promoting the use of mother's milk and the use of breast milk fortification and micronutrient supplementation.

Growth measures

Fenton growth chart (13) was used as a reference for all growth assessments in both units in determining Z-scores. It was chosen for this study for its advantage of using more recent and larger sample of preterm infants' data from many countries which link to the WHO growth data. In this study, only weight and head circumference (HC) measurements were assessed, as length is not routinely measured in the UK unit.

The marker for growth used in this study is the change in weight-for-age Z-scores (WAZ) from birth to discharge which was determined by subtracting the WAZ at birth from the WAZ at discharge. This was used due to the better sensitivity of weight than HC measurements in determining short term growth and Z-score as the best system for presentation and evaluation of anthropometric data (14) especially in indicating change over time. Postnatal growth failure was defined as a decrease in WAZ between birth and discharge of ≥ 1.28 as used in previous studies (15,16). SGA was defined as birth weight < 10th centile for birth weight (17).

Statistical analysis

All statistical analyses were performed using STATA 16.0 (Stata Corp. College Station, TX). Descriptive statistics were used to summarise the demographic and clinical characteristics of infants and their mothers. Infants' EN, PN and combined intakes in weeks 1-4 and weeks 5-8 and the cumulative deficits accrued in this period were analysed. Growth outcomes and other variables collected at discharge were also compared. The characteristics of infants and mothers, feeding practices as well as growth outcomes in the UK and Malaysia cohorts were compared using the Student's t-test or Mann-Whitney U test for continuous variables and by Chi squared or Fisher's exact tests for categorical variables, as appropriate. Mean or median difference and 95% confidence intervals were calculated for nutritional intakes and growth outcomes value comparison between sites.

Univariable analyses were used to explore factors that predicted changes in WAZ separately for each unit. In the exploratory analysis, variables with missing data such as intakes on weeks 5-8 for infants who were discharged before this period were excluded. Given the small sample size, clinical conditions where fewer than 10 babies experienced that outcome were also excluded. Variables which were statistically significant at the 5% significance level in the univariable analysis or those considered clinically important, were entered into a multivariable model. Likelihood ratio tests were used to build a final parsimonious multivariable model. Collinearity between variables was assessed using the variance inflation factor (VIF) with a VIF of less than 5 taken to indicate no substantial collinearity (18).

Regulatory approvals

Ethical approval was obtained from the Health Research Authority (HRA) and Health and Care Research Wales (HCRW) Approval (United Kingdom) [IRAS project ID: 258817, Protocol number: 19012] and Research Ethics Committee,

National University of Malaysia, UKM (Malaysia) [JEP-2019-325]. No parental consent was sought as this was an observational study using routinely recorded clinical data.

Patient and Public Involvement

Patients or the public were not involved in the design, conduct, reporting or distribution plans of our study.

RESULTS

In this study, infants in Malaysia and the UK units were of similar GA, but Malaysian infants were lighter and had a lower WAZ and length-for-age Z-scores at birth although the HC Z-scores were not different (Table 1). There were more SGA infants in Malaysia (12/50; 24%) compared to the UK unit (3/50; 6%) (p=0.039). In Malaysia unit, there were fewer multiple births, more morbidities, mothers were older and had had more previous births (Table 1).

Enteral feeding

Milk feeding was started on median day of life (DOL) of 2 (p=0.833) in both units. Full milk feeds (defined as 150 ml/kg/day EN with no PN) was reached on median (IQR) DOL 9 (7-12) in Malaysia and DOL 8 (7-10) in the UK, p=0.400 (Table 2).

More infants in Malaysia received any mother's own milk (MOM) during admission (Malaysia: 98% vs UK: 76%, p=0.001) and more infants in the UK received formula milk (Malaysia: 80% vs. UK: 94%, p=0.037). Among infants who were fed their MOM, 86% infants had BMF added on median (IQR) DOL 11 (8-16) in Malaysia when they were receiving a median (IQR) milk volume of 154 (149-164) ml/kg/d while 26% infants had BMF added on median (IQR) DOL 15 (10-20) at median

(IQR) milk volume of 157 (132-167) ml/kg/d, p=0.655 in the UK. At discharge, 52% infants were exclusively breast milk-fed in Malaysia compared to 32% in the UK (p=0.043) (Table 2).

Parenteral feeding

40 (80%) infants received PN in Malaysia compared to 19 (38%) in the UK. PN was started on a median DOL 2 in both units (p=0.414) but was given for longer in Malaysia than in the UK (median (IQR) days of PN in Malaysia: 9 (6-14) vs. UK: 6 (5-8), p=0.031 (Table 2).

Nutritional intakes

There was no significant difference in energy intakes in weeks 1-4 between the two units (p=0.238). However, Malaysian infants received more protein (Malaysia: 3.0±0.5 g/kg/d vs UK: 2.7±0.6 g/kg/d, p=0.004) and had smaller cumulative energy and protein deficits over this period, than the UK infants (Malaysia (energy): 191.6±129.8 vs UK: 254.5±152.0 kcal/kg, p=0.028 and Malaysia (protein):11.4±6.1 vs UK: 15.4±8.0g/kg, p=0.006). Protein energy ratio (PER) was also higher in the Malaysia unit (Malaysia: 3.03±0.31 g/100kcal/d vs. UK: 2.61±0.48 g/100kcal/d, p<0.001) (Table 2).

For those infants who remained in the hospital in weeks 5-8 of life (Malaysia: n=28, UK: n=23), better energy intakes were shown in both units although energy deficits in the UK cohort persisted. No significant difference in protein intakes was found between units but cumulative protein deficits in Malaysian infants improved while the magnitude of the deficit worsened in UK infants (Malaysia: 8.7±11.8 g/kg vs UK: 24.5 ±25.6 g/kg, p=0.005).

Postnatal growth

There were no significant differences in growth outcomes at discharge between infants from the two units (Table 3). WAZ declined by ≥1.28 in 52% and 54% of infants in Malaysia and the UK, respectively. The mean±SD change in WAZ between birth and discharge was similar between the two cohorts (Malaysia: -1.31±0.57; UK: -1.33 ±0.58; p=0.975) (Table 3).

Factors associated with change in WAZ from birth to discharge

In Malaysia, in univariable analyses, birthweight, HC and length at birth, GA at birth, being very/extremely preterm/low birthweight, length of stay, diagnosis of IVH and CLD, the use of IV fluid, PN, duration of PN, and DOL to reach full feed and first BMF use, were associated with changes in WAZ at discharge. After adjustment, the final multivariable regression model showed that length of stay was the only predictor that remained significant, showing negative changes in WAZ with longer hospital stay (adjusted β of -0.01, $p<0.001$, adjusted R^2 of 0.35) (Table 4).

In the UK, birthweight Z-score, mother's age, length of stay, protein intake in weeks 1-4, PER in weeks 1-4 and DOL reaching full enteral feeds, were significant in univariable models and remained so in the multivariable model (adjusted R^2 of 0.62). Of these variables, protein intakes and PER weeks 1-4 showed positive association with growth at discharge, indicating improved changes in WAZ with higher intakes of protein and PER in weeks 1-4 (Table 4).

DISCUSSION

The study found that more Malaysian infants received breast milk as compared to UK infants. This is consistent with each countries' national reports (19,20) that record a higher rate of breastfeeding among Malaysian infants. The higher rate of breastmilk feeding among Malaysian infants is possibly related to older maternal age and higher parity among mothers, as shown in many studies (21,22). The Malaysian unit has an established accreditation as Baby Friendly Hospital (BFH) (23) which is favourably related to the high rate of initiation and continuation of breastfeeding (24,25). The UK unit has achieved stage 1 of BFI accreditation and is building towards a stage 2 (26).

More Malaysian infants received PN which could be related to more SGA infants and higher rates of co-morbidities in this unit where clinicians are more likely to give PN to enhance nutrition. Infants in the UK unit were larger and less unwell and hence more likely to establish enteral feeding and avoid initial or prolonged need for PN. Furthermore, more BMF use and higher use of protein supplementation were also practiced in Malaysia unit, while BMF was used more selectively in the UK unit. The more frequent and longer use of PN and BMF resulted in differences in nutrient intakes particularly where Malaysian infants had higher protein intakes, lower cumulative deficits and earlier recovery of deficits. Additionally, any change to feeding strategies for the individual infants would also, understandably, be a response to infants' clinical conditions which might not be detected in this study.

Despite the differences in intakes, weight changes were similar in both units. Hospital stay was shown to be the only predictor for WAZ changes at discharge for Malaysian infants. This may be due to smaller infants with greater burden of illnesses have longer stay and sub-optimal growth (27,28) while larger, healthier infants are more likely to be discharged earlier. In addition, more aggressive

nutritional practices are practiced in Malaysia unit, enabling faster weight gain among clinically stable infants. This is to encourage earlier discharge due to limited space and resources in the unit, while sicker infants stay longer.

However, hospital stay accounted for only 35% of variation in changes in WAZ in this cohort. The remaining unexplained variation could be a combination of several other underlying factors. For example, this study shows that Malaysian infants were generally lighter and shorter than infants in the UK. This could be attributed to genetic influence (29) and generally higher rates of LBW in Malaysian infants as previously reported (30). However, there is a possibility that these differences are not entirely genetic and factors such as maternal and in-utero undernutrition underlie the smaller size at birth especially as there was no significant difference observed in HC between the two units (31).

In the UK unit, protein intakes and PER, which accounted for the largest variation in changes in WAZ, have also been shown to affect postnatal growth in previous studies (9,32). Even though formula milk offers higher protein intakes than unfortified breast milk (33,34), MOM is the optimal food for preterm infants and can be fortified when needed. Nearly half of the infants in this cohort received a mix of formula milk (2.0-2.6g protein/100ml) and unfortified breast milk (1.3-1.9 g protein/100ml). However, as a group, they did not achieve the recommended intake at 3.5 g/kg/d. Previous studies show that protein intakes aimed at >3.5-3.8 g/kg/d led to decreased cumulative deficits and better growth (35,36). Fortifying breast milk in more infants would increase protein intake although this would also involve using a cow's milk product and interfere with the exclusive breast milk feeding at least in some infants.

Despite notable differences in intake, there were no significant differences in the short-term growth at discharge between the units. The differences in infant characteristics, possibly co-morbidities may explain this. Therefore, with this data, it would be pertinent to re-evaluate if the current nutritional recommendations (5) used should be similarly applied for all preterm infants considering the heterogeneity in intrauterine growth and co-morbidities that might affect growth. Besides, pushing for more aggressive nutrition to achieve target weights should be considered with caution, as 'optimal growth' outcome should also include longer-term growth and the neurodevelopmental and metabolic outcomes in later life. Studies show that preterm infants fed mainly breast milk have slower weight gain but show better neurodevelopmental outcomes (37,38).

The strengths of this study are that it is a two-centre cohort study with detailed daily actual nutritional intake and weekly growth data collected prospectively. However, the study is limited to a small number of infants and a larger sample size is needed to further evaluate reasons for growth failure. Maternal details including nutritional status and antenatal care should also be considered as these are vital determinants of fetal nutrition and infants' outcomes (39). Also, the predominant use of breastmilk, especially in Malaysian cohort, means that intakes were analysed by using the best available estimates (12) and may not reflect the true nutritional composition of the milk received.

CONCLUSION

There was variation in nutritional practices between these two units in the UK and Malaysia. Current nutritional practices often do not meet recommended intakes, especially protein in preterm infants. Early use of PN and EN with fortified breast milk may improve nutrient intakes. Some demographic factors and nutritional practice differences affecting the high prevalence of postnatal growth failure in both

units were identified. More efforts are needed to produce evidence-based nutritional intake recommendations for settings that care for a large number of smaller or sicker infants.

Acknowledgements We would like to acknowledge the support of all the staff at Royal Derby Hospital and Hospital Canselor Tuanku Muhriz neonatal units for their assistance during the data collection process of this study. We also would like to acknowledge Janine Abramson and Coral Smith who assisted in the electronic data collection in the UK unit, Drs Cho Cho Latt and Tian-Lee Tan for the data collection in Malaysia unit.

Contributors HAH, SO, LS, HB and FCC conceptualised and designed the study and reviewed and revised the manuscript. HAH performed the data collection in the UK unit, completed the data analysis and drafted the initial manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Funding HAH is supported by a PhD scholarship from the Ministry of Higher Education Malaysia and Universiti Kebangsaan Malaysia (UKM).

Competing interests None declared.

Patient consent Not required.

Provenance and peer review Yes

References

1. Young A, Andrews ET, Ashton JJ, Pearson F, Beattie RM, Johnson MJ. Generating longitudinal growth charts from preterm infants fed to current recommendations. Arch Dis Child - Fetal Neonatal Ed. 2020 Nov;105(6):646–51.

2. Stoltz Sjöström E, Öhlund I, Ahlsson F, Engström E, Fellman V, Hellström A, et al. Nutrient intakes independently affect growth in extremely preterm infants: Results from a population-based study. Acta Paediatr Int J Paediatr. 2013;102(11):1067–74.

3. Maas C, Poets CF, Franz AR. Avoiding postnatal undernutrition of vlbw infants during neonatal intensive care: Evidence and personal view in the absence of evidence. Arch Dis Child Fetal Neonatal Ed. 2015;100(1):F76–81.

4. de Waard M, Li Y, Zhu Y, Ayede AI, Berrington J, Bloomfield FH, et al. Time to Full Enteral Feeding for Very Low-Birth-Weight Infants Varies Markedly Among Hospitals Worldwide But May Not Be Associated With Incidence of Necrotizing

Enterocolitis: The NEOMUNE-NeoNutriNet Cohort Study. J Parenter Enter Nutr. 2018;

5. Agostoni C, Buonocore G, Carnielli VP, De Curtis M, Darmaun D, Decsi T, et al. Enteral nutrient supply for preterm infants: Commentary from the european society of paediatric gastroenterology, hepatology and nutrition committee on nutrition. J Pediatr Gastroenterol Nutr. 2010;50(1):85–91.

6. Koletzko B, Poindexter B, Uauy R. Nutrition of the preterm infant: Scientific Basis and Practical Guidelines. Basel: Karger; 2014.

7. Andrews ET, Ashton JJ, Pearson F, Mark Beattie R, Johnson MJ. Early postnatal growth failure in preterm infants is not inevitable. Arch Dis Child Fetal Neonatal Ed. 2018;10–2.

8. Horbar JD, Ehrenkranz RA, Badger GJ, Edwards EM, Morrow KA, Soll RF, et al. Weight Growth Velocity and Postnatal Growth Failure in Infants 501 to 1500 Grams: 2000-2013. Pediatrics. 2015;136(1):e84–92.

9. Cormack BE, Jiang Y, Harding JE, Crowther CA, Bloomfield FH. Relationships between Neonatal Nutrition and Growth to 36 Weeks' Corrected Age in ELBW Babies–Secondary Cohort Analysis from the Provide Trial. Nutrients. 2020 Mar 13;12(3):760.

10. British Association of Perinatal Medicine (BAPM) (2010). Service standards for hospitals providing neonatal care, 3rd edition. [Internet]. 2010. Available from: http://www.bapm.org/publications/documents/guidelines/BAPM_Standards_Final_Au g2010.pdf

11. Ministry of Health Malaysia. The Operational Policy for Paediatric Services. he Medical Services Development Section; 2012.

12. Gidrewicz DA, Fenton TR. A systematic review and meta-analysis of the nutrient content of preterm and term breast milk. BMC Pediatr. 2014 Aug 30;14:216.

13. Fenton T, Kim J. A systematic review and meta-analysis to revise the Fenton growth chart for preterm infants. BMC Pediatr. 2013;13:59.

14. Geneva: World Health Organization. Physical status: the use and interpretation of anthropometry. Report of a WHO Expert Committee. WHO Technical Report Series No. 854. 1995.

15. Lin Z, Green RS, Chen S, Wu H, Liu T, Li J, et al. Quantification of EUGR as a measure of the quality of nutritional care of premature infants. PLoS ONE. 2015;10(7):1–10.

16. Lee SM, Kim N, Namgung R, Park M, Park K, Jeon J. Prediction of Postnatal Growth Failure among Very Low Birth Weight Infants. Sci Rep. 2018;8(1):1–8.

17. Darmaun D, Lapillonne A, Simeoni U, Picaud J-C, Rozé J-C, Saliba E, et al. Parenteral nutrition for preterm infants: Issues and strategy. Arch Pediatr Organe Off Soc Francaise Pediatr. 2018 May;25(4):286–94.

18. Kim J. Multicollinearity and misleading statistical results. Korean J Anesthesiol. 2019 Dec 1;72(6):558–69.

19. Institute for Public Health. The National Health and Morbidity Survey (NHMS) 2016 [Internet]. Kuala Lampur: Institute for Public Health, National Institutes of Health, Ministry of Health Malaysia; 2016. Available from: http://iku.moh.gov.my/images/IKU/Document/REPORT/2016/NHMS2016ReportVolumeII-MaternalChildHealthFindingsv2.pdf

20. NHS Maternity Statistics, England 2017-18. Maternity and Breastfeeding [Internet]. Available from: https://www.england.nhs.uk/statistics/statistical-work-areas/maternity-and-breastfeeding/

21. Casey PH, Whiteside-Mansell L, Barrett K, Bradley RH, Gargus R. Impact of prenatal and/or postnatal growth problems in low birth weight preterm infants on school-age outcomes: an 8-year longitudinal evaluation. Pediatrics. 2006 Sep;118(3):1078–86.

22. Bonnet C, Blondel B, Piedvache A, Wilson E, Bonamy AE, Gortner L, et al. Low breastfeeding continuation to 6 months for very preterm infants: A E uropean multiregional cohort study. Matern Child Nutr [Internet]. 2019 Jan [cited 2021 Feb 15];15(1). Available from: https://onlinelibrary.wiley.com/doi/abs/10.1111/mcn.12657

23. Ministry of Health Malaysia. National Breastfeeding Policy 2005 [Internet]. 2005. Available from: http://nutrition.moh.gov.my/wp-content/uploads/penerbitan/poster/polisi%20penyusuan%20ibu.jpg

24. Spaeth A, Zemp E, Merten S, Dratva J. Baby-Friendly Hospital designation has a sustained impact on continued breastfeeding. Matern Child Nutr. 2018 Jan;14(1):e12497.

25. Broadfoot M, Britten J, Tappin DM, MacKenzie JM. The Baby Friendly Hospital Initiative and breast feeding rates in Scotland. Arch Dis Child Fetal Neonatal Ed. 2005 Mar;90(2):F114-116.

26. UNICEF UK. Accreditation [Internet]. 2019. Available from: https://www.unicef.org.uk/babyfriendly/accreditation/

27. Maier RF, Blondel B, Piedvache A, Misselwitz B, Petrou S, Van Reempts P, et al. Duration and Time Trends in Hospital Stay for Very Preterm Infants Differ Across European Regions*: Pediatr Crit Care Med. 2018 Dec;19(12):1153–61.

28. Zainal H, Dahlui M, Soelar SA, Su TT. Cost of preterm birth during initial hospitalization: A care provider's perspective. Isangula KG, editor. PLOS ONE. 2019 Jun 25;14(6):e0211997.

29. Chen ST. Growth chart based on longitudianal study of Malaysian children from birth to six years. Med J Malays. 1985 Jun;40(2).

30. United Nations Children's Fund (UNICEF), World Health Organization (WHO). UNICEF-WHO Low birthweight estimates: Levels and trends 2000–2015 [Internet]. Geneva: World Health Organization; 2019. Available from: https://apps.who.int/iris/bitstream/handle/10665/324783/WHO-NMH-NHD-19.21-eng.pdf?ua=1

31. Fleiss B, Wong F, Brownfoot F, Shearer IK, Baud O, Walker DW, et al. Knowledge Gaps and Emerging Research Areas in Intrauterine Growth Restriction-Associated Brain Injury. Front Endocrinol. 2019 Mar 29;10:188.

32. Fenton TR, Al-Wassia H, Premji SS, Sauve RS. Higher versus lower protein intake in formula-fed low birth weight infants. Cochrane Neonatal Group, editor. Cochrane Database Syst Rev [Internet]. 2020 Jun 23 [cited 2020 Oct 21]; Available from: http://doi.wiley.com/10.1002/14651858.CD003959.pub4

33. Schanler RJ, Shulman RJ, Lau C, Smith EO, Heitkemper MM. Feeding strategies for premature infants: randomized trial of gastrointestinal priming and tube-feeding method. Pediatrics. 1999 Feb;103(2):434–9.

34. Carlson SJ, Ziegler EE. Nutrient intakes and growth of very low birth weight infants. J Perinatol Off J Calif Perinat Assoc. 1998 Aug;18(4):252–8.

35. Senterre T, Rigo J. Reduction in postnatal cumulative nutritional deficit and improvement of growth in extremely preterm infants. Acta Paediatr Int J Paediatr. 2012;101(2):64–70.

36. Embleton NE, Pang N, Cooke RJ. Postnatal Malnutrition and Growth Retardation: An Inevitable Consequence of Current Recommendations in Preterm Infants? Pediatrics. 2001;107(2):270–3.

37. Rozé J-C, Darmaun D, Boquien C-Y, Flamant C, Picaud J-C, Savagner C, et al. The apparent breastfeeding paradox in very preterm infants: relationship between breast feeding, early weight gain and neurodevelopment based on results from two cohorts, EPIPAGE and LIFT. BMJ Open. 2012 Jan 1;2(2):e000834.

38. Vohr BR, Poindexter BB, Dusick AM, McKinley LT, Higgins RD, Langer JC, et al. Persistent beneficial effects of breast milk ingested in the neonatal intensive care unit on outcomes of extremely low birth weight infants at 30 months of age. Pediatrics. 2007 Oct;120(4):e953-959.

39. McCowan L, Roberts C, Dekker G, Taylor R, Chan E, Kenny L, et al. Risk factors for small-for-gestational-age infants by customised birthweight centiles: data from an international prospective cohort study: Risk factors for SGA infants by customised centiles. BJOG Int J Obstet Gynaecol. 2010 Dec;117(13):1599–607.

Tables

Table 1: Infant and maternal characteristics of infants born at <34 weeks' gestational age and cared for in a neonatal unit in Malaysia and one in the UK

Variables	Infants in the Malaysian unit n=50	Infants in the UK unit n=50	p-value
Female, n (%)	21 (42)	22 (44)	0.84
Gestational age at birth (weeks) median (IQR)	32 (29-32, 25-33)	31 (30-33, 26-33)	0.736
Birthweight (grams) mean (SD)	1448 (458)	1649 (409)	0.022
Birthweight-for-age z-score mean (SD)	-0.53 (0.93)	-0.10 (0.70)	0.009
Small for gestational age, n (%)	12 (24)	3 (6)	0.012
HC at birth (cm), mean (SD)	28 (2.68)	28.9 (2.35)	0.106
HC-for-age z-score at birth Mean (SD)	-0.26 (-0.98 to 0.59, -4.2 to 2.05)	0.06 (-0.57 to 0.59, -3.3 to 1.54)	0.310
Length at birth (cm) mean (SD)	38.4 (3.65)	41.9 (4.08)	<0.001
Length at birth-for-age z-score mean (SD)	-0.92 (1.05)	0.21(1.23)	<0.001
Singleton birth, n (%)	45 (90)	34 (68)	0.007
Mother's age (years) mean (SD)	32 (5)	29 (5)	0.009
Parity, median (IQR)	3 (1-4, 1-8)	0 (0-1, 0-6)	<0.001
Caesarean section, n (%)	37 (74)	32 (64)	0.280
Apgar score at 5 minutes, median (IQR)	9 (8-10, 3-10)	9 (9, 6-10)	0.844
Antenatal steroid use, n (%)	47 (94)	42 (84)	0.194
Received positive pressure ventilation, n (%)	21 (42)	27 (54)	0.230
Late onset sepsis (confirmed), n (%)	13 (26)	4(8)	<0.001
Necrotising enterocolitis (suspected), n (%)	6 (12)	3 (6)	0.243
Intraventricular haemorrhage, n (%)	36 (72)	2 (4)	<0.001
Retinopathy of prematurity, n (%)	4 (8)	1 (2)	0.181
Periventricular leukomalacia, n (%)	7 (14)	0	0.006
Chronic lung disease, n (%)	10 (20)	3 (6)	0.036
Patent ductus arteriosus, n (%)	16 (32)	6 (12)	0.014

HC, head circumference; IQR, inter-quartile range; SD, standard deviation. P-values for comparisons between the two groups were determined by the Student's t-test or Mann-Whitney U test for continuous variables and by Chi squared or Fisher's exact tests for categorical variables, as appropriate.

Table 2: Feeding practices and nutritional intakes in infants born at <34 weeks' gestational age and cared for in a neonatal unit in Malaysia and one in the UK

Variables, n (%)	Malaysian group n=50	UK group n=50	p-value
Received any breast milk	49 (98)	38 (76)	0.001
Any breast milk at discharge	46 (92)	25 (50)	<0.001
Exclusively breast milk feeding at discharge	26 (52)	16 (32)	0.043
Received infant formula milk	40 (80)	47 (94)	0.037
Energy proportion (%) from breast milk during admission**	66.5 (40-83)	15.5 (2-82)	0.010
Energy proportion (%) from formula milk during admission±	19.2 (2.2-52.3)	78.8 (12.7-93.9)	<0.001
Day of life at first enteral milk feed**	2 (1-3)	2 (1-2)	0.833
Day of life reaching 120 mL/kg/d feed**	4 (4-5)	5 (4-5)	0.044
Day of life reaching full enteral feed at 150 ml/kg/d**	9 (7-12)	8 (7-10)	0.400
Rate of feeding advancement to full feed**	13 (6-16)	16 (9-20)	0.390
Received breast milk fortifier	43 (86)	13 (26)	<0.001
Day of life at first breast milk fortifier received±	11 (8-16)	15 (10-20)	0.039
Received parenteral nutrition	40 (80)	19 (38)	<0.001
Day of life at first parenteral nutrition**	2 (1-2)	2 (1-2)	0.414
Duration of parenteral nutrition**	9 (6-14)	6 (5-8)	0.031
Energy intake, kcal/kg/d*			
Week 1-4	103 (13)	100 (11)	0.238
Week 5-8	110 (18)	115 (15)	0.363
Cumulative energy deficits/excess±, kcal/kg*			
Week 1-4	-191.6 (129.8)	-254.5 (152.0)	0.028
Week 5-8	93.2(237.4)	-93.8 (539.3)	0.105
Protein intake, g/kg/d*			
Week 1-4	3.0 (0.5)	2.7 (0.6)	0.004
Week 5-8	3.4 (0.7	3.0 (0.8)	0.088
Cumulative protein deficits/excess±, g/kg*			
Week 1-4	-11.4 (6.1)	-15.4 (8.0)	0.006
Week 5-8	-8.7 (11.8)	-24.5 (25.6)	0.005
Protein energy ratio, g/100 kcal/d*			
Week 1-4	2.82 (0.28)	2.61 (0.48)	0.008
Week 5-8	3.03 (0.31)	2.57 (0.38)	<0.001
Fat intake, g/kg/d*			
Week 1-4	4.8 (0.7)	4.8 (0.6)	0.627
Week 5-8	5.3 (1.0)	5.8 (0.7)	0.058
Carbohydrate intake, g/kg/d*			
Week 1-4	11.4 (1.9)	10.7(1.4)	0.020
Week 5-8	11.9 (2.0)	12.2(1.7)	0.607
Fluid intake, ml/kg/d*			
Week 1-4	137.1 (12.9)	138.8 (10.9)	0.491
Week 5-8	141.4 (22.4)	153.9 (13.9)	0.024

**Median (IQR); * Mean (SD); ±Negative value indicates deficits. P-values for comparisons between the two groups were determined by the Student's t-test or Mann-Whitney U test for continuous variables and by Chi squared or Fisher's exact tests for categorical variables.

Table 3: Postnatal growth measurements in infants born at <34 weeks' gestational age and cared for in a neonatal unit in Malaysia and one in the UK

Variables	Malaysia n=50	UK n=50	MD (95% CI)	p-value
Days to regain birth weight**	12 (11-14)	13 (10-16)	-1 (-3.17 to 1.17)	0.247
Maximum weight loss from birth weight (%) **	4.4 (1.9-7.5)	5.7 (2.5-9.4)	-1.25 (-3.63 to 1.14)	0.275
Weight (g) at discharge**	2060 (1890-2390)	2165 (2050-2380)	-105 (-252.02 to 42.02)	0.221
Weight Z-score at discharge**	-1.65 (-2.3 to-1.0)	-1.3 (-1.8 to-0.80)	-0.35 (-0.77 to 0.08)	0.088
Changes in weight Z-score from birth to discharge*	-1.31 (0.57)	-1.33 (0.58)	0.01 (-0.22 to 0.23)	0.975
Infants with weight Z- score change ≥-1.28 from birth to discharge, n (%)	26 (52)	27 (54)	-	0.841
Head circumference at discharge, (cm)*	31.5 (1.61)	31.4 (1.39)	0.34(-0.29 to 0.98)	0.287
Head circumference Z-score at discharge**	-1.33 (-1.69 to -0.59)	-0.91 (-1.61 to -0.4)	-0.42 (-0.87 to 0.04)	0.383
Gestational age at discharge**	36.5 (35-38)	36 (35-37)	0.50 (-0.53 to1.52)	0.060
Length of stay (days) **	36 (22-55)	28.5 (20-52)	7.5 (-3.87 to 18.87)	0.157

** Median (IQR); * Mean (SD); MD, mean or median difference, CI, Confidence Interval. P-values and MD for comparisons between the two groups were determined by the Student's t-test or Mann-Whitney U test for continuous variables and by Chi squared or Fisher's exact tests for categorical variables, as appropriate.

Table 4: Factors associated with the change in weight-for-age Z-score between birth and discharge

Factors	Malaysia n=50		UK n=50	
	Unadjusted β (95% CI), p-value	**Adjusted β (95% CI), p-value**	**Unadjusted β (95% CI), p-value**	**Adjusted β (95% CI), p-value**
Maternal and infant characteristics				
Mother's age (years)	-0.02 (-0.05 to 0.01), p=0.159		-0.04 (-0.07 to -0.02), p=0.003	-0.03 (-0.05 to -0.01) p=0.011
Birthweight-for-age Z-score	0.06 (-0.11 to 0.24), p= 0.482		-0.25 (-0.48 to -0.02), p=0.038	-0.29 (-0.45 to -0.13), p=0.001
Length of stay	-0.01(-0.02 to -0.01), p<0.001	-0.01 (-0.02 to -0.01), p<0.001	-0.01(-0.02 to 0.001), p=0.065	-0.01 (-0.02 to -0.005), p=0.001
Day of life reaching full enteral feed	-0.05 (-0.08 to -0.02), p=0.001		-0.08 (-0.14 to -0.02), p=0.013	-0.05 (-0.09 to -0.004), p=0.030
Nutritional intakes in weeks 1-4				
Protein intake, g/kg/d	-0.21(-0.51 to 0.10) p=0.178		0.47 (0.20 to 0.74), p=0.001	0.36 (0.12 to 0.59), p=0.004
Protein energy ratio, g/100kcal/d	-0.41(-0.98 to 0.16), p=0.158		0.48 (0.15 to 0.80), p=0.005	0.34 (0.04 to 0.65), p=0.027

CI, Confidence Interval. Adjusted β values are displayed only for variables that are included in the final model of regression

BMJ Paediatrics Open

Nutritional practices and growth of preterm infants in two neonatal units in the UK and Malaysia: a prospective exploratory study

Journal:	*BMJ Paediatrics Open*
Manuscript ID	bmjpo-2021-001153.R2
Article Type:	Original research
Date Submitted by the Author:	11-Aug-2021
Complete List of Authors:	Abdul Hamid, Haslina; University of Nottingham, Population and Lifespan Sciences, School of Medicine; Universiti Kebangsaan Malaysia, Dietetic Programme, Faculty of Health Sciences Szatkowski, Lisa; University of Nottingham, Population and Lifespan Sciences, School of Medicine Budge, Helen; University of Nottingham, Population and Lifespan Sciences, School of Medicine Cheah, Fook-Choe; Universiti Kebangsaan Malaysia, Department of Paediatrics, Faculty of Medicine Ojha, Shalini; University of Nottingham, Population and Lifespan Sciences, School of Medicine; University Hospitals of Derby and Burton NHS Foundation Trust, Neonatal Unit
Keywords:	Neonatology, Growth

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Nutritional practices and growth of preterm infants in two neonatal units in the UK and Malaysia: a prospective exploratory study

Haslina Binti Abdul Hamid[1,2], Lisa Szatkowski[1], Helen Budge[1], Fook Choe Cheah[3], Shalini Ojha[1,4]

Corresponding author: Shalini Ojha

Room 4117, Medical School Building, Royal Derby Hospital, Derby, DE23 3DT.

Email: shalini.ojha@nottingham.ac.uk

Telephone: +44 1332 724691

Haslina Binti Abdul Hamid

[1]Population and Lifespan Sciences, School of Medicine, University of Nottingham, UK

[2]Dietetic Programme, Faculty of Health Sciences, Universiti Kebangsaan Malaysia, 50300 Kuala Lumpur

Lisa Szatkowski

[1]Population and Lifespan Sciences, School of Medicine, University of Nottingham, UK

Helen Budge

[1]Population and Lifespan Sciences, School of Medicine, University of Nottingham, UK

Fook Choe Cheah

[3]Department of Paediatrics, Faculty of Medicine, Universiti Kebangsaan Malaysia, 56000 Kuala Lumpur

Shalini Ojha

[1]Population and Lifespan Sciences, School of Medicine, University of Nottingham, UK

[4]Neonatal Unit, University Hospitals of Derby and Burton, Derby, DE23 3DT

Word Count: 2485

Key words: infant, preterm, nutrition, growth, small for gestational age, breastfeeding, breast milk fortifier

ABSTRACT

Objective To explore differences in nutritional practices and growth outcomes among preterm infants in neonatal units in Malaysia and the UK

Design Prospective exploratory study of infants born at <34 weeks gestational age (GA).

Setting Two neonatal units, one in Malaysia and one in the UK (May 2019 to March 2020).

Methods Data collected from birth until discharge and compared between units.

Results From 100 infants included, median GA (IQR) was 31(30-33) and mean±SD birthweight was 1549±444g. There were more small-for-gestational age (SGA) infants in Malaysian unit: 12/50 (24%) vs UK: 3/50 (6%), p=0.012 and more morbidities. More Malaysian infants received breast milk (Malaysia: 49 (98%) vs UK: 38 (76%), p=0.001), fortified breast milk (Malaysia: 43 (86%) vs UK: 13 (26%), p<0.001), and exclusive breast milk at discharge (Malaysia: 26 (52%) vs UK: 16 (32%), p=0.043). There was higher parenteral nutrition use among Malaysian infants (40 (80%)) vs UK (19 (38%)) (p<0.001) with higher protein intake (mean±SD Malaysia: 3.0±0.5 vs UK: 2.7±0.6g/kg/d, p=0.004) in weeks 1-4 and smaller cumulative protein deficits (mean±SD Malaysia: 11.4±6.1 vs UK: 15.4±8.0g/kg, p=0.006). There were no significant differences in short-term growth between units and more than half of the infants in both units had >-1.28 changes in weight-for-age Z-score at discharge (p=0.841).

Conclusions An exploratory comparison of practices showed differences in patient characteristics and nutritional practices which impacted growth. Future studies with larger sample sizes and detailed analysis of maternal characteristics and infants' outcomes are needed for improving care of preterm infants in all settings.

Word count: 250

What is already known on this topic

1. There is high rate of postnatal growth failure among preterm infants in neonatal units worldwide.

2. Postnatal growth failure in neonatal units in high income countries is well studied, but in upper middle-income countries, nutritional practices and growth outcomes are less explored despite rapid advancement in neonatal care.

3. Varied nutritional practices such as parenteral nutrition and protein intakes are independent predictors of the growth outcomes of preterm infants at discharge.

What this study adds

1. In this exploratory study, we found that infants in the Malaysian unit were more likely to be small for gestational age and have co-morbidities.

2. Mother's own milk (MOM) is more frequently used in the Malaysian unit and more infants received supplementation with breast milk fortifiers.

3. More infants in the Malaysian unit received parenteral nutrition, although this may be a response to the greater nutritional needs of SGA infants.

INTRODUCTION

Growth is one of the most important outcomes in determining the well-being of a preterm infant (1), and provision of optimal nutrition is a modifiable independent factor that could facilitate growth (2). Factors such as clinical traditions and resource limitations in hospitals may influence the adoption of effective feeding practices (3). Internationally, nutritional recommendations (4,5) have been created and growth studies were evaluated among preterm populations in the UK (6), USA (7) and other high-income settings (8). However, there is a paucity of studies in this area among low, middle and upper-middle-income countries, despite the growing availability of neonatal intensive care in these settings. Malaysia, as an upper-middle income country, has one of the lowest Neonatal Mortality Rates (NMR) in ASEAN countries at 5 per 1,000 live births in 2019, in line with its advancement in neonatal care services, which is comparable to the UK's NMR of 3 per 1,000 live births (9). A study on nutritional practices and growth outcomes from a neonatal unit in Malaysia was last performed in 2011, showing that more than 80% of very low birth weight infants had a >1 SD decline in weight-for-age Z-score (WAZ) by 36 weeks corrected gestational age (GA) (10). This study was over a decade ago and not much research has explored the impact of improvements in neonatal care or considered whether it is feasible to compare nutritional practices in upper-middle income settings with a higher income country setting. This exploratory study aimed to describe nutritional practices and postnatal growth outcomes in a neonatal unit in Malaysia, as an upper-middle-income country, as compared to one in the UK.

METHODS

The study was carried out in the neonatal units of the Royal Derby Hospital, UK and the Hospital Canselor Tuanku Muhriz, Malaysia, from May 2019 to March 2020. The UK unit is a Local Neonatal Unit (level II) (11) routinely caring for infants born at >25

weeks GA. More immature infants and those requiring surgical care are transferred to appropriate centres. The Malaysian unit is a tertiary neonatal unit (level IIIb) (12) which also provides surgical support on-site (except for cardiac surgery). In RDH, the neonatal unit has 24 neonatal cots and caters for 6000-7000 birth per year, while in HCTM, its neonatal unit has 26 cots and also caters for approximately 6000 birth per year. With an exception for not providing inhouse surgical support in the UK unit, both units provide similar types of care which comprises of care for the stable to intensive care infants. Both hospitals follow similar discharge criteria including weight of at least 1800g, not needing any additional medical support, and fully milk fed.

Infants <34 weeks' GA who were admitted to either unit were recruited consecutively and followed to discharge until the sample size of 50 was reached at each site. Infants were included if admitted within 24 hours of birth, not transferred out for any part of their care and had length of stay of ≥ 14 days. Infants with major congenital anomalies, genetic abnormalities or missing records for ≥3 days were excluded. As this was an exploratory study, the sample size was determined based on the usual monthly admissions and length of stay at the respective units. Therefore, collection of data from 50 infants from each unit (total of 100) was deemed to be feasible within the time and resources available for the study.

Anonymised data were extracted from paper or electronic medical records (accessed from BadgerNet (Client version 2.9.1.0) in the UK, and the Caring Hospital Enterprise System (C-HEtS) in Malaysia).

Baseline and feeding data

Infant and maternal characteristics including sex, GA at birth, maternal age, and parity as well as infants' clinical characteristics were collected prospectively. In the

Malaysian unit, GA was determined by using early first trimester ultrasound or by estimation based on last menstrual period for those who presented in later pregnancy. In the UK unit, GA was determined by early first trimester ultrasound. These records were retrieved from both paper and electronic medical records. For feeding data, daily nutritional intakes including parenteral nutrition (PN) and enteral nutrition (EN) were recorded. Volume of breast milk intakes were recorded only from bottle-feeding (expressed breast milk) as units do not routinely record before and after feeding weight for direct breastfeeding. The nutritional content of EN and PN (protein, lipid, and carbohydrate content) were calculated based on the manufacturers' literature while the composition of breast milk was based on current evidence (13). Nutrient deficits were calculated as the difference between actual intake and the minimum intake recommended by ESPGHAN (2010) guidelines (4).

Similar feeding protocols are used in both units. Generally, minimal enteral feeding (5-15ml/kg/d) is started within the first 24 hours. The units have guidelines on advancing feeds, promoting the use of mother's milk and the use of breast milk fortification and micronutrient supplementation.

Growth measures

The Fenton growth chart (14) was used as a reference for all growth assessments in both units in determining Z-scores. We used the same charts for both groups to enable a comparison of postnatal growth trajectories. The Fenton chart was chosen for this study for its advantage of using more recent and larger sample of preterm infants' data from many countries which link to the WHO growth data. It is routinely used in the Malaysian unit. In this study, only weight and head circumference (HC) measurements were assessed, as length is not routinely measured in the UK unit.

The marker for growth used in this study is the change in weight-for-age Z-scores (WAZ) from birth to discharge which was determined by subtracting the WAZ at birth from the WAZ at discharge. This was used due to the better sensitivity of weight than HC measurements in determining short term growth and Z-score as the best system for presentation and evaluation of anthropometric data (15) especially in indicating change over time. Postnatal growth failure was defined as a decrease in WAZ between birth and discharge of ≥ 1.28 as used in previous studies (16,17). SGA was defined as birth weight < 10th centile for birth weight (18).

Statistical analysis

All statistical analyses were performed using STATA 16.0 (Stata Corp. College Station, TX). Descriptive statistics were used to summarise the demographic and clinical characteristics of infants and their mothers. Infants' EN, PN and combined intakes in weeks 1-4 and weeks 5-8 and the cumulative deficits accrued in this period were analysed. Growth outcomes and other variables collected at discharge were also compared. The characteristics of infants and mothers, feeding practices as well as growth outcomes in the UK and Malaysia cohorts were compared using the Student's t-test or Mann-Whitney U test for continuous variables and by Chi squared or Fisher's exact tests for categorical variables, as appropriate. Mean or median difference and 95% confidence intervals were calculated for nutritional intakes and growth outcomes value comparison between sites.

Regulatory approvals

Ethical approval was obtained from the Health Research Authority (HRA) and Health and Care Research Wales (HCRW) Approval (United Kingdom) [IRAS project ID: 258817, Protocol number: 19012] and Research Ethics Committee, Universiti Kebangsaan Malaysia (UKM) (Malaysia) [JEP-2019-325]. No parental

consent was sought as this was a prospective exploratory study using routinely recorded clinical data and this approach received no objection from the Ethics Committee in both study sites.

Patient and Public Involvement

Patients or the public were not involved in the design, conduct, reporting or distribution plans of our study.

RESULTS

In this study, infants in Malaysia and the UK units were of similar GA, but Malaysian infants were lighter and had a lower WAZ and length-for-age Z-scores at birth although the HC Z-scores were not different (Table 1). There were more SGA infants in Malaysia (12/50; 24%) compared to the UK unit (3/50; 6%) (p=0.039). In Malaysia unit, there were fewer multiple births, more morbidities, mothers were older and had had more previous births (Table 1).

Enteral feeding

Milk feeding was started on median day of life (DOL) of 2 (p=0.833) in both units. Full milk feeds (defined as 150 ml/kg/d EN with no PN) was reached on median (IQR) DOL 9 (7-12) in Malaysia and DOL 8 (7-10) in the UK, p=0.400 (Table 2).

More infants in Malaysia received any mother's own milk (MOM) during admission (Malaysia: 98% vs UK: 76%, p=0.001) and more infants in the UK received formula milk (Malaysia: 80% vs. UK: 94%, p=0.037). Among infants who were fed their MOM, 86% infants had BMF added on median (IQR) DOL 11 (8-16) in Malaysia when they were receiving a median (IQR) milk volume of 154 (149-164) ml/kg/d while 26% infants had BMF added on median (IQR) DOL 15 (10-20) at median (IQR) milk volume of 157 (132-167) ml/kg/d, p=0.655 in the UK. At discharge, 52%

infants were exclusively breast milk-fed in Malaysia compared to 32% in the UK (p=0.043) (Table 2).

Parenteral feeding

40 (80%) infants received PN in Malaysia compared to 19 (38%) in the UK. PN was started on a median DOL 2 in both units (p=0.414) but was given for an average of three days longer in Malaysia than in the UK (median (IQR) days of PN in Malaysia: 9 (6-14) vs. UK: 6 (5-8), p=0.031 (Table 2).

Nutritional intakes

There was no significant difference in energy intakes in weeks 1-4 between the two units (p=0.238). However, Malaysian infants received more protein (Malaysia: 3.0±0.5 g/kg/d vs UK: 2.7±0.6 g/kg/d, p=0.004) and had smaller cumulative energy and protein deficits over this period, than the UK infants (Malaysia (energy): 191.6±129.8 vs UK: 254.5±152.0 kcal/kg, p=0.028 and Malaysia (protein):11.4±6.1 vs UK: 15.4±8.0g/kg, p=0.006). Protein energy ratio (PER) was also higher in the Malaysia unit (Malaysia: 3.03±0.31 g/100kcal/d vs. UK: 2.61±0.48 g/100kcal/d, p<0.001) (Table 2).

For those infants who remained in the hospital in weeks 5-8 of life (Malaysia: n=28, UK: n=23), better energy intakes were shown in both units although energy deficits in the UK cohort persisted. No significant difference in protein intakes was found between units but cumulative protein deficits in Malaysian infants improved while the magnitude of the deficit worsened in UK infants (Malaysia: 8.7±11.8 g/kg vs UK: 24.5 ±25.6 g/kg, p=0.005). This was despite a significantly lower total fluid intake at week 5-8 in the Malaysia unit (median, 141.4 ml/kg/d versus UK unit, 153.9 ml/kg/d) (Table 2).

Postnatal growth

There were no significant differences in growth outcomes at discharge between infants from the two units (Table 3). WAZ declined by ≥1.28 in 52% and 54% of infants in Malaysia and the UK, respectively. The mean±SD change in WAZ between birth and discharge was similar between the two cohorts (Malaysia: -1.31±0.57; UK: -1.33 ±0.58; p=0.975) (Table 3). For weekly WAZ (Figure 1), there was a decreasing trend in mean WAZ from postnatal week 1 to week 8 in both the UK and Malaysian unit. Infants in the UK unit had consistently higher mean weekly WAZ than infants in Malaysian unit.

DISCUSSION

In this study, we observed more Malaysian infants received breast milk as compared to UK infants. This is consistent with each countries' national reports (19,20) that record a higher rate of breastfeeding among Malaysian infants. The higher rate of breast milk feeding among Malaysian infants is possibly related to older maternal age and higher parity among mothers, as shown in many studies (21,22). Experienced mothers may have an easier start to breastfeeding and their previous experiences could help with continuation of breastfeeding in the unit. Cultural differences in attitudes to breastfeeding between the UK and Malaysia, where breastfeeding is the norm and the prevalence is increasing (23) may also underlie some of the differences between breastfeeding rates in the two units. The Malaysian unit has an established accreditation as Baby Friendly Hospital (BFH) (24) which is favourably related to the high rate of initiation and continuation of breastfeeding (25,26). The UK unit has achieved stage 1 of BFI accreditation and is building towards a stage 2 (27).

Supplementation of breast milk with BMF or protein supplements was more frequent in the Malaysian unit while BMF was used more selectively in the UK unit. The

standard protocol recommends the addition of BMF at 75-100ml/kg/d milk feeds in Malaysian unit while in the UK unit, protocol suggests the addition of BMF when feeding reaches 150-180 ml/kg/ but only at clinician's discretion when there are significant concerns about growth. The majority of infants who were fed breast milk in the Malaysian unit received some fortification, while the majority of infants who received breast milk in the UK unit received some supplemental formula feeding instead. Interestingly, in the Malaysian unit, infants on mixed feeds i.e. who had breast and formula milk, continued fortification if predominantly breast milk fed while most mixed fed infants in the UK unit did not receive BMF.

More Malaysian infants received PN which could be related to more SGA infants and higher rates of co-morbidities in this unit. Although they were given some enteral feeds, they were also started on PN possibly due to anticipation of feed intolerance and slower advancement of milk feeds. PN was used in this scenario possibly, with a view to boost nutrition while milk feeds were established. Additionally, PN support was provided for a longer duration. Infants in the UK unit were larger and less unwell and hence more likely to establish enteral feeding quicker and hence PN use was restricted. However, this study showed no difference between units with reference to the postnatal age when full feeds were established. The more frequent and longer use of PN and BMF resulted in significantly higher protein intake among the Malaysian infants when compared to those in the UK unit.

Despite the high use of formula milk which has more protein than that estimated for breast milk, average protein intakes in the UK unit did not meet the recommended intake of 3.5 g/kg/d. Previous studies showed that protein intakes aimed at >3.5-3.8 g/kg/d could decrease cumulative deficits and achieve better growth (28,29). Fortifying breast milk can increase protein intake although this would also involve cow's milk protein exposure and interfere with exclusive human milk feeding.

Additionally, any change to feeding strategies for the individual infant would also, understandably, be a response to infants' clinical conditions which might not be detected in this study.

Despite notable differences in intake, there were no significant differences in the short-term growth at discharge between the units. Throughout admission, the UK infants were observed to have consistently higher weekly weight Z-score than Malaysian infants, although both groups had a decline in growth trajectories. The differences in infant characteristics, possibly birthweight and co-morbidities, may explain this. Baseline anthropometric assessment showed that there was a significantly higher proportion of SGA infants in the Malaysian unit. This is possibly due to the centre acting as a referral hospital for high-risk obstetric cases involving mothers with pre-eclampsia, diabetes and fetal growth restriction. In addition, the Fenton growth chart that was used in this study may not represent the Asian population as much as it was constructed based on mostly a Caucasian population (14), which could also lead to higher SGA infants classified in the Malaysian unit. Studies showed that there were significant deviations in the assessments of growth depending on the growth charts used (30,31). Infants in the Malaysian unit were also challenged with a higher incidence of co-morbidities such as chronic lung disease and patent ductus arteriosus that likely necessitated the restriction of total fluid intake which could affect growth. However, any interpretation for 'optimal growth' outcome should explore factors other than weight only, including longer-term growth, neurodevelopmental, and metabolic outcomes in later life. Studies show that preterm infants fed mainly breast milk have better long-term outcome despite slower weight gain in early life (32,33).

The strengths of this study are that it is the first attempt to explore comparison of nutritional practices between two-centres in different settings. Prospective collection

of details of daily actual nutritional intake and weekly growth allowed a comprehensive analysis of nutritional practices. However, as this is an exploratory study, the sample size was small and not powered for differences in outcomes. A larger sample size is needed for evaluating the reasons for the differences observed in this study affecting growth failure. Estimation of nutritional intakes in breastfed infants cannot be accurate as intakes were analysed by using the best available estimates (13) and may not reflect the true nutritional composition of the milk received. Maternal details including her nutritional status, clinical conditions, and antenatal care should also be considered as these are vital determinants of fetal nutrition and infants' outcomes including SGA status (34).

Despite these limitations, studies comparing nutritional intakes and growth outcomes are feasible to do in these two countries. Malaysia is an upper middle-income country with similar government-funded healthcare system and NMR as the UK. The nutritional protocols used in these two units were based on the similar international guideline but were applied differently perhaps due to differences in patient characteristics and cultural differences making such comparisons an interesting area of study. Studies with an adequately powered sample, collection of more data on maternal characteristics and infants' longer term outcomes and the use of a more representative growth chart would provide evidence to ensure that preterm infants receive adequate nutrition, hopefully, in all care settings globally.

CONCLUSION

In our exploratory analyses, there were variations in nutritional practices between the two units included in this study. Current nutritional practices often do not meet recommended intakes, especially for protein in preterm infants. We found that with international collaboration, future comparison studies involving units in varied

income settings are feasible and may provide evidence to support equity in care of preterm infants.

Acknowledgements We would like to acknowledge the support of all the staff at Royal Derby Hospital and Hospital Canselor Tuanku Muhriz neonatal units for their assistance during the data collection process of this study. We also would like to acknowledge Janine Abramson and Coral Smith who assisted in the electronic data collection in the UK unit, Drs Cho Cho Latt and Tian-Lee Tan for the data collection in Malaysia unit.

Contributors HAH, SO, LS, HB and FCC conceptualised and designed the study and reviewed and revised the manuscript. HAH performed the data collection in the UK unit, completed the data analysis and drafted the initial manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Funding HAH is supported by a PhD scholarship from the Ministry of Higher Education Malaysia and Universiti Kebangsaan Malaysia (UKM).

Competing interests None declared.

Patient consent Not required.

Provenance and peer review Yes

References

1. Young A, Andrews ET, Ashton JJ, Pearson F, Beattie RM, Johnson MJ. Generating longitudinal growth charts from preterm infants fed to current recommendations. Arch Dis Child - Fetal Neonatal Ed. 2020 Nov;105(6):646–51.

2. Stoltz Sjöström E, Öhlund I, Ahlsson F, Engström E, Fellman V, Hellström A, et al. Nutrient intakes independently affect growth in extremely preterm infants: Results from a population-based study. Acta Paediatr Int J Paediatr. 2013;102(11):1067–74.

3. de Waard M, Li Y, Zhu Y, Ayede AI, Berrington J, Bloomfield FH, et al. Time to Full Enteral Feeding for Very Low-Birth-Weight Infants Varies Markedly Among Hospitals Worldwide But May Not Be Associated With Incidence of Necrotizing Enterocolitis: The NEOMUNE-NeoNutriNet Cohort Study. J Parenter Enter Nutr. 2018;

4. Agostoni C, Buonocore G, Carnielli VP, De Curtis M, Darmaun D, Decsi T, et al. Enteral nutrient supply for preterm infants: Commentary from the european

society of paediatric gastroenterology, hepatology and nutrition committee on nutrition. J Pediatr Gastroenterol Nutr. 2010;50(1):85–91.

5. Koletzko B, Poindexter B, Uauy R. Nutrition of the preterm infant: Scientific Basis and Practical Guidelines. Basel: Karger; 2014.

6. Andrews ET, Ashton JJ, Pearson F, Mark Beattie R, Johnson MJ. Early postnatal growth failure in preterm infants is not inevitable. Arch Dis Child Fetal Neonatal Ed. 2018;10–2.

7. Horbar JD, Ehrenkranz RA, Badger GJ, Edwards EM, Morrow KA, Soll RF, et al. Weight Growth Velocity and Postnatal Growth Failure in Infants 501 to 1500 Grams: 2000-2013. Pediatrics. 2015;136(1):e84–92.

8. Cormack BE, Jiang Y, Harding JE, Crowther CA, Bloomfield FH. Relationships between Neonatal Nutrition and Growth to 36 Weeks' Corrected Age in ELBW Babies–Secondary Cohort Analysis from the Provide Trial. Nutrients. 2020 Mar 13;12(3):760.

9. UNICEF. UNICEF Data Warehouse [Internet]. 2019. Available from: https://data.unicef.org/resources/data_explorer/unicef_f/?ag=UNICEF&df=GLOBAL_DATAFLOW&ver=1.0&dq=GBR.CME_MRM0.&startPeriod=1970&endPeriod=2021

10. Lee LY, Lee J, Niduvaje K, Seah SS-Y, Atmawidjaja RW, Cheah F-C. Nutritional therapies in the neonatal intensive care unit and post- natal growth outcomes of preterm very low birthweight Asian infants. J Paediatr Child Health. 2020;8.

11. British Association of Perinatal Medicine (BAPM) (2010). Service standards for hospitals providing neonatal care, 3rd edition. [Internet]. 2010. Available from: http://www.bapm.org/publications/documents/guidelines/BAPM_Standards_Final_Au g2010.pdf

12. Ministry of Health Malaysia. The Operational Policy for Paediatric Services. he Medical Services Development Section; 2012.

13. Gidrewicz DA, Fenton TR. A systematic review and meta-analysis of the nutrient content of preterm and term breast milk. BMC Pediatr. 2014 Aug 30;14:216.

14. Fenton T, Kim J. A systematic review and meta-analysis to revise the Fenton growth chart for preterm infants. BMC Pediatr. 2013;13:59.

15. Geneva: World Health Organization. Physical status: the use and interpretation of anthropometry. Report of a WHO Expert Committee. WHO Technical Report Series No. 854. 1995.

16. Lin Z, Green RS, Chen S, Wu H, Liu T, Li J, et al. Quantification of EUGR as a measure of the quality of nutritional care of premature infants. PLoS ONE. 2015;10(7):1–10.

17. Lee SM, Kim N, Namgung R, Park M, Park K, Jeon J. Prediction of Postnatal Growth Failure among Very Low Birth Weight Infants. Sci Rep. 2018;8(1):1–8.

18. Darmaun D, Lapillonne A, Simeoni U, Picaud J-C, Rozé J-C, Saliba E, et al. Parenteral nutrition for preterm infants: Issues and strategy. Arch Pediatr Organe Off Soc Francaise Pediatr. 2018 May;25(4):286–94.

19. Institute for Public Health. The National Health and Morbidity Survey (NHMS) 2016 [Internet]. Kuala Lampur: Institute for Public Health, National Institutes of Health, Ministry of Health Malaysia; 2016. Available from: http://iku.moh.gov.my/images/IKU/Document/REPORT/2016/NHMS2016ReportVolumeII-MaternalChildHealthFindingsv2.pdf

20. NHS Maternity Statistics, England 2017-18. Maternity and Breastfeeding [Internet]. Available from: https://www.england.nhs.uk/statistics/statistical-work-areas/maternity-and-breastfeeding/

21. Casey PH, Whiteside-Mansell L, Barrett K, Bradley RH, Gargus R. Impact of prenatal and/or postnatal growth problems in low birth weight preterm infants on school-age outcomes: an 8-year longitudinal evaluation. Pediatrics. 2006 Sep;118(3):1078–86.

22. Bonnet C, Blondel B, Piedvache A, Wilson E, Bonamy AE, Gortner L, et al. Low breastfeeding continuation to 6 months for very preterm infants: A E uropean multiregional cohort study. Matern Child Nutr [Internet]. 2019 Jan [cited 2021 Feb 15];15(1). Available from: https://onlinelibrary.wiley.com/doi/abs/10.1111/mcn.12657

23. Fatimah S, Siti Saadiah HN, Tahir A, Hussain Imam MI, Ahmad Faudzi Y. Breastfeeding in Malaysia: Results of the Third National Health and Morbidity Survey (NHMS III) 2006. Malays J Nutr. 2010 Aug;16(2):195–206.

24. Ministry of Health Malaysia. National Breastfeeding Policy 2005 [Internet]. 2005. Available from: http://nutrition.moh.gov.my/wp-content/uploads/penerbitan/poster/polisi%20penyusuan%20ibu.jpg

25. Spaeth A, Zemp E, Merten S, Dratva J. Baby-Friendly Hospital designation has a sustained impact on continued breastfeeding. Matern Child Nutr. 2018 Jan;14(1):e12497.

26. Broadfoot M, Britten J, Tappin DM, MacKenzie JM. The Baby Friendly Hospital Initiative and breast feeding rates in Scotland. Arch Dis Child Fetal Neonatal Ed. 2005 Mar;90(2):F114-116.

27. UNICEF UK. Accreditation [Internet]. 2019. Available from: https://www.unicef.org.uk/babyfriendly/accreditation/

28. Senterre T, Rigo J. Reduction in postnatal cumulative nutritional deficit and improvement of growth in extremely preterm infants. Acta Paediatr Int J Paediatr. 2012;101(2):64–70.

29. Embleton NE, Pang N, Cooke RJ. Postnatal Malnutrition and Growth Retardation: An Inevitable Consequence of Current Recommendations in Preterm Infants? Pediatrics. 2001;107(2):270–3.

30. Kim Y, Shin SH, Cho H, Shin SH, Kim SH, Song IG, et al. Extrauterine growth restriction in extremely preterm infants based on the Intergrowth-21st Project Preterm Postnatal Follow-up Study growth charts and the Fenton growth charts.

Eur J Pediatr [Internet]. 2020 Sep 9 [cited 2021 Feb 15]; Available from: http://link.springer.com/10.1007/s00431-020-03796-0

31. Neubauer V, Fuchs T, Griesmaier E, Pupp-Peglow U, Kiechl-Kohlendorfer U. Comparing growth charts demonstrated significant deviations between the interpretation of postnatal growth patterns in very preterm infants. Acta Paediatr Int J Paediatr. 2016;105(3):268–73.

32. Rozé J-C, Darmaun D, Boquien C-Y, Flamant C, Picaud J-C, Savagner C, et al. The apparent breastfeeding paradox in very preterm infants: relationship between breast feeding, early weight gain and neurodevelopment based on results from two cohorts, EPIPAGE and LIFT. BMJ Open. 2012 Jan 1;2(2):e000834.

33. Vohr BR, Poindexter BB, Dusick AM, McKinley LT, Higgins RD, Langer JC, et al. Persistent beneficial effects of breast milk ingested in the neonatal intensive care unit on outcomes of extremely low birth weight infants at 30 months of age. Pediatrics. 2007 Oct;120(4):e953-959.

34. McCowan L, Roberts C, Dekker G, Taylor R, Chan E, Kenny L, et al. Risk factors for small-for-gestational-age infants by customised birthweight centiles: data from an international prospective cohort study: Risk factors for SGA infants by customised centiles. BJOG Int J Obstet Gynaecol. 2010 Dec;117(13):1599–607.

Tables

Table 1: Infant and maternal characteristics of infants born at <34 weeks' gestational age and cared for in a neonatal unit in Malaysia and one in the UK

Variables	Infants in the Malaysian unit n=50	Infants in the UK unit n=50	p-value
Female, n (%)	21 (42)	22 (44)	0.84
Gestational age at birth (weeks) median (IQR)	32 (29 to 32)	31 (30 to 33)	0.736
Birthweight (grams) mean (SD)	1448 (458)	1649 (409)	0.022
Birthweight-for-age z-score mean (SD)	-0.53 (0.93)	-0.10 (0.70)	0.009
Small for gestational age, n (%)	12 (24)	3 (6)	0.012
HC at birth (cm), mean (SD)	28 (2.68)	28.9 (2.35)	0.106
HC-for-age z-score at birth, median (IQR)	-0.26 (-0.98 to 0.59)	0.06 (-0.57 to 0.59)	0.310
Length at birth (cm) mean (SD)	38.4 (3.65)	41.9 (4.08)	<0.001
Length at birth-for-age z-score mean (SD)	-0.92 (1.05)	0.21(1.23)	<0.001
Singleton birth, n (%)	45 (90)	34 (68)	0.007
Mother's age (years) mean (SD)	32 (5)	29 (5)	0.009
Parity, median (IQR)	3 (1 to 4)	0 (0 to 1)	<0.001
Caesarean section, n (%)	37 (74)	32 (64)	0.280
Apgar score at 5 minutes, median (IQR)	9 (8 to10)	9 (9 to 9)	0.844
Antenatal steroid use, n (%)	47 (94)	42 (84)	0.194
Received positive pressure ventilation, n (%)	21 (42)	27 (54)	0.230
Late onset sepsis (confirmed)#, n (%)	13 (26)	4 (8)	<0.001
Necrotising enterocolitis (suspected) #, n (%)	6 (12)	3 (6)	0.243
Intraventricular haemorrhage#, n (%)	36 (72)	2 (4)	<0.001
Retinopathy of prematurity#, n (%)	4 (8)	1 (2)	0.181
Periventricular leukomalacia#, n (%)	7 (14)	0	0.006
Chronic lung disease#, n (%)	10 (20)	3 (6)	0.036
Patent ductus arteriosus#, n (%)	16 (32)	6 (12)	0.014

HC, head circumference; IQR, inter-quartile range; SD, standard deviation. P-values for comparisons between the two groups were determined by the Student's t-test or Mann-Whitney U test for continuous variables and by Chi squared or Fisher's exact tests for categorical variables, as appropriate.

#Diagnoses were noted from clinical records: late onset sepsis (culture proven sepsis after 72 h of birth); necrotising enterocolitis (based on clinical or radiological features that needed at least 5 days of withheld feeding and antibiotics); retinopathy of prematurity (any stage diagnosed on screening examination); periventricular leukomalacia (any lesion reported on cranial ultrasound); chronic lung disease (infants requiring respiratory support including any supplemental oxygen at 36 weeks' corrected gestational age) and patent ductus arteriosus (diagnosed on echocardiography).

Table 2: Feeding practices and nutritional intakes in infants born at <34 weeks' gestational age and cared for in a neonatal unit in Malaysia and one in the UK

Variables, n (%)	Malaysian group n=50	UK group n=50	p-value
Received any breast milk	49 (98)	38 (76)	0.001
Any breast milk at discharge	46 (92)	25 (50)	<0.001
Exclusively breast milk feeding at discharge	26 (52)	16 (32)	0.043
Received infant formula milk	40 (80)	47 (94)	0.037
Energy proportion (%) from breast milk during admission**	66.5 (40-83)	15.5 (2-82)	0.010
Energy proportion (%) from formula milk during admission±	19.2 (2.2-52.3)	78.8 (12.7-93.9)	<0.001
Day of life at first enteral milk feed**	2 (1-3)	2 (1-2)	0.833
Day of life reaching 120 mL/kg/d feed**	4 (4-5)	5 (4-5)	0.044
Day of life reaching full enteral feed at 150 ml/kg/d**	9 (7-12)	8 (7-10)	0.400
Rate of feeding advancement to full feed**	13 (6-16)	16 (9-20)	0.390
Received breast milk fortifier	43 (86)	13 (26)	<0.001
Day of life at first breast milk fortifier received±	11 (8-16)	15 (10-20)	0.039
Received parenteral nutrition	40 (80)	19 (38)	<0.001
Day of life at first parenteral nutrition**	2 (1-2)	2 (1-2)	0.414
Duration of parenteral nutrition**	9 (6-14)	6 (5-8)	0.031
Energy intake, kcal/kg/d*			
Week 1-4	103 (13)	100 (11)	0.238
Week 5-8	110 (18)	115 (15)	0.363
Cumulative energy deficits/excess±, kcal/kg*			
Week 1-4	-191.6 (129.8)	-254.5 (152.0)	0.028
Week 5-8	93.2(237.4)	-93.8 (539.3)	0.105
Protein intake, g/kg/d*			
Week 1-4	3.0 (0.5)	2.7 (0.6)	0.004
Week 5-8	3.4 (0.7	3.0 (0.8)	0.088
Cumulative protein deficits/excess±, g/kg*			
Week 1-4	-11.4 (6.1)	-15.4 (8.0)	0.006
Week 5-8	-8.7 (11.8)	-24.5 (25.6)	0.005
Protein energy ratio, g/100 kcal/d*			
Week 1-4	2.82 (0.28)	2.61 (0.48)	0.008
Week 5-8	3.03 (0.31)	2.57 (0.38)	<0.001
Fat intake, g/kg/d*			
Week 1-4	4.8 (0.7)	4.8 (0.6)	0.627
Week 5-8	5.3 (1.0)	5.8 (0.7)	0.058
Carbohydrate intake, g/kg/d*			
Week 1-4	11.4 (1.9)	10.7(1.4)	0.020
Week 5-8	11.9 (2.0)	12.2(1.7)	0.607
Fluid intake, ml/kg/d*			
Week 1-4	137.1 (12.9)	138.8 (10.9)	0.491
Week 5-8	141.4 (22.4)	153.9 (13.9)	0.024

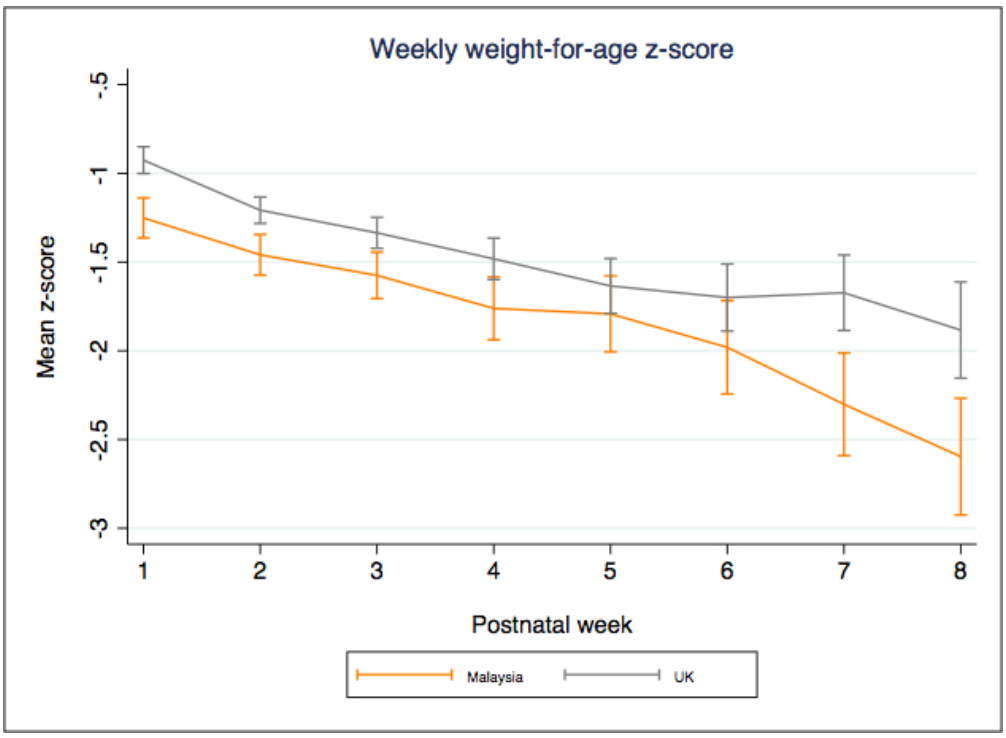
**Median (IQR); * Mean (SD); ±Negative value indicates deficits. P-values for comparisons between the two groups were determined by the Student's t-test or Mann-Whitney U test for continuous variables and by Chi squared or Fisher's exact tests for categorical variables.

Table 3: Postnatal growth measurements in infants born at <34 weeks' gestational age and cared for in a neonatal unit in Malaysia and one in the UK

Variables	Malaysia n=50	UK n=50	MD (95% CI)	p-value
Days to regain birth weight**	12 (11-14)	13 (10-16)	-1 (-3.17 to 1.17)	0.247
Maximum weight loss from birth weight (%) **	4.4 (1.9-7.5)	5.7 (2.5-9.4)	-1.25 (-3.63 to 1.14)	0.275
Weight (g) at discharge**	2060 (1890-2390)	2165 (2050-2380)	-105 (-252.02 to 42.02)	0.221
Weight Z-score at discharge**	-1.65 (-2.3 to-1.0)	-1.3 (-1.8 to-0.80)	-0.35 (-0.77 to 0.08)	0.088
Changes in weight Z-score from birth to discharge*	-1.31 (0.57)	-1.33 (0.58)	0.01 (-0.22 to 0.23)	0.975
Infants with weight Z- score change ≥-1.28 from birth to discharge, n (%)	26 (52)	27 (54)	-	0.841
Head circumference at discharge, (cm)*	31.5 (1.61)	31.4 (1.39)	0.34(-0.29 to 0.98)	0.287
Head circumference Z-score at discharge**	-1.33 (-1.69 to -0.59)	-0.91 (-1.61 to -0.4)	-0.42 (-0.87 to 0.04)	0.383
Gestational age at discharge**	36.5 (35-38)	36 (35-37)	0.50 (-0.53 to1.52)	0.060
Length of stay (days) **	36 (22-55)	28.5 (20-52)	7.5 (-3.87 to 18.87)	0.157

** Median (IQR); * Mean (SD); MD, mean or median difference, CI, Confidence Interval. P-values and MD for comparisons between the two groups were determined by the Student's t-test or Mann-Whitney U test for continuous variables and by Chi squared or Fisher's exact tests for categorical variables, as appropriate.

Figure 1: Mean weekly weight-for-age z-score (WAZ) (error bars represent the standard error (SE))



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