

REVIEW

Feeding growth restricted preterm infants with abnormal antenatal Doppler results

J Dorling, S Kempley, A Leaf

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Absence or reversal of end diastolic flow (AREDF) in the umbilical artery is associated with poor outcome, and elective premature delivery is common. Feeding these infants is a challenge. They often have poor tolerance of enteral feeding, and necrotising enterocolitis may develop. This review explores current practice to see if there is evidence on which to base guidelines. The incidence of necrotising enterocolitis is increased in infants with fetal AREDF, especially when complicated by fetal growth restriction. Abnormalities of splanchnic blood flow persist postnatally, with some recovery during the first week of life, providing justification for a delayed and careful introduction of enteral feeding. Such a policy exposes babies to the risks of parenteral nutrition, with no trials to date showing any benefit of delayed enteral nutrition. Trials are required to determine the optimum timing for introduction of enteral feeds in growth restricted infants with fetal AREDF.

variable duration in five. Abnormal Doppler ultrasound results for fetal blood vessels, polycythaemia, presence of umbilical catheters, and absence of breast milk made delay more likely. Within the 15 hospitals in the Eastern Region,² five units started feeds on day 1, two delayed until day 7, with the remainder starting feeds between day 2 and 5. The main reason cited for delaying feeds was to try to prevent NEC. Is this justified?

WHICH INFANTS ARE AT INCREASED RISK OF NEC?

Infants with intrauterine growth restriction (IUGR)

Early case-control studies of NEC tended to match cases with controls on the basis of birth weight. Many did not specifically evaluate IUGR as a risk factor,³ but even when they did, the marginal excess of SGA infants in the NEC cases was not statistically significant.⁴ Matching by birth weight may have led to the inclusion of similar numbers of SGA infants in the controls. More recent case-control studies which have matched controls by gestation have shown that IUGR may be a clinical risk factor for NEC. The case-control study by Beeby and Jeffrey⁵ of 82 infants with NEC revealed a different spectrum of associated factors for different gestational age groups: for babies of 30–36 weeks gestation, IUGR and markers of birth asphyxia were significant risk factors: odds ratio (OR) 6 (95% confidence interval (CI) 1.3 to 26.8) for birth weight <10th centile, and OR 9 (95% CI 1.1 to 71) for birth weight <3rd centile. For infants below 30 weeks gestation, formula milk feeding was a significant risk factor (OR 4, 95% CI 1.1 to 14.1), but neither timing of first feed (3.1 v 2.5 days for controls) nor use of formula were significant factors for those born at 30–36 weeks. In an observational study of 69 cases of suspected or proven NEC,⁶ 49% of infants were SGA (birth weight <10th centile), with 71% of those born at 30–36 weeks being SGA. Analysis of the effect of IUGR on outcome of 19 759 singleton infants born at 25–30 weeks gestation and enrolled in the Vermont-Oxford Database revealed an increased risk of NEC when corrected for significant covariates (OR 1.27, 95% CI 1.05 to 1.53).⁷

Antenatal ultrasound with Doppler assessment of fetal blood flow velocities has made it possible to detect a population of fetuses with poor growth and abnormal circulation. Absence or reversal of end diastolic flow (AREDF) in the umbilical artery is associated with poor outcome,¹ and thus elective premature delivery is common. Feeding these infants is a challenge: they are already under-nourished at birth and good nutrition and growth are essential. They often have poor tolerance of enteral feeding, and there is anxiety about development of necrotising enterocolitis (NEC). We set out to explore current practice and to determine whether there is evidence on which to base guidelines.

CURRENT PRACTICE

There is a lack of published information on current feeding practices for these infants. Recent surveys carried out in two English Health Regions (Southwest and Eastern) revealed considerable variations in practice. In the Southwest, enteral feeding was delayed in 9/12 hospitals for small for gestational age (SGA) babies <32 weeks gestation (“always” in three, “usually” in six), and “usually” in four hospitals for babies born at 32–36 weeks. Feeds were delayed for less than five days in five hospitals, more than five days in one hospital, and for a

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Abbreviations: AREDF, absence or reversal of end diastolic flow; IUGR, intrauterine growth restriction; MEF, minimal enteral feeding; NEC, necrotising enterocolitis; SGA, small for gestational age; SMA, superior mesenteric artery

The Santulli theory for pathogenesis of NEC involves a triad of ischaemia, bacteria, and substrate.⁸ The development of antenatal Doppler ultrasound of fetal blood vessels⁹ made it possible to study the fetal circulation, and reports soon appeared confirming that growth restricted fetuses often showed abnormal flow velocities in the descending aorta, with absence or even reversal of forward flow during diastole.

Infants with abnormal antenatal Doppler studies

In the IUGR fetus, hypoxaemia produces circulatory redistribution towards the brain and away from the viscera and placenta, culminating in umbilical artery or aortic AREFD in the most severely affected. There is little doubt that AREFD is associated with poor fetal outcome, but are these infants at increased risk of developing NEC once delivered?

We identified 14 unequivocally independent case series¹⁻¹⁰⁻²² comparing NEC rates in infants who exhibited fetal AREFD with a control group (fig 1). Nine studies show an excess of NEC in the AREFD infants, with an overall OR for developing NEC of 2.13 (95% CI 1.49 to 3.03) compared with controls with forward fetal end diastolic flow.

Eight studies classified NEC using the stricter definition of radiological or surgical confirmation, of which six showed an excess of confirmed NEC in the AREFD group.¹⁻¹⁰⁻¹⁴ A large study by Kirsten *et al*¹⁵ showed the reverse pattern, but their study population was defined by maternal pregnancy induced hypertension, rather than suspected IUGR. Adiotomre *et al*²¹ had only one patient in each group with NEC. Overall, confirmed NEC was not significantly increased in these studies (OR 1.6, 95% CI 0.9 to 2.8), but the six studies examining confirmed NEC in preterm infants with IUGR¹⁰⁻¹¹⁻¹³⁻¹⁴⁻²¹ show greatly increased odds of confirmed NEC in infants with fetal AREFD (OR 6.9, 95% CI 2.3 to 20)

In many studies, fetuses with AREFD required earlier delivery than controls. It could be argued that the higher risk of NEC in these studies was primarily related to the known risk factors of low gestation and birth weight. The excess of

confirmed NEC was also found in the two series that matched controls for gestation and weight (OR 5.5, 95% CI 1.1 to 28).¹⁰⁻¹¹

MECHANISMS OF INCREASED RISK OF NEC IN INFANTS WITH AREFD

Several mechanisms, acting both before and after delivery, may explain the excess of NEC seen in growth restricted infants who exhibited fetal AREFD.

Abnormalities of the fetal mesenteric circulation have been shown to be part of brain sparing circulatory redistribution and AREFD.²³ A combination of fetal hypoxia and increased mesenteric vascular resistance could produce hypoxic-ischaemic injury of the intestine or its mucosa before birth. Even if direct tissue injury does not occur, prolonged exposure to these conditions may modulate the development of motor, secretory, and mucosal function so that postnatally the intestine is more susceptible to stasis, abnormal colonisation, and bacterial invasion. Pseudo-obstruction has been documented in growth retarded infants, particularly in the presence of echogenic bowel and abnormal Doppler studies.²⁴⁻²⁵ Pregnancy induced hypertension with fetal growth restriction is also associated with neutropenia in early postnatal life, which may affect susceptibility to infective factors.²⁶

After delivery, these infants are no longer hypoxic and it might be expected that any circulatory redistribution would rapidly resolve. However, postnatal physiological studies have shown persistent abnormalities in superior mesenteric artery (SMA) blood flow velocity in infants who experienced fetal AREFD.²⁷⁻²⁹ Both SMA and coeliac axis blood flow velocity are dramatically reduced on the first day of postnatal life. There is a slow recovery in baseline values during the first week of life, with SMA values at day 7 similar to those found in unfed appropriately grown infants.²⁸⁻²⁹ Despite this recovery in baseline SMA blood flow velocity values, the dynamic

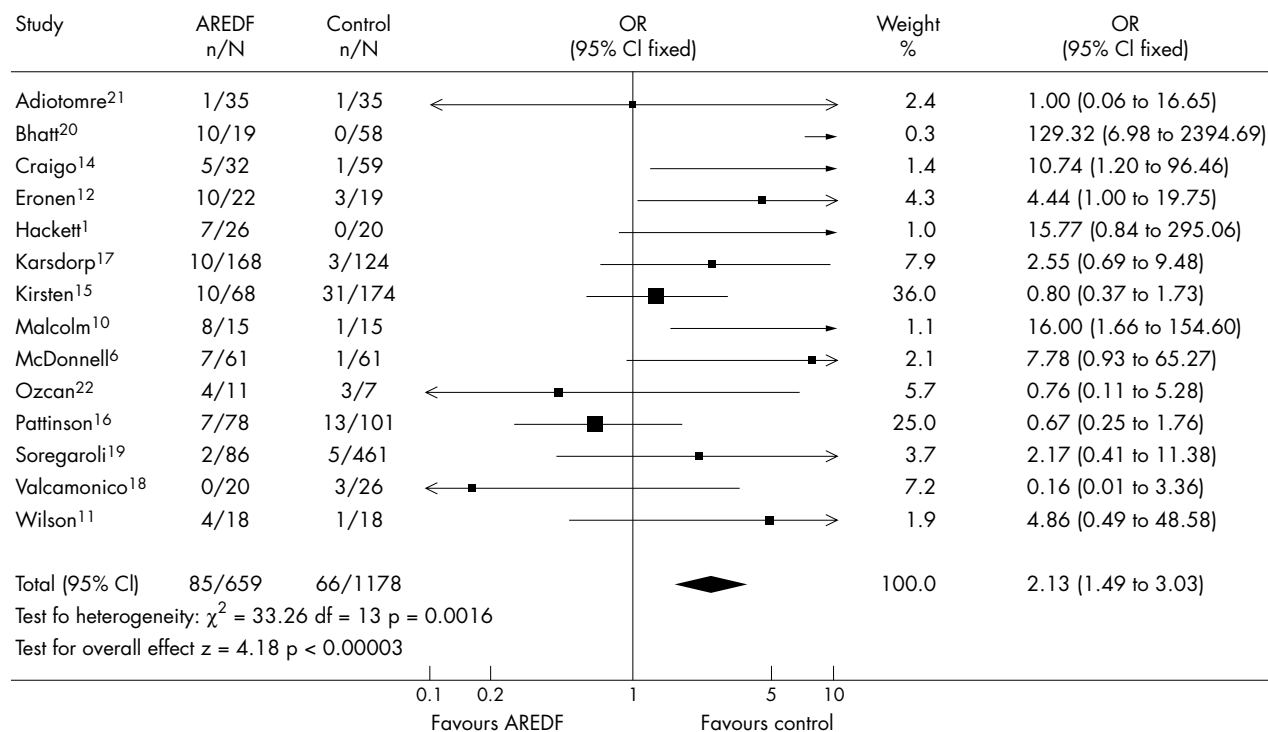


Figure 1 Studies comparing rates of necrotising enterocolitis (NEC) in fetuses with absent or reversed end diastolic flow (AREFD) in the umbilical artery or aorta, compared with controls who had forward end diastolic flow. Total number of cases of NEC (all grades, confirmed or unconfirmed) per live births in each group. The odds ratio (OR) and its 95% confidence interval (CI) are given.

response to the first enteral feed is still impaired in SGA infants.³⁰

Experimental studies in animals show that hypoxia reduces intestinal blood flow and oxygen delivery through adrenergic vasoconstriction.³¹ Increased oxygen extraction can compensate for a 30% reduction in gut blood flow,³² but enteral feeding reduces the ability of oxygen extraction to compensate for the effects of hypoxia.³³ The metabolic demands of enteral feeding increase oxygen consumption by the intestine.³⁴

The combination of antenatal and persisting postnatal disturbances of gut perfusion, interacting with the metabolic demands of feeding, may adversely affect intestinal tissue oxygenation, combining with stasis and immunological factors to contribute to the development of NEC. In infants with AREFD, the recovery of parameters of intestinal perfusion during the first week provides a sound rationale for a modest delay in enteral feeding in these infants, to ensure that the metabolic stress of feeding is only imposed when baseline intestinal perfusion is as healthy as possible.

Data from the recently published GRIT study is reassuring with regard to the overall risk of NEC in infants with intrauterine growth failure, with only 30 of 587 infants (5.1%) developing NEC.³⁵ This study comprised fetuses with growth failure and abnormal Doppler studies, in which obstetricians were in a situation of equipoise over whether or not to deliver.

CURRENT EVIDENCE ON FEEDING HIGH RISK INFANTS

Which milk to feed?

In a large prospective randomised trial of early diet in preterm infants, Lucas and Cole³⁶ identified a protective effect of breast milk on NEC (OR 10.6 (95% CI 3.0 to 37.3) for confirmed cases and OR 3.5 (95% CI 1.5 to 8.1) for all cases) and showed a protective effect of delaying onset of formula feeding ($p < 0.05$). Owing to the difficulty of recruiting infants to a randomised trial of human or formula milk when mothers have strong preferences, few trial data are available to confirm this.³⁷

When to start feeds? Early versus delayed feeding

Although feeds are commonly delayed in high risk infants, there is little evidence that this approach is beneficial. A Cochrane review³⁸ identified two small studies by Khayata *et al*³⁹ and Davey *et al*⁴⁰ in 72 preterm infants. Outcomes studied included days feedings held, weight gain, conjugated jaundice, NEC, and death. No statistically significant benefits were seen, and more studies are required to determine the optimal time of feed commencement.

Delaying feeds could be detrimental. Parenteral nutrition is usually used as an alternative source of carbohydrate, amino acids, and lipid, but side effects are common, especially catheter related sepsis, which occurs in up to 40% of preterm infants receiving parenteral nutrition through a percutaneous central catheter.⁴¹⁻⁴² Other important side effects include cardiac tamponade, drug administration errors, cholestasis, osteopenia of prematurity, and metabolic complications.⁴³⁻⁴⁵

Minimal enteral feeding

An alternative approach to delaying feeds is to start small volumes of milk (10–20 ml/kg/day) and continue this for a period of time before advancing the volume of each feed. This approach, known as minimal enteral feeding (MEF) or trophic feeding, has recognised benefits, including enhanced endocrine and exocrine hormonal activity, improved growth of intestinal mucosa, and maturation of gut motility.⁴⁶⁻⁴⁸ Unfortunately, this approach has yet to be subjected to a large enough randomised trial to exclude a potential increase

in the incidence of NEC. Tyson and Kennedy⁴⁹ reviewed six studies of MEF compared with no feeding up to the third week of life in 397 preterm infants. Outcomes significantly affected by MEF were length of stay (weighted mean difference 15.6 days less stay in MEF group; 95% CI 8.5 to 22.8) and days to full feeding (weighted mean difference 2.7 days less in MEF group; 95% CI 0.98 to 4.4).

Since this review was last updated in 1997, three further trials of MEF have been published. Van Ellburg *et al*⁵⁰ studied 42 infants, seeing only one case of NEC in the unfed group. McClure and Newell⁵¹ studied 100 infants, seeing one and two cases of NEC in trophic and control infants respectively. The trial of Schanler *et al*⁵² contained 171 infants, with 13 cases of NEC in the trophic group, compared with 10 cases in the control infants. Combining these results with those of the meta-analysis of Tyson and Kennedy⁴⁹, in 692 infants, NEC rates are similar at 10.5% for MEF and 9.4% for control infants (relative rate 1.07, 95% CI 0.84 to 1.36). Further studies with adequate sample sizes are needed. If trophic feeding is shown to be safe with regard to NEC, substantial savings from reduced length of stay, use of parenteral nutrition, and episodes of septicaemia should be realised.

How fast to advance the feeding volumes

Data from retrospective studies have suggested that rapid advancement of feed volumes may increase the incidence of NEC, leading to a cautious approach by many clinicians.⁵³⁻⁵⁴ Trial data are reassuring, but relatively few patients (369) from three trials were included in the Cochrane review of feed advancement.⁵⁵ In infants randomised to a faster increase in feed volumes, there was a reduction in days to full enteral feeding and days to regain birth weight, but no effect on NEC (relative risk 0.90, 95% CI 0.46 to 1.77); further research is needed once again. Unfortunately the situation in extremely low birthweight infants is less clear, as only Rayyis *et al*⁵⁶ included this population. A study published since this review⁵⁷ compared 15 and 30 ml/kg/day increments in 53 infants under 1250 g birth weight; two cases of NEC were seen in the faster advancement group. The only significant difference was a reduction in days to full feeding in the advancing group (10 v 14.8 days). A recent trial comparing MEF with a regimen of advancing feeds in 141 infants born before 32 weeks gestation was stopped early as seven infants in the advancing group developed NEC compared with one control infant.⁵⁸ The incidence of late onset sepsis and death were similar between the groups, with feed advancement leading to earlier establishment of feeds, reduced length of stay, and reduced use of parenteral nutrition. It is difficult to confidently generalise these results; the mean day of starting feeds was late in both groups at 9.3 v 10.3 days, and fortifier was added when feeds reached 120 ml/kg/day and was doubled on reaching 140 ml/kg/day. In addition, feeds were given by a two hour infusion, followed by a two hour fast. These practices are not commonly used: feeds tend to be started earlier, given by continuous infusion or regular boluses without fasting, and fortifier is usually added to milk feeds when infants have reached 150 ml/kg/day.⁵⁹

SUMMARY AND CONCLUSIONS

The incidence of NEC is increased in infants who exhibit fetal AREFD, especially when this is detected in pregnancies complicated by fetal growth restriction. The association of NEC with abnormal fetal Doppler studies is present even when compared with infants from pregnancies complicated by IUGR and when controlled for birth weight and gestation. Abnormalities of splanchnic blood flow persist postnatally, with some recovery during the first week of life, providing physiological justification for a delayed and careful introduction of enteral feeding. Such a policy exposes babies to the

risks of parenteral nutrition, with no trials to date showing any benefit of delayed enteral nutrition. Trials are urgently required to determine the optimum timing for introduction of enteral feeds in the particular subgroup of growth restricted infants with fetal AREDF. This review is limited to looking at abnormal flow in the umbilical blood vessels, although other antenatal abnormalities of flow such as in the ductus venosus, cerebral arteries, or mesenteric arteries may also be important.

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