Early enteral feeding in high-risk preterm infants

This article describes the challenge of feeding extremely preterm infants in the context of immature gut development. The pathogenesis of necrotising enterocolitis (NEC) is explored. Aspects of early enteral feeding are discussed – including when to start, the role of 'minimal enteral feeding' and how to advance feeds. Preterm growth-restricted infants born after abnormal antenatal Doppler blood flow velocities are a particularly high-risk group and are discussed in detail. An on-going randomised controlled trial (ADEPT) which is trying to establish when milk feeds should best be introduced in these babies is described.

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Key points

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1. Preterm infants are at increased risk of necrotising enterocolitis (NEC); those who are growth restricted following abnormal antenatal Doppler studies are at highest risk.
2. There is no good evidence to support delaying feeds excessively.
3. Minimal enteral feeding compared to no feeds is associated with an earlier time to reach full milk feeds and time to discharge, with no increase in NEC but the optimal duration has not been defined.

Premature birth occurs at a time of rapid fetal growth and nutrient accumulation. Establishing postnatal nutrition is therefore essential. The aims of neonatal nutrition are to achieve appropriate growth, to maintain biochemical normality, to avoid toxicity or damage and to achieve full *enteral* feeding, The babies for whom this is most challenging are those who are born very early and those who are both premature and have intra-uterine growth restriction (IUGR). Parenteral nutrition (PN) has an important role in early stabilisation – it has advantages of allowing early calorie intake and preventing catabolism. However there are significant risks, including infection and cholestasis, and PN is expensive. In addition, 'starving' the gut may be harmful – with thinning of mucosa, shortening of villi, reduction of cell growth and division, and impairment of enzyme production[1]. Enteral feeding has many advantages including higher calorie intake and more appropriate nutrients. It also promotes growth and development of the gut and reduces the risk of infection. It is therefore important to establish enteral feeding as early as is safely possible.

Gut development

The mature gut is a complex organ with villi and microvilli providing a huge surface for absorption. Cells are specialised to produce enzymes and hormones and there is a well-developed gut immune system. However in very preterm babies there is considerable immaturity of both structural development and function.

During the first twelve weeks of embryonic life the tissues and basic structure of the gut develop and rotate within the abdominal cavity. During the second trimester the villi form and in the third trimester the gut grows considerably in size with development of micro-villi, and the brush-border, where enzymes are produced[2]. Regarding functional development – digestive enzymes and gastric acid are present by the end of the second trimester and pancreatic enzymes start to be produced at about 25 weeks[3]. Gut motility is obviously important for enteral feeding but co-ordinated peristalsis does not occur until about 30 weeks[3]. Thus for babies born below 30 weeks – the gut is structurally formed, but functionally immature and with an immature immune system. The challenge is – how and when to start enteral feeds.

Necrotising enterocolitis

One of the main problems in establishing enteral feeding is a fear of necrotising enterocolitis (NEC). This is an inflammatory condition of the bowel, characterised by ischaemic necrosis[4], which is most common in very low birthweight babies and correlates inversely with gestational age. There is a high morbidity and mortality. The triad of pathogenic features – including bacteria, ischaemia and enteral feeding – was recognised in the early report by Santulli[5].

The incidence of NEC varies depending on the population in question. Among 2,681 babies with birth weight 501-1500 grams born in, or transferred to, hospitals

participating in the NICHD Neonatal Network, in the USA, between February 1988 and August 1989, the incidence of 'proven NEC' was 10.5%, with 'suspected NEC' at 17.2%[6]. The Vermont Oxford Network (VON) low birthweight database, which includes infants 401-1500 grams, shows an overall incidence of NEC (clinical and radiographic diagnosis) of 6% (VON Annual Reports 2002 and 2003). Analysis of VON data previously showed an increased risk of NEC in babies with evidence of IUGR (birth weight below 10th centile): OR 1.27 (95% CI 1.05-1.53)[7] but information on antenatal Doppler studies was not collected.

NEC is a serious disease. The severity can be defined by staging using the 'Modified Bell's Criteria'[8]. The overall mortality is 20-40% – but up to 62% in Stage 3 NEC[9], and long-term morbidity may include bowel strictures and malnutrition secondary to short-gut syndrome.

Starting enteral feeds

The fetus swallows amniotic fluid *in utero*, so the gut is active before birth. In the postnatal period it is important to avoid mucosal atrophy, but also to avoid NEC. The evidence available to guide early feeding – including when to start, and the role of 'minimal enteral feeding' – is discussed below.

Information on when to start feeds is limited. A systematic review in the Cochrane Database published in 2000 looked at 'Early versus delayed initiation of progressive enteral feedings for parenterally fed low birthweight or preterm infants'[10]. Only two studies were included, with a total of seventy-two babies. Early feeds were started on or before day four of life. Babies starting feeds earlier required less PN and had fewer episodes of suspected sepsis. There was no difference in the incidence of NEC, weight gain, conjugated jaundice or death.

Minimal enteral feeding (MEF) – also called 'non-nutritive feeding', 'gut-priming' or 'trophic feeding', has been studied in quite some detail in preterm infants. It is usually defined as small volume feeds of 12-24 mL/kg/day. MEF has been shown to have direct beneficial effects on the gut mucosa, but has also been shown to have non-mucosal effects such as improved gut motility, increased gut hormone production and possibly increased gut blood flow[11,1]. The clinical effects of MEF in preterm infants have been summarised in a recent Cochrane Review, which was first published in 1997 and recently updated[12]. In the latest review ten trials compared MEF with no enteral feeds and one compared MEF with advancing enteral feeds. Trophic feeds compared to no feeds had a beneficial effect on time to reach full milk feeds (weighted mean difference 2.7 days less in the MEF group) and time to discharge (15.6 days less in the MEF group) with no increase in NEC. The one trial comparing advancing feeds with MEF showed a reduction in time to full milk feeds, but also an increased incidence of NEC. Looking at this study in more detail: 141 infants were randomised to either MEF or advancing feeds. In the MEF group enteral feeding was continued at 20 mL/kg/day for 10 days, while in the advancing group feeds were increased by 20 mL/kg/day every day. Both groups started feeds quite late (mean 10.3 days in MEF group; mean 9.3 days in advancing group) and feeds were given as 2-hourly bolus followed by 2-hours' fast. Breast milk fortifier was added before full enteral feeding was achieved. This is not recognised as a typical feeding practice in the UK. Seven infants in the MEF group and one infant in the advancing group developed NEC and the trial was discontinued[13].

In summary – for extremely preterm babies there is no good evidence to support delaying feeds excessively. A period of MEF appears safe and may be beneficial, but optimal duration is still not clear.

Some of the complications of prematurity – and their treatments – are recognised to affect gut blood flow. Presence of a patent ductus arteriosus may reduce diastolic blood flow in the descending aorta and mesenteric blood vessels, while treatment with indomethacin causes vasoconstriction. Use of dopamine also causes arterial vasoconstriction and early use of steroids in extremely low birthweight infants has been associated with increased risk of gut perforation[14]. There are no good randomised controlled trials of enteral feeding versus controls in these situations and at present the decision to withhold feeds or to continue with even small enteral volumes has to rest on clinical judgement.

Advancing enteral feeds

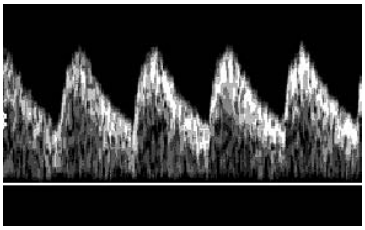
Another Cochrane Review looked at 'Rapid versus slow rate of advancement of feedings for promoting growth and preventing necrotizing enterocolitis in parenterally fed low-birthweight infants'[15]. Rapid was defined as 20-35 mL/kg/day increase and slow as 10-20 mL/kg/day. Three hundred and sixty nine babies were included in three studies. The rapid increase group achieved full milk feeds faster with no increase in NEC. When advancing enteral feeds it is important to be guided by the baby's clinical condition. The abdomen should be examined regularly to check for distension or tenderness, and passage of stools should be assessed. Feeds are often stopped for 'residuals' or gastric aspirates. Mihatsch studied 90 extremely low birthweight babies and found that if the baby is otherwise well, small residuals – up to 3 mL in 1kg baby or 2 mL in 750 gram baby – are often physiological, and feeds can safely be continued[16].

Type of milk

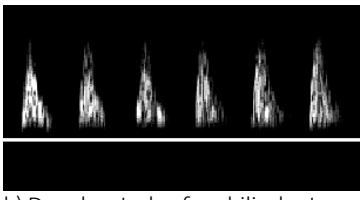
A large prospective randomised trial of early diet in preterm infants carried out in the 1980s demonstrated a protective effect of breast milk on NEC – OR 10.6 (95%CI 3.0, 37.3) for confirmed cases – those with definite intramural gas on X-ray, or specific pathological findings at laparotomy or post-mortem – and 3.5 (95%CI 1.5, 8.1) for all cases. There was a protective effect of delaying onset of formula feeding ($p<0.05$)[17]. Due to the difficulty of recruiting infants to a randomised trial of human or formula milk, little trial data is available to confirm this. If there is no breast milk available, the choice lies between term formula and preterm formula. Preterm formulas have higher nutrient content and the osmolality is usually similar to term formula: there is currently no evidence of advantage for one over the other in the introduction of enteral feeds in preterm infants.

Intra-uterine growth restriction (IUGR) and abnormal antenatal Dopplers

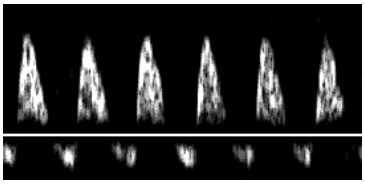
For some time it has been recognised that growth restricted preterm infants are at particularly high-risk of NEC and of feed intolerance. This was first described in case control studies of babies with NEC. Two similar studies, one in Sydney, Australia[18], and one in Oxford, UK[19], identified that for babies below 30 weeks, prematurity was the greatest risk factor for NEC. However



a) Doppler study of umbilical artery with forward flow in both systole and diastole.



b) Doppler study of umbilical artery with absent end-diastolic flow velocity.



c) Doppler study of umbilical artery with reversed end-diastolic flow velocity.

FIGURE 1 Antenatal Doppler studies of umbilical artery blood flow.

for those babies between 30 and 36 weeks' gestation, IUGR was a significant additional risk factor. Many of these babies are born after pregnancies complicated by placental dysfunction and increased vascular resistance. This can be monitored with antenatal Doppler ultrasound and the occurrence of absent or reversed end-diastolic flow velocities (**FIGURE 1**) has been associated with poor fetal outcome[20]. Evidence soon appeared to suggest a correlation between abnormal antenatal Dopplers and NEC[21].

A systematic review of 14 studies comparing the NEC rate in babies born after abnormal Doppler studies compared to those born after normal Dopplers, showed a significantly increased risk of NEC in the abnormal Doppler group (OR 2.3, 95% CI 1.49-3.03).

In these fourteen studies, which included a total of 659 infants, the incidence of NEC varied from 0-59%, with an average of 12.9%[22].

Surveys of feeding practice of growth-restricted babies among neonatal units in two health regions of England – Southwest and East Anglia – revealed considerable variation in practice. In the Southwest, enteral feeding was delayed in 9/12 hospitals for IUGR babies of less than 32 weeks' gestation ('always' in three, 'usually' in six), and 'usually' in four hospitals for babies at 32-36 weeks. Feeds were delayed for less than five days in five hospitals, greater than five in one hospital and for variable duration in five. Abnormal Dopplers, polycythaemia, presence of umbilical artery catheter and the absence of breast milk made delay more likely. Within the fifteen hospitals in the Eastern Region, five units commenced feeds on day one, two delayed until day seven, with the remainder commencing feeds between day two and day five. The main reason cited for delaying feeds was to try to prevent NEC.

There is thus genuine uncertainty about how to feed these highest risk babies and no clear evidence on which to base practice. For this reason ADEPT – the Abnormal Doppler Enteral Prescription Trial – has been established to try and answer the question: 'Is early or late introduction of enteral feeding beneficial or harmful for IUGR babies born after abnormal Dopplers?' This is a randomised controlled trial, but not blinded, which is aiming to recruit 400 babies over two years. Eligibility and exclusion criteria are listed in **TABLE 1**. The babies are randomly allocated to early feeds – starting between 24 and 48 hours of age, or to late feeds starting after 5 days. Feeding advancement then follows a standard protocol, which varies depending on birthweight, so that the smallest babies have several days of minimal enteral nutrition and advance more slowly (**FIGURE 2**), but which is the same for both the early and late feeding groups. Primary outcomes are the age in days to established full milk feeds and the occurrence of NEC. Secondary outcomes include survival, growth, duration of level 1 and level 2 intensive care[23] and occurrence of various medical complications such as sepsis, cholestasis and bronchopulmonary dysplasia[24].

Conclusion

Premature infants present a significant nutritional challenge. Enteral feeding is the safest and best method, but immature physiology puts these babies at high risk of NEC. Minimal enteral feeding appears to be a safe way to promote gut function, but there is a lack of good evidence on which to base many other aspects of feeding strategy. The ADEPT study is a randomised controlled trial currently in progress investigating whether it is safe and beneficial to start enteral feeds early in a particularly high-risk group of preterm infants with IUGR. There is a need for further research in this important area of neonatal care.

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Entry criteria

- Gestational age up to and including 34 weeks + 6 days (dated by antenatal ultrasound or clinically).
- Antenatal ultrasound showing either:
  - absent or reversed end diastolic flow velocities on at least 50% of the Doppler waveforms from the umbilical artery on at least one occasion during pregnancy *or*
  - cerebral redistribution, defined as occuring when both the umbilical artery pulsatility index is greater than the 95th centile and the middle cerebral artery pulsatility index is less than the 5th centile for gestational age.
- Small for gestational age (birth weight <10th centile for gestational age based on Child Growth Foundation Charts).
- Postnatal age 20-48 hours.

Exclusion criteria

- Major congenital abnormality including known chromosomal abnormality.
- Twin-twin transfusion.
- Intra-uterine transfusion or exchange transfusion.
- Rhesus iso-immunisation.
- Significant multi-organ failure prior to trial entry.
- Inotropic drug support prior to trial entry.
- Already received any enteral feeding.

TABLE 1 ADEPT eligibility and exclusion criteria.

Day of feeding	Volume of milk according to birth weight (mL/kg/day) birth weight (mL/kg/day)				
	<600g	600-749g	750-999g	1000-1249g	≥1250g
1	12	12	12	12	24
2	12	12	12	24	36
3	12	24	24	36	48
4	24	36	36	48	60
5	36	48	48	60	72
6	48	60	60	72	84
7	60	72	72	84	96-108
8	72	84	84	96-108	120-132
9	84	96	96-108	120-132	144-150
10	96	108-120	120-132	144-150	
11	108-120	132-144	144-150		
12	132-144	150			
13	150				
14		Increase as required			

FIGURE 2 ADEPT feeding strategy.

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For further information about the ADEPT trial, please see the ADEPT website www.npeu.ox.ac.uk/adept