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Notes

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Enteral feeding regimens and necrotising enterocolitis in preterm infants: a multicentre case–control study

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ABSTRACT

Background: Most preterm infants who develop necrotising enterocolitis (NEC) have received enteral feeds. Uncertainty exists about which aspects of the feeding regimen affect the risk of NEC.

Aim: To examine associations between various enteral feeding practices and the development of NEC in preterm infants.

Methods: Multicentre case–control study. 53 preterm infants with NEC were enrolled together with a gestational age frequency-matched control without NEC from a randomly selected neonatal unit. Clinical and feeding data were extracted and compared between the groups.

Results: Significantly fewer cases than controls had received human breast milk (75% vs 91%; OR 0.32, 95% CI 0.11 to 0.98). The day on which enteral feeding was started did not differ significantly (mean (SD) days after birth: cases 2.9 (2.8) and controls 2.8 (1.8)). The mean (SD) duration of trophic feeding (<1 ml/kg/h) was significantly shorter in the cases (3.3 (3.1) days) than controls (6.2 (6.7) days) (mean difference (MD) -2.9, 95% CI -4.9 to -0.9) days. Cases were fully fed significantly earlier than controls (mean (SD) days after birth: cases 9.9 (4.2) and controls 14.3 (9.8); MD -4.4, 95% CI -7.3 to -1.5).

Conclusions: These data suggest that the duration of trophic feeding and rate of advancement of feed volumes may be modifiable risk factors for NEC in preterm infants. Further randomised controlled trials are warranted to assess the effect of different rates of feed advancement on the incidence of NEC, as well as other outcomes.

What is already known on this topic

► Inter-unit variation in the incidence if NEC in preterm infants is not fully explained by case mix.
► Enteral feeding regimens for preterm infants affect the risk of development of NEC but current data are insufficient to guide clinical practice.

What this study adds

► The duration of trophic feeding and rate of advancement of enteral feeding may be modifiable risk factors for the development of NEC in preterm infants.

Most preterm infants who develop necrotising enterocolitis (NEC) will have received enteral feeds. The timing of the introduction of milk feeds, and their rate of advancement, may be important determinants of the risk of NEC.[1–3] However, prospective studies have so far provided only limited evidence about the effect of different enteral feeding strategies on the risk of NEC in preterm infants.[4–7] Thus there is a need for further randomised controlled trials to determine how different feeding regimens for preterm infants affects their risk of developing NEC. Data from observational studies may inform the development of such trials, and identify and prioritise specific interventions for assessment. However, examination of associations between different feeding practices and NEC has been limited for two reasons. Studies based in centres or networks where feeding protocols for preterm infants are standardised cannot examine whether different feeding regimens affect the risk of NEC. Studies from larger neonatal networks generally use routinely collected data but these datasets contain only limited information on infants' enteral feeding regimens.[8 9]

This case–control study was undertaken in 10 independent neonatal centres, where there was evidence of marked variation in feeding practices with respect to type of milk used, timing of introduction of enteral feeds, and the rate of feed advancement.[10] Controls from a separate unit to each individual case were randomly selected to allow determination of any associations between the different feeding practices and the development of NEC.

METHODS

We conducted a case–control study in 10 neonatal units (appendix 1) in the north of Britain between January 2004 and December 2005. The Northern and Yorkshire multicentre research ethics committee approved the study.

Cases were preterm infants (<37 completed weeks' gestation) with NEC diagnosed using modified Bell criteria or at laparotomy or autopsy examination (table 1).[11]

When a case was reported, a participating neonatal centre was randomly selected and a control infant who had not developed NEC was identified. Controls were more than 34 weeks' postmenstrual age at recruitment and therefore unlikely to develop NEC subsequently. Cases and controls were frequency matched for gestational age at birth in one of three bands (<28 weeks,

Table 1 Case definition of necrotising enterocolitis

Stage I	Abdominal distension or abdominal x ray showing gaseous distension or frothy appearance of bowel lumen (or both); blood in stool; hypotonia, apnoea, or bradycardia (or combination of these)
Stage II	Abdominal tenderness or rigidity; absent bowel sounds; tissue in stool; abdominal x ray showing gas in the bowel wall or portal tree; abnormal bleeding with trauma; thrombocytopenia; lymphocytopenia
Stage III	Marked abdominal distension or rigidity; free gas in the peritoneum; spontaneous bleeding; coagulopathy; severe metabolic acidosis

28–32 weeks, >32 weeks). We obtained parental consent to access details of the infants' clinical history, and compared the antenatal, perinatal and postnatal clinical risk factors between the groups.

RESULTS

We enrolled a total of 53 cases (32 male, 21 female). Thirteen infants fulfilled the case definition for stage I NEC and 40 for stage II/III NEC; 18 cases were confirmed at laparotomy, and 3 at autopsy. The cases were diagnosed at a median postnatal age of 15 days (range 2–71 days). Controls matched by gestational age band were recruited at a median postnatal age of 54 days (range 12–144 days).

The two groups did not differ significantly with regard to mean (SD) gestational age at birth (cases 27.9 (3.1) weeks vs controls 28.0 (2.7) weeks) or birth weight (cases 1114 (427) g vs controls 1179 (478) g). Also, there were no significant differences between the groups with regard to rates of maternal pre-eclampsia, diabetes mellitus (including gestational), documented umbilical arterial absent or reversed end-diastolic flow velocity (AREDFV), history of maternal smoking during pregnancy and exposure to antenatal corticosteroids (more than 24 h before delivery), tocolytics or antibiotics within 1 week before delivery. Only three mothers (two controls and one case) received co-amoxiclav in the week prior to delivery. There were no significant differences between the groups with regard to the incidence of prolonged preterm rupture of the membranes (more than 24 h before delivery) or maternal fever in labour (table 2).

The mean (SD) Apgar scores were not significantly different at 1 min (cases 5.74 (2.47) vs controls 5.73 (2.45)) or 5 min after birth (cases 8.09 (1.56) vs controls 7.92 (1.74)). Nor was there any significant difference in the mean (SD) umbilical arterial pH levels (available for 19 cases and controls) of the two groups (cases 7.25 (0.16) vs controls 7.27 (0.13)).

Postnatal management

The rates of umbilical artery catheter use, mechanical ventilation (positive pressure ventilation or continuous positive airway pressure for more than 4 h), surfactant replacement, or use of non-steroidal anti-inflammatory (NSAID) therapy for patent ductus arteriosus (PDA) closure were not significantly different between the groups (table 3). Restricting analyses to the cases with stage II/III NEC (n = 40) did not alter any of these findings.

Feeding practices

All cases had commenced enteral milk feeding prior to diagnosis. Significantly fewer cases received expressed breast milk (40/53 vs 48/53; odds ratio (OR) 0.32, 95% CI 0.11 to 0.98; p<0.05). Of cases with stage II/III NEC (n = 40), 28 received breast milk versus 37 of matched controls (OR 0.19, 95% CI 0.05 to 0.73; p<0.05).

The mean (SD) day on which enteral feeding was commenced did not differ significantly between the groups (cases 2.9 (2.8) and controls 2.8 (1.8) days after birth). The mean (SD) duration of trophic feeding (<1 ml/kg/h) was significantly shorter in the cases (excluding seven infants diagnosed while still receiving trophic feeds) (cases 3.3 (3.1) and controls 6.2 (6.7) days; mean difference (MD) −22.9, 95% CI −24.9 to −20.9; p<0.05). Forty-two cases achieved full enteral feeds before diagnosis of NEC. These infants were fully fed significantly earlier than controls (cases 9.9 (4.2) and controls 14.3 (SD 9.8) days after birth; MD −24.4, 95% CI −27.3 to −21.5; p<0.05). The significant differences remained when analyses were restricted to cases with stage II/III NEC (mean duration of trophic feeding: 2.9 (3.3) days; time to full enteral feeds: 9.5 (4.7) days after birth; p<0.05).

Effect of type of milk feeding

The findings were not altered when analyses were stratified by type of milk feeding (formula fed versus partially or exclusively breast milk fed) (Mantel–Haenszel weighted MD in duration of trophic feeding: −2.9 days (95% CI −4.9 to −0.9); and weighted MD in time to full enteral feeding: −4.4 days (95% CI −7.3 to −1.5)).

Effect of AREDFV

Seven cases and five controls had an antenatal finding of AREDFV. There were no significant differences between infants with or without documented AREDFV in the time of feed commencement, duration of trophic feeding, or time to full enteral feeding in either the case or the control group. Stratified analyses (AREDFV detected versus undetected) did not alter the significant differences between cases and controls in duration of trophic feeding or time to achieve full feeds.

DISCUSSION

It has long been postulated that differences in enteral feeding regimens contribute to inter-unit variation in the incidence of NEC in preterm infants. Multicentre benchmarking studies have suggested that those units which introduce enteral feeding earlier, and advance feeding volumes more quickly, tend to have a higher incidence of NEC.[9] However, such studies, using routinely collected data, have been unable to examine whether the feeding regimens of individual infants are associated with the risk of developing NEC.

This case–control study was undertaken within an informal collaborative network of neonatal units with a relatively homogeneous population but without a cross-unit standardised policy for enteral feeding of preterm infants.[10] This allowed us to examine whether the regimens used to feed individual preterm infants were associated with NEC. Another strength of this study is that we removed the confounding effect of

Table 2 Antenatal characteristics

	Cases n (%)	Controls n (%)	OR (95% CI)
Maternal pre-eclampsia	10 (19)	14 (26)	0.65 (0.26 to 1.63)
Diabetes mellitus	2 (4)	3 (4)	0.65 (0.10 to 4.08)
Documented AREDFV	7 (13)	5 (9)	1.46 (0.43 to 4.93)
Maternal smoking	19 (36)	19 (36)	1.00 (0.45 to 2.21)
Antenatal corticosteroids	34 (64)	38 (72)	0.71 (0.31 to 1.60)
Tocolytic therapy	5 (9)	4 (8)	1.28 (0.32 to 5.04)
Maternal antibiotics	20 (38)	26 (49)	0.63 (0.29 to 1.36)
Membranes ruptured >24 h	15 (28)	12 (23)	1.35 (0.56 to 3.25)
Maternal fever (>38 °C) in labour	5 (9)	3 (6)	1.74 (0.39 to 7.67)

AREDFV, arterial absent or reversed end-diastolic flow velocity.

Original article

Table 3 Postnatal management

	Cases n (%)	Controls n (%)	OR (95% CI)
Mechanical ventilation	47 (89)	46 (87)	1.19 (0.37 to 3.82)
Surfactant replacement	41 (77)	42 (79)	0.89 (0.36 to 2.26)
Umbilical artery catheter	25 (47)	22 (42)	1.26 (0.58 to 2.71)
NSAID treatment for PDA	13 (25)	22 (42)	0.46 (0.20 to 1.05)

NSAID, non-steroidal anti-inflammatory drug; PDA, patent ductus arteriosus.

gestational age by frequency matching. Since short gestation remains the single most important determinant of the risk of NEC in preterm infants, older studies that matched solely for birth weight may have been subject to bias.[12]

We found that feeding with human breast milk was associated with lower risk of NEC, consistent with findings from previous observational studies.[13][14] Although this association may, in part, be due to other confounding variables, recent meta-analyses of randomised trials have also indicated that feeding preterm infants with breast milk reduces their risk of developing NEC.[15–17] These findings endorse the current practice of encouraging mothers to express breast milk for their preterm infants, and of supporting them to do so with evidence-based interventions.[18–20] The question of whether donor breast milk is the best alternative when maternal milk is not available requires consideration of feasibility, costs, acceptability and the effect on other important outcomes, principally nutrient intake, growth and development.

We did not find any evidence that commencing enteral feeds within the first few days after birth was associated with the risk of NEC. However, we did find that the subsequent feeding experience of these infants differed significantly between cases and controls. Cases received about three days of trophic feeds on average compared with six days in controls. The rate of feeds advancement was faster in cases, and infants achieved full enteral feeding on average about 5 days earlier than controls.

These findings should be interpreted cautiously. We have accounted for the major confounding variable, gestational age at birth, by frequency matching our cases with controls. However, although we did not find any significant differences in other potential antenatal and perinatal risk factors between the groups, unknown confounding variables may have affected the study results. In common with all unblinded studies of enteral feeding in preterm infants, two other sources of bias exist.

First, clinicians may have been more likely to investigate and diagnose NEC in infants they considered to be at higher risk, for example infants fed only formula milk (surveillance bias). A second major potential source of bias in feeding studies is the "substrate effect". Since the generation of gas in the bowel wall (pneumatosis intestinalis) or portal tract requires the presence of milk substrate, there may be a tendency to diagnose stage II/III NEC more often in infants who have received more enteral feeds.[4–6] Our primary analyses therefore included infants with all stages of NEC rather than only those where the diagnosis was "confirmed" radiologically. However, the differences we detected in duration of trophic feeding and time to full feeding persisted when analyses were restricted to infants with stage II/III NEC.

We did not find any evidence that an antenatal finding of AREDFV was associated with the risk of NEC in this study. However, the 95% CI for the effect size was wide because few participants in either group had documented AREDFV. Previous observational studies that have examined associations between AREDFV and the risk of developing NEC have reported inconsistent findings.[21] This may be related to differences in study design, especially with regard to management of confounding variables that are risk factors for NEC. Notably, none of the studies that have used a study design that accounted for birth weight and gestational age found a significant association between AREDFV and NEC.[22–24] This uncertainty may be resolved, and clinical practice better informed, when the findings of an ongoing multicentre randomised controlled trial comparing early versus delayed enteral feeding for infants with AREDFV become available (see Abnormal Enteral Doppler Prescription Trial: http://www.npeu.ox.ac.uk/adept/).

Although these and other data suggest that the more rapid advancement of enteral feeding volumes beyond trophic feeds is associated with a higher risk of developing NEC, a firm practice recommendation can only be made when sufficient data from randomised controlled trials are available. The currently available trial data indicate that compared with enteral fasting, trophic feeding reduces the time to full feeding and the length of hospital stay without increasing in the risk of NEC.[6] In addition, infants of mothers who express breast milk for early trophic feeding are more likely to receive breast milk as their ongoing principal form of nutrition.[25] However, the only trial that has compared trophic feeding with progressive advancement of enteral feeds in preterm infants was stopped early because of a borderline significant higher incidence of NEC in the advanced feeding group.[7] There is a high chance that this represents a spurious result.[26] Furthermore the findings of this single-centre study are unlikely to be widely generalisable—the trial excluded small for gestational age infants, enteral feeds were not introduced at all until about 10 days after birth in both cases and control groups, and fewer than a third of the study participants received breast milk.

A large multicentre trial of progressive advancement of enteral feeds versus prolonged trophic feeding appears to be a research priority. Because of the potential for feeding interventions to affect other competing outcomes (such as duration of use of parenteral nutrition, the risk of nosocomial infection, length of hospital stay),[27] as well as the problems inherent in minimising bias in (unblinded) feeding studies, it is recommended that any future trials should also aim to assess the effect on objective outcomes including mortality and longer-term neurological disability.[6]

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APPENDIX 1

Participating centres (local investigators)

- ► Royal Jubilee Maternity, Belfast (Dr S Craig)
- ► Princess Royal Maternity Hospital, Glasgow (Dr N Matta)
- ► Queen Mother's Hospital, Glasgow (Dr B Holland)
- ► Ninewells Hospital, Dundee (Dr M Schwager)
- ► Royal Infirmary, Edinburgh (Dr B Stenson)
- ► Forth Park Hospital, Kirkcaldy (Dr S Ainsworth)
- ► Antrim Hospital, Antrim (Dr S Bali)
- ► Ayrshire Central Hospital, Irvine (Dr S Kinmond)
- ► Royal Victoria Infirmary, Newcastle (Dr S Oddie)
- ► Royal Alexandra Hospital, Paisley (Dr G Stewart)