

PEER REVIEW HISTORY

BMJ Paediatrics Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

This paper was submitted to a another journal from BMJ but declined for publication following peer review. The authors addressed the reviewers' comments and submitted the revised paper to BMJ Paediatrics Open. The paper was subsequently accepted for publication at BMJ Paediatrics Open.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Multicentre prospective observational study of feeding practices in 30–33 weeks preterm infants
AUTHORS	Kwok, T'ng Chang; Ojha, Shalini; Dorling, Jon

VERSION 1 - REVIEW

REVIEWER	Huertas-Ceballos, Angela Neonatal Unit University College London NHS Trust UK Competing interests: None declared
REVIEW RETURNED	01-May-2017

GENERAL COMMENTS	I think this is an important topic that needs addressing. I believe that the authors did a great job trying to build a sample from several hospitals although in the end the sample size was not very long. I thought the NEC prevalence was high and would want NEC to be described more in detail, who made the diagnosis and also the chronological age of diagnosis I'd like Ethics methods to be described as well.
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REVIEWER	Leaf, Alison Department of Child Health, University of Southampton, UK Competing interests: None Declared
REVIEW RETURNED	27-Apr-2017

GENERAL COMMENTS	This is an interesting topic, as there have been few studies of feeding of moderate and late preterm infants, however the number of infants studied is small and there is relatively little detail of feeding practice. The paper serves to draw attention to some of the issues of feeding this population, but does not provide particularly novel information. The Abstract, Introduction and Methods are all appropriate, although no mention is made of Ethical or Institutional approvals, nor of any protocols which were in place to guide feeding practice. The inclusion of eight different hospitals is valuable in making the results more generalised, however a longer study period and greater number of cases would have provided more information, particularly
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	on clinical outcomes. Assessing incidence of NEC and LOS in 80 infants of this gestation is hard to interpret. Having said that, two infants did develop NEC and one died. More detail on their feeding history would be interesting - did they receive breast milk or formula? The results state that higher gestational age was significantly related to earlier enteral feeding and that 11 infants (14%) achieved total enteral feeding on day one. Did these findings reflect a higher tolerance of formula feeding in more mature infants? Or was 'total volume per kg per day' lower at higher gestations? Or is faster establishment of lactation possible at later gestation? The finding that feeds were delayed in 54% due to 'waiting for breast milk' seems to be a crucial issue here. Is it possible to tease out how that was achieved in those with more rapid achievement of full feeds? The other reasons for delay in introducing feeds are mainly medical conditions for which intravenous fluids would currently be part of standard practice. If we wish to achieve full enteral feeding from birth in this population - which would be of major benefit in resource poor settings - it will require a re-evaluation of both policy and practice and a greater understanding of the physiology of lactation and placental/enteral transition in this population of babies. Perhaps some of these concepts could be explored in the discussion, in relation to how a randomised controlled trial would be implemented?
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VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Comments to the Author

This is an interesting topic, as there have been few studies of feeding of moderate and late preterm infants, however the number of infants studied is small and there is relatively little detail of feeding practice. The paper serves to draw attention to some of the issues of feeding this population, but does not provide particularly novel information.

Thank you for your comments and interest in our work. We agree that there is limited research in nutrition of moderate and late preterm infants despite the population encompassing a significant workload in neonatal units. Hence, we carried out this piece of work. The main aim of this prospective observational study was to provide an overview of the current feeding practice in 30 – 33 weeks preterm infants so that it could be reflected against emerging evidence in the literature. It was not intended to provide novel information. Due to the time constraint, only a small number of infants were studied. This limitation was discussed in the paper. However, we felt that ten consecutive infants recruited from eight neonatal units across the UK provided a good overview of their enteral feeding practice.

The Abstract, Introduction and Methods are all appropriate, although no mention is made of Ethical or Institutional approvals, nor of any protocols which were in place to guide feeding practice.

No ethical approval was sought as this was purely an observational study auditing the feeding practice within each neonatal unit. There was no new intervention or protocol proposed as part of the study. Each participating unit was advised to register the work with their local audit department.

The inclusion of eight different hospitals is valuable in making the results more generalised, however a longer study period and greater number of cases would have provided more information, particularly on clinical outcomes.

Due to constraint in resources, only eighty infants were studied. A longer study period and sample size would provide more information. However, we felt that studying ten consecutive infants from eight neonatal units across the UK provided a good overview of the feeding practice of these infants and its impact on feeding tolerance, morbidity (necrotising enterocolitis (NEC) and late onset sepsis (LOS)) and duration of hospital stay. It would be interesting to explore longer term outcome such as neurodevelopment. However, this was beyond the remit of this work.

Assessing incidence of NEC and LOS in 80 infants of this gestation is hard to interpret. Having said that, two infants did develop NEC and one died. More detail on their feeding history would be interesting - did they receive breast milk or formula?

We agree that it is difficult to interpret the incidence of NEC and LOS in 80 infants. Further information on the feeding history for the two infants who developed NEC has been provided in the paper. In both infants, there was no antenatal concerns of abnormal umbilical artery end diastolic flow on antenatal scans.

The first case was a 31+5 week preterm dichorionic diamniotic twin 2 who was born just below the 25th centile for birthweight. She had predominantly formula milk with her feeds increased at an average rate of 19ml/kg/day to achieve volume of 45ml/kg/day by day 3 of age before she developed stage 3 NEC. Her NEC was diagnosed based on surgical findings at day 3 of age. Unfortunately, she died two days later. Her twin brother who was born just above the 25th centile for birthweight did not develop Stage 2 or 3 NEC despite being managed similarly.

The second infant was born at 30+1 weeks of gestation on the 50th centile for birthweight. He was exclusively formula fed with feeds increasing at an average rate of 23ml/kg/day to achieve full enteral feeds defined as 150ml/kg/day by day 9 of age. He developed Stage 2 NEC four days later after achieving full enteral feeds. His NEC was diagnosed based on radiological findings and was managed conservatively.

The results state that higher gestational age was significantly related to earlier enteral feeding and that 11 infants (14%) achieved total enteral feeding on day one. Did these findings reflect a higher tolerance of formula feeding in more mature infants? Or was 'total volume per kg per day' lower at higher gestations? Or is faster establishment of lactation possible at later gestation?

Our study found that infants of higher gestational age were enterally fed earlier and achieved total enteral feeding earlier. This may indeed reflect either higher formula feeding tolerance or earlier lactation establishment in more mature infants. As our study was only an observational study, our results were likely to be confounded by gestational age. Hence, as discussed in the paper, an adequately powered clinical trial will be crucial in answering this question. The total volume/kg/day of enteral feeds remained the same for infants of various gestation. Full enteral feeding was defined as achieved when infant tolerated $\geq 150\text{ml/kg/day}$ of feeds for three days.

The finding that feeds were delayed in 54% due to 'waiting for breast milk' seems to be a crucial issue here. Is it possible to tease out how that was achieved in those with more rapid achievement of full feeds?

Availability of breast milk appeared to be a crucial issue in our study. All the 11 infants (14%) who achieved total enteral feeds by day one of age received formula milk as their first enteral feeds. Hence, this raised an important question as to whether alternative milk such as donor breastmilk or formula milk should be used during this period or whether it is best to wait for maternal breast milk. (1) However, our study did not allow us to identify factors leading to rapid achievement of full feeds.

The other reasons for delay in introducing feeds are mainly medical conditions for which intravenous fluids would currently be part of standard practice. If we wish to achieve full enteral feeding from birth in this population - which would be of major benefit in resource poor settings –

Total enteral feeding from birth was found to be of benefit in resource poor settings in two recent Indian studies. (2, 3) However, total enteral feeding from birth may also be beneficial for moderate preterm infants born in resource rich settings like the UK. It may prevent the unnecessary use of peripheral or central venous access for intravenous nutrition which is associated with late onset sepsis and metabolic complications. Besides, total enteral feeding from birth may provide more opportunities for maternal-infant bonding through earlier establishment of enteral feeding and earlier discharge.

it will require a re-evaluation of both policy and practice and a greater understanding of the physiology of lactation and placental/enteral transition in this population of babies. Perhaps some of these concepts could be explored in the discussion, in relation to how a randomised controlled trial would be implemented?

We agree that a review of current enteral feeding practice and better understanding of lactation as well as enteral feeding physiology in the moderate preterm infants are needed to achieve total enteral feeding from birth in these populations of infants. However, this could only be achieved through a well designed pragmatic randomised clinical trials. The trial should incorporate a clear pathway for obtaining consent and for study protocol deviation for medical needs. High risk infants such as those requiring ventilatory support or infants with congenital abnormalities making enteral feeding from birth impossible should be excluded from the clinical trial.

Reviewer: 2

Comments to the Author

I think this is an important topic that needs addressing.

Thank you for your comment and interest in our work.

I believe that the authors did a great job trying to build a sample from several hospitals although in the end the sample size was not very long.

Due to resource constraint, only eighty infants were studied. This limitation was acknowledged in the paper. However, we felt that studying ten consecutive infants from eight neonatal units across the UK provided a good overview of the feeding practice of these infants.

I thought the NEC prevalence was high and would want NEC to be described more in detail, who made the diagnosis and also the chronological age of diagnosis.

Unfortunately, there were two cases of NEC in our cohort of infants. This has now been described in detail in the paper.

The first case was a 31+5 week preterm dichorionic diamniotic twin 2 who was born just below the 25th centile for birthweight. She had predominantly formula milk with her feeds increased at an average rate of 19ml/kg/day to achieve volume of 45ml/kg/day by day 3 of age before she developed stage 3 NEC. Her NEC was diagnosed based on surgical findings at day 3 of age. Unfortunately, she died two days later. Her twin brother who was born just above the 25th centile for birthweight did not develop Stage 2 or 3 NEC despite being managed similarly.

The second infant was born at 30+1 weeks of gestation on the 50th centile for birthweight. He was exclusively formula fed with feeds increasing at an average rate of 23ml/kg/day to achieve full enteral feeds defined as 150ml/kg/day by day 9 of age. He developed Stage 2 NEC four days later after achieving full enteral feeds. His NEC was diagnosed based on radiological findings and was managed conservatively.

I'd like Ethics methods to be described as well.

This was an observational study auditing the feeding practice within each participating neonatal unit with no new intervention proposed. Hence, ethical approval was deemed not necessary. However, participating neonatal unit was encouraged to seek approval from local audit department.

Editor's Comments to Author:

Associate Editor

Comments to the Author:

Two external reviewers, both supportive, but both raise the issue of EC registration procedure and consent. The paper reads as an interventional prospective study, so the aspects related to consent should be covered, otherwise we do have a relevant issue.

Thank you for the feedback and interest in our work. This was purely an observational study auditing the feeding practice within each neonatal unit. There was no new intervention or protocol proposed as part of the study. Hence, ethical approval was deemed not necessary. However, each participating unit was advised to register the work with their local audit department. This has now been explained in the paper.

The other specific comments of the reviewers should also be considered and implemented;

The other comments have been reflected and implemented accordingly.

Reference

1. Quigley M, McGuire W. Formula versus donor breast milk for feeding preterm or low birth weight infants. *Cochrane Database Syst Rev*. 2014(4):CD002971.
2. Sanghvi KP, Joshi P, Nabi F, Kabra N. Feasibility of exclusive enteral feeds from birth in VLBW infants > 1200g-an RCT. *Acta Paediatrica*. 2013;102(7): PubMed e299-e304.
3. Chetry S, Kler N, Saluja S, Garg P, Soni A, Thakur A, Modi M. A randomised control trial comparing initiation of total enteral feeds on 1st day of life with standard feeding regimen in stable very low birth weight infants born between $\geq$ 30-34 weeks gestation and 1000-1500g. *Proceedings of the Pediatric Academic Societies and Asian Society for Pediatric Research*; 2014 May 3-6; Vancouver. 2014.