Delayed introduction of progressive enteral feeds to prevent necrotising enterocolitis in very low birth weight infants (Review)

Bombell S, McGuire W

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in The Cochrane Library 2009, Issue 3

http://www.thecochranelibrary.com

Copyright © 2009 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>HEADER</td>
<td>1</td>
</tr>
<tr>
<td>ABSTRACT</td>
<td>1</td>
</tr>
<tr>
<td>PLAIN LANGUAGE SUMMARY</td>
<td>2</td>
</tr>
<tr>
<td>BACKGROUND</td>
<td>2</td>
</tr>
<tr>
<td>OBJECTIVES</td>
<td>3</td>
</tr>
<tr>
<td>METHODS</td>
<td>3</td>
</tr>
<tr>
<td>RESULTS</td>
<td>4</td>
</tr>
<tr>
<td>DISCUSSION</td>
<td>5</td>
</tr>
<tr>
<td>AUTHORS’ CONCLUSIONS</td>
<td>6</td>
</tr>
<tr>
<td>ACKNOWLEDGEMENTS</td>
<td>7</td>
</tr>
<tr>
<td>REFERENCES</td>
<td>7</td>
</tr>
<tr>
<td>CHARACTERISTICS OF STUDIES</td>
<td>9</td>
</tr>
<tr>
<td>DATA AND ANALYSES</td>
<td>13</td>
</tr>
<tr>
<td>Analysis 1.1. Comparison 1 Delayed versus early introduction of progressive enteral feeding, Outcome 1 Necrotising enterocolitis</td>
<td>13</td>
</tr>
<tr>
<td>Analysis 1.2. Comparison 1 Delayed versus early introduction of progressive enteral feeding, Outcome 2 Mortality prior to discharge</td>
<td>14</td>
</tr>
<tr>
<td>Analysis 1.3. Comparison 1 Delayed versus early introduction of progressive enteral feeding, Outcome 3 Weight gain (g/kg/week)</td>
<td>14</td>
</tr>
<tr>
<td>Analysis 1.4. Comparison 1 Delayed versus early introduction of progressive enteral feeding, Outcome 4 Duration of hospital admission (postmenstrual weeks at discharge)</td>
<td>15</td>
</tr>
<tr>
<td>WHAT’S NEW</td>
<td>15</td>
</tr>
<tr>
<td>HISTORY</td>
<td>15</td>
</tr>
<tr>
<td>CONTRIBUTIONS OF AUTHORS</td>
<td>16</td>
</tr>
<tr>
<td>DECLARATIONS OF INTEREST</td>
<td>16</td>
</tr>
<tr>
<td>INDEX TERMS</td>
<td>16</td>
</tr>
</tbody>
</table>
ABSTRACT

Background

The introduction of progressive enteral feeds for very low birth weight infants is often delayed for several days or longer after birth due to concern that earlier introduction may not be tolerated and may increase the risk of necrotising enterocolitis. However, delaying enteral feeding could diminish the functional adaptation of the gastrointestinal tract and prolong the need for parenteral nutrition with its attendant infectious and metabolic risks.

Objectives

To determine the effect of delayed introduction of progressive enteral feeds on the incidence of necrotising enterocolitis, mortality and other morbidities in very low birth weight infants.

Search strategy

The standard search strategy of the Cochrane Neonatal Group was used. Searches were made of the Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library, Issue 1, 2009), MEDLINE (1966 - February 2009), EMBASE (1980 - February 2009), CINAHL (1982- February 2009), conference proceedings, and previous reviews.

Selection criteria

Randomised or quasi-randomised controlled trials that assessed the effect of delayed (after 96 hours' postnatal age) versus earlier introduction of progressive enteral feeds on the incidence of necrotising enterocolitis, mortality and other morbidities in very low birth weight infants.

Data collection and analysis

The standard methods of the Cochrane Neonatal Group were used with separate evaluation of trial quality and data extraction by two review authors. Data were synthesised using a fixed effects model and reported using typical relative risk, typical risk difference and weighted mean difference.
Main results

Three small trials in which a total of 115 very low birth weight infants participated were eligible for inclusion. Only a minority of participants were of extremely low birth weight or extreme preterm gestation. These trials provided no evidence that delayed introduction of progressive enteral feeds affected the incidence of necrotising enterocolitis, mortality or other neonatal morbidities. In view of the small number of participants, important beneficial or harmful effects cannot be excluded.

Authors’ conclusions

The available data are insufficient to inform clinical practice. Further large pragmatic randomised controlled trials are needed to determine how the timing of the introduction of progressive enteral feeds affects important clinical outcomes in very low birth weight infants and particularly in extremely low birth weight or growth restricted infants.

Plain Language Summary

Delayed introduction of progressive enteral feeds to prevent necrotising enterocolitis in very low birth weight infants

There is insufficient evidence to determine whether delaying the introduction of enteral milk feeds given to very low birth weight infants reduces the incidence of necrotising enterocolitis.

Very low birth weight infants (birth weight less than 1500 grams) are at risk of developing a severe bowel disorder called “necrotising enterocolitis”. It is thought that one possible way to prevent this condition is to delay the introduction of milk feeds until several days (or longer) after birth. Only two small trials have assessed the effect of delayed rather than early introduction of milk feeds for very low birth weight infants. Data from these trials are insufficient to guide clinical practice. Further trials are needed to provide evidence to inform this key area of care.

Background

Necrotising enterocolitis is an important cause of morbidity, mortality and long term neurodisability in very low birth weight infants. Extremely low birth weight and extremely preterm infants are at greatest risk (Bisquera 2002; Holman 2006; Rees 2007). Intrauterine growth restriction may be an additional specific risk factor, especially if associated with circulatory redistribution demonstrated by absent or reversed end-diastolic flow velocities in antenatal Doppler studies of the fetal aorta or umbilical artery (Bernstein 2000; Garite 2004; Dorling 2005).

Most very low birth weight infants who develop necrotising enterocolitis have received enteral milk feeds. Evidence exists that feeding with formula milk increases the risk (Quigley 2007). The timing of the introduction and the rate of progression of enteral feed volumes may be modifiable risk factors for the development of necrotising enterocolitis (Brown 1978; Uauy 1991). Data from observational studies suggest that adopting standardised feeding regimens that include delaying the introduction of progressive enteral feeds for about five to seven days after birth reduces the risk of necrotising enterocolitis (Patole 2005).

In current clinical practice, the introduction of progressive enteral feeds for very low birth weight infants is often preceded by a period of enteral fasting or “trophic feeding” (feed volumes up to 24 ml/kg/day) (Boyle 2004; Patole 2004; Dorling 2005). However, there may also be potential disadvantages associated with delaying the introduction of progressive enteral feeds. Because gastrointestinal hormone secretion and motility are stimulated by enteral milk, delayed enteral feeding could diminish the functional adaptation of the gastrointestinal tract (Berseth 1990; Burrin 2002). Prolonging the duration of use of parenteral nutrition may be associated with infectious and metabolic complications that have adverse consequences for survival, duration of hospital stay, growth and development (Flidel-Rimon 2004; Stoll 2004). It has been argued that the risk of necrotising enterocolitis should not be considered in isolation of these other potential clinical outcomes when determining feeding policies and practice for very low birth weight in-
fants (Flidel-Rimon 2006).

This review focuses on the comparison of delayed versus earlier introduction of progressive enteral feeding; that is, advancing the volume of milk feeds beyond “trophic” levels. The effect of trophic feeding, the early introduction of small volume enteral feeds (up to 24 ml/kg/day) without advancing the feed volumes for at least five days versus enteral fasting is addressed in the Cochrane review “Early trophic feeding for very low birth weight infants” (Bombell 2009).

**OBJECTIVES**

To determine the effect of delayed introduction of progressive enteral feeds on the incidence of necrotising enterocolitis, mortality and other morbidities in very low birth weight infants.

The following subgroup analyses were planned:

1. Exclusively formula milk-fed infants.
2. Infants were fully or partially fed with breast milk (maternal or donor).
3. Extremely low birth weight (less than 1000 grams) or extremely preterm (less than 28 weeks' gestation at birth).
4. Infants with intrauterine growth restriction or infants with absent or reversed end-diastolic flow velocities detected on antenatal Doppler studies of the fetal aorta or umbilical artery.

**METHODS**

**Criteria for considering studies for this review**

**Types of studies**

Randomised or quasi-randomised controlled trials or cluster randomised trials.

**Types of participants**

Very low birth weight (less than 1500 grams) or very preterm (less than 32 weeks' gestation) newborn infants.

**Types of interventions**

Delayed introduction of progressive enteral feeds (more than four days after birth) versus earlier introduction of enteral feeds. Progressive enteral feeding was defined as feed volumes in excess of trophic feeds (24 ml/kg/day or 1 ml/kg/hour). Infants should have received the same type of milk (breast milk or formula), the same route and mode of feeding (intragastric or transpyloric, bolus gavage or continuous) and the same rate of feed volume advancement in both groups.

**Types of outcome measures**

**PRIMARY OUTCOMES:**

1. Necrotising enterocolitis confirmed by at least two of the following features:
   - abdominal radiograph showing pneumatositis intestinalis or gas in the portal venous system or free air in the abdomen
   - abdominal distension with abdominal radiograph with gaseous distension or frothy appearance of bowel lumen (or both)
   - blood in stool
   - lethargy, hypotonia, or apnoea (or combination of these);
   - or a diagnosis confirmed at surgery or autopsy (Walsh 1986).

2. All-cause mortality during the neonatal period and prior to hospital discharge.

**SECONDARY OUTCOMES:**

3. Growth: (i) Time to regain birth weight and subsequent rates of weight gain, linear growth, head growth, or skinfold thickness up to 6 months' age corrected for preterm birth.
   (ii) Long-term growth: weight, height, or head circumference and/or proportion of infants who remain below the tenth percentile for the index population's distribution assessed at intervals from six months of age.

4. Neurodevelopment: (i) Death or severe neurodevelopmental disability defined as any one or combination of the following: non-ambulatory cerebral palsy, developmental delay (developmental quotient less than 70), auditory and visual impairment. Each component will be analysed individually as well as part of the composite outcome.
   (ii) Neurodevelopmental scores in survivors aged greater than or equal to 12 months' of age measured using validated assessment tools.
   (iii) Cognitive and educational outcomes in survivors aged more than five years old.

5. Time to establish full enteral feeding (days)

6. Time to establish oral feeding independently of parenteral nutrition and/or enteral tube feeding (days)

7. Episodes of feed intolerance resulting in an interruption or cessation of progression of enteral feeds.
8. Incidence of invasive infection as determined by culture of bacteria or fungus from blood, cerebrospinal-spinal fluid, urine or from a normally sterile body space

9. Duration of hospital stay (days)

**Search methods for identification of studies**

The standard search strategy of the Cochrane Neonatal Group was used. Searches were made of the Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library, Issue 1, 2009), MEDLINE (1966 - February 2009), EMBASE (1980 - February 2009), and CINAHL (1982 - February 2009) [via OVID] using the following text words and MeSH terms: [Infant, Newborn OR Infant, Premature OR Infant, Low Birth Weight OR infant* OR neonat*] AND "Infant-Nutrition"/all subheadings Newborn OR Infant, Premature OR Infant, Low Birth Weight OR Infant Formula OR milk OR formula OR trophic feeding OR minimal enteral nutrition OR gut priming ]. The search outputs were limited with the relevant search filters for clinical trials. No language restriction was applied.

References in previous reviews and studies were examined. The abstracts presented at the Society for Pediatric Research and European Society for Pediatric Research between 1990 and 2008 were searched. Trials reported only as abstracts were eligible if sufficient information was available from the report, or from contact with the authors, to fulfil the inclusion criteria. The UK National Research Register (http://www.crn.nhs.uk), and Current Controlled Trials (http://www.controlled-trials.com) websites was searched for completed or ongoing trials.

**Data collection and analysis**

1. The title and abstract of all studies identified by the above search strategy were screened and the full articles for all potentially relevant trials obtained. The full text of any potentially eligible reports was reassessed and those studies that did not meet all of the inclusion criteria were excluded. Any disagreements were discussed until consensus was achieved.

2. The criteria and standard methods of the Cochrane Neonatal Review Group were used to independently assess the methodological quality of any included trials in terms of allocation concealment, blinding of parents or caregivers and assessors to the intervention, and completeness of assessment in all randomised individuals. Additional information from the trial authors was requested to clarify methodology and results as necessary.

3. A data collection form was used to aid extraction of relevant information from each included study. Each review author extracted the data separately. Any disagreements were discussed until consensus was achieved. If data from the trial reports were insufficient, the trialists were contacted for further information.

4. Meta-analyses were performed using the fixed effects model. Relative risk and risk difference were calculated for dichotomous data and weighted mean difference for continuous data, with respective 95% confidence intervals (CI). The number needed to treat and associated 95% CI were determined for a statistically significant reduction in the risk difference. The treatment effects of individual trials and heterogeneity between trial results was examined by inspecting the forest plots. The impact of heterogeneity in any meta-analysis was assessed using the I-squared statistic. If statistical heterogeneity was noted, the possible causes (for example, differences in study quality, participants, intervention regimens, or outcome assessments) were explored using post-hoc subgroup analyses.

**RESULTS**

**Description of studies**

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of ongoing studies.

Three small trials fulfilled the review eligibility criteria (Davey 1994; Ostertag 1986; Khayata 1987; see table 'Characteristics of Included Studies'). Four studies were excluded (Glass 1984; Higgs 1974; LaGamma 1985; Wilson 1997; see table 'Characteristics of Excluded Studies').

Davey 1994: Clinically stable preterm infants of birth weight less than 2000 grams who had a low umbilical artery catheter in situ (N = 62) were randomly allocated to either initiation of progressive enteral feeding before the catheter was removed (median two days after birth) or delayed introduction of feeding 24 hours after the catheter was removed (median five days after birth). Participating infants were fed with formula milk or breast milk (subgroup data no available). The concentration and volume of enteral feeds were increased at the same rates in both groups. Reported outcomes included days to regain birth weight, days to achieve full enteral feeding, duration of hospital stay, discharge weight, feed intolerance, necrotising enterocolitis, and mortality.

Khayata 1987: Very low birth weight infants (N = 12) were randomised to either an early progressive feeding group (started within 96 hours after birth) or a late feeding group started at 10 days or later using the same schedule as the early feeding group. The trial was reported in abstract form and only limited information on methodology and outcomes is available.

Ostertag 1986 Very low birth weight infants assessed with a risk score to be at high risk of developing necrotising enterocolitis (N = 41) were randomised to early (day one) or delayed (day seven) enteral feeding. Feeds were delivered as a continuous infusion of 1ml/hour for seven days then in incremental advances of 10 ml/kg/day. Reported outcomes were necrotising enterocolitis, and mortality.

Delayed introduction of progressive enteral feeds to prevent necrotising enterocolitis in very low birth weight infants (Review)
Risk of bias in included studies

Quality assessments are included in the Table, 'Characteristics of Included Studies'.

Davey 1994: Allocation was concealed using sequentially-num bered opaque sealed envelopes. Caregivers and investigators were aware of the allocated feeding regimen but it is likely that the clinicians who assessed abdominal radiographs were blinded to treatment group. Follow-up was nearly complete; two infants in the 'early feeding' group were excluded from the trial post-randomisation because of protocol violation (umbilical artery catheter removed before feeding).

Khayata 1987: The method of randomisation was not described. It is likely that caregivers and investigators were not blind to the intervention. Follow-up assessments were likely to have been undertaken on all participants.

Ostertag 1986: The precise method of randomisation was not described. Caregivers and investigators were not blind to the intervention. Follow-up assessments were reported for all participants.

Effects of interventions

DELAYED VS. EARLY INTRODUCTION OF ENTERAL FEEDS (COMPARISON 1)

PRIMARY OUTCOMES

Necrotising enterocolitis (Outcome 1.1: two trials): Davey 1994 and Ostertag 1986 did not detect a statistically significant effect: typical relative risk 1.27 (95% CI 0.54, 3.00); typical risk difference 0.04 (95% CI -0.10, 0.18).

Mortality (Outcome 1.2: two trials): Davey 1994 and Ostertag 1986 did not detect a statistically significant effect: typical relative risk 0.31 (95% CI 0.01, 7.38); typical risk difference -0.03 (95% CI -0.12, 0.05).

SECONDARY OUTCOMES

Growth (Outcome 1.3: two trials): Davey 1994 did not detect a statistically significant difference in the median time to regain birth weight (13 days for both groups). Khayata 1987 reported no significant difference in the rate of weight gain during the first six weeks after birth: mean difference -1.00 (95% CI -127.4, 125.4) g/kg/week. Long-term growth parameters were not reported by either of the trials.

Neurodevelopment: Neither trial assessed neurodevelopmental outcomes.

Time to establish full enteral feeding (one trial): Davey 1994 did not find a statistically significant difference in time taken to establish enteral feeding (median 19 versus 22.5 days after birth) but the median duration of use of parenteral nutrition was longer in the delayed (30 days) compared with the early introduction group (13 days).

Time to establish full oral feeding: Not reported by either of the included trials.

Feed intolerance: Davey 1994 found no statistically significant differences in the proportion of infants who had gastric residual volumes more than 20% of the preceding feed volume, abdominal distention (daily increment in abdominal girth of at least 2 cm) or enteral feeding interrupted or ceased because of feed intolerance.

Incidence of invasive infection: Not reported by either trial. Davey 1994 found that significantly more infants in the delayed group underwent ‘sepsis evaluations’ (52% versus 17% in the early group).

Duration of hospital stay (Outcome 01.04: one trial): Davey 1994 did not find a statistically significant difference in the median duration of hospital admission (60 versus 47 days). There was no significant difference in the postmenstrual age at discharge: mean difference 0.90 (95% CI -1.21, 3.01) weeks.

Subgroup analyses

1. Exclusively formula milk-fed infants: No subgroup data available.
2. Infants were at least partially fed with breast milk: No subgroup data available.
3. Extremely low birth weight or extremely preterm: It is likely that less than one-third of all participants were extremely low birth weight or extremely preterm but no subgroup data were available.
4. Infants with intrauterine growth restriction, or infants with absent or reversed end-diastolic flow velocities detected on antenatal Doppler studies of the fetal aorta or umbilical artery: No subgroup data available.

DISCUSSION

The trials that have assessed the effect of delaying the introduction of progressive enteral feeds in very low birth weight infants do not provide sufficient evidence to guide clinical practice. All were small and were underpowered to exclude important effects on the risk of necrotising enterocolitis, mortality, and other morbidities. None assessed any long-term outcomes. Given this paucity of trial evidence, current practice is largely informed by data from observational studies that have found that delaying the introduction of progressive enteral feeds is associated with a reduced risk of necrotising enterocolitis. However, since delaying the introduction of progressive enteral feeds may also have potential disadvantages related to the prolonged use of parenteral nutrition, this practice may not result in an overall benefit for very low birth weight infants (Flidel-Rimon 2004; Flidel-Rimon 2006).

Further large randomised controlled trials are needed to provide robust evidence to inform this fundamental area of neonatal care. Trials could assess the effects of delayed introduction of progressive enteral feeding preceded either by a period of enteral fasting or trophic feeding. Initial trophic feeding may be preferred given that it is not associated with a statistically significant effect on the risk of...
necrotising enterocolitis (Bombell 2009). Furthermore, mothers who express breast milk for early trophic feeding are more likely to continue to provide breast milk as the on-going principal form of nutrition for their infants (Schanler 1999). Evidence exists that feeding with breast milk compared to formula reduces the risk of necrotising enterocolitis in very low birth weight infants (Lucas 1990; Quigley 2007).

Undertaking trials of feeding interventions in this population is problematic (Tyson 2007). It is difficult to design a pragmatic trial that will ensure that caregivers and investigators are unaware of the allocated feeding regimen. This lack of blinding may cause surveillance and ascertainment biases that result in over-estimation of the incidence of feed intolerance and necrotising enterocolitis in infants whose feeds are introduced earlier. A priori agreements on objective definitions of feed intolerance and indications for interruption of enteral feeding and for investigation of necrotising enterocolitis may help minimise the impact of this source of bias. Diagnosing “confirmed” necrotising enterocolitis on the basis of radiological detection of gas in the bowel wall or portal tract is also prone to bias because intraluminal milk is a substrate for the microbial generation of intestinal gas. Infants who have received more enteral milk may be more likely to demonstrate radiological signs than infants with equally severe bowel disease who have less intraluminal substrate. Given these problems, and since conservative feeding strategies may result in other competing outcomes such as nosocomial infection secondary to prolonged use of parenteral nutrition, it is essential that trials are powered and structured to assess more objective outcomes, principally long-term disability-free survival rates.

The definition of delayed introduction of progressive feeds may vary between different subpopulations of very low birth weight infants who have different empiric risks for developing feed intolerance and necrotising enterocolitis. For example, the effects of enteral feeding are likely to be very different for a ventilator and/or inotrope dependent infant of birth weight less than 700 grams compared with a clinically-stable infant of birth weight more than 1400 grams. For this Cochrane review, delayed introduction was defined as later than four days after birth since various observational studies have found the risk of necrotising enterocolitis to be lower when feeds are introduced five to seven days after birth (Patole 2005). For extremely low birth weight or extremely preterm infants, it may be more appropriate to define delayed introduction as more than seven days after birth (or even later). Small intestinal motility is poorly organised before about 28 weeks’ gestation resulting in a higher risk of feed intolerance. Additionally, enteral feeds are often delayed in this population because of respiratory or metabolic instability or because of other putative risk factors for necrotising enterocolitis such as the existence of a patent ductus arteriosus, the use of non-steroidal anti-inflammatory agents, or the presence of a umbilical arterial catheter.

Infants who are growth restricted because of suboptimal placental support are also considered to be at greater risk of developing necrotising enterocolitis (Stoll 2004). Despite the potential for nutritional disadvantage, enteral feeding is often delayed for a week or more after birth in infants who are severely growth restricted, especially if there is evidence of circulatory redistribution or reduced gastrointestinal perfusion (Dorling 2005). Paradoxically, this population of infants has been specifically excluded from participating in many trials of early enteral feeding practices. There are no data on this subgroup for the two small trials included in this review. However, an on-going multicentre trial is currently examining the effect of delayed introduction of progressive enteral feeds on the risk of necrotising enterocolitis and other morbidities in infants with severe growth restriction and evidence of circulatory redistribution (see: www.npeu.ox.ac.uk/adept/). When data from this trial are available they will be included in an update of this review.

Finally, the applicability of trials undertaken in high-income settings to neonatal care in middle- and low-income countries (and vice versa) is unclear. Conservative strategies such as delayed introduction or slow advancement of feed volumes may confer less nutritional disadvantage in settings where adjunctive parenteral nutrition is readily and safely available. In settings with less technologically-developed healthcare provision where parenteral nutrition is not available and where severe infection (diarrhoea, pneumonia, septicaemia) is much more important cause of mortality and morbidity, the nutritional and immunological advantages of early feeding with breast milk may outweigh any risks associated with enteral feeding for very low birth weight infants (Narayanan 1982; de Silva 2004).

**Authors’ Conclusions**

**Implications for practice**

There are insufficient data from randomised controlled trials to determine the effect of delaying the introduction of progressive enteral feeds on the risk of necrotising enterocolitis, mortality, and other morbidities in very low birth weight infants.

**Implications for research**

Further randomised controlled trials are needed to determine the optimal time to introduce progressive enteral feeds for very low birth weight infants. Future trials should be simple and pragmatic to ensure high levels of acceptance and participation. Trials should aim to ensure the participation of extremely low birth weight and extremely preterm infants as well as infants with evidence of compromised intrauterine growth so that subgroup analyses can be planned for these populations at high risk of necrotising enterocolitis. Masking caregivers and investigators to the nature of this intervention is unlikely to be possible. Since the unblinded evaluation of feed intolerance and necrotising enterocolitis is subject to surveillance and ascertainment biases, trials should aim to as-
sess more objective outcomes, principally mortality and long-term
growth and development. Furthermore, since conservative feed-
ing strategies may result in other competing outcomes that may
affect long-term survival and neurodisability rates, it is essential
that trials are powered and structured to assess these outcomes.

ACKNOWLEDGEMENTS

We gratefully acknowledge the contributions of Drs Kennedy,
Tyson, and Chamnanvanakij, the authors of the previous version
of this Cochrane review (Kennedy 2000).

We are grateful to Ms Kate Light (Information Specialist, CRD,
University of York) for developing and running the updated elec-
tronic search.

The Cochrane Neonatal Review Group has been funded in part
with Federal funds from the Eunice Kennedy Shriver National
Institute of Child Health and Human Development National In-
istitutes of Health, Department of Health and Human Services,
USA, under Contract No. HHSN267200603418C.

REFERENCES

References to studies included in this review

Davey 1994 (published data only (unpublished sought but not used))
Davey AM, Wagner CL, Cox C, Kendig JW. Feeding premature
infants while low umbilical artery catheters are in place: a
prospective, randomized trial. Journal of Pediatrics 1994;124:
795–9.

Khayata 1987 (published data only (unpublished sought but not used))
of low birth weight (LBW) infants: Effect on growth and
hyperbilirubinemia. Pediatric Research 1987;21:431A.

Ostertag 1986 (published and unpublished data)
Ostertag SG, LaGamma EF, Reisen CE, Ferrentino FL. Early
enteral feeding does not affect the incidence of necrotizing

References to studies excluded from this review

Glass 1984 (published data only)
Glass EJ, Hume R, Lang MA, Forfar JO. Parenteral nutrition
compared with transpyloric feeding. Archives of Disease in

Higgs 1974 (published data only)
Higgs SC, Malan AE, DeV Heese H. A comparison of oral feeding
and total parenteral nutrition in infants of very low birthweight.

LaGamma 1985 (published data only)
LaGamma EF, Ostertag S, Birenbaum H. Failure of delayed oral
feedings to prevent necrotizing enterocolitis. American Journal of

Wilson 1997 (published data only)
Wilson DC, Cairns P, Halliday HL, Reid M, McClure G, Dodge
JA. Randomised controlled trial of an aggressive nutritional
regimen in sick very low birthweight infants. Archives of Disease in
Childhood 1997;77:F4–11.

References to ongoing studies

ADEPT (published data only)
Abnormal Doppler Enteral Prescription Trial

Additional references

Bernstein 2000
Bernstein IM, Hoobar JD, Badger GJ, Ohlsson A, Golan A.
Morbidity and mortality among very-low-birth-weight neonates
with intrauterine growth restriction. The Vermont Oxford
Network. American Journal of Obstetrics and Gynecology 2000;182:
198–206.

Berseh 1990
Berseh CL. Neonatal small intestinal motility: Motor responses to
feeding in term and preterm infants. Journal of Pediatrics 1990;117:
777–82.

Bisquera 2002
Bisquera JA, Cooper TR, Berseh CL. Impact of necrotizing
enterocolitis on length of stay and hospital charges in very low birth
Delayed introduction of progressive enteral feeds to prevent necrotising enterocolitis in very low birth weight infants (Review)

Copyright © 2009 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Bomfell 2009

Boyle 2004

Brown 1978

Burrin 2002

de Silva 2004

Dorling 2005

Flidell-Rimon 2004

Flidell-Rimon 2006

Garite 2004

Holman 2006

Lucas 1990

Narayanan 1982

Patole 2004

Patole 2005

Quigley 2007

Rees 2007

Schanler 1999

Stoll 2004

Tyson 2007

Uauy 1991

Walsh 1986

References to other published versions of this review

Bomfell 2008

Kennedy 2000
Delayed introduction of progressive enteral feeds to prevent necrotising enterocolitis in very low birth weight infants (Review)

Cochrane Database of Systematic Reviews 2005, Issue 1.

* Indicates the major publication for the study
### Characteristics of included studies  
*ordered by study ID*

#### Davey 1994

| Methods | Blinding of randomisation: yes.  
|         | Blinding of intervention: no.  
|         | Complete follow-up: yes.  
|         | Blinding of outcome measurement: no. |
| Participants | Preterm infants with birth weight less than 2000 grams who were clinically stable and who had an umbilical artery catheter in place. Infants who had a lethal condition or who had received a double-volume exchange transfusion were excluded. |
| Interventions | Delayed introduction of enteral feeds (median age five days; N = 31) vs. earlier introduction (median age two days; N = 31). Infants received either breast milk or diluted formula (no subgroup data available). Volumes and rates of advancement were the same in both groups. |
| Outcomes | Days to regain birth weight, days to full enteral feeding, duration of hospital stay, incidence of necrotising enterocolitis, mortality. |
| Notes | The trial inclusion criterion for birth weight was less than 2000 grams. Since more than 80% of participants were very low birth weight or very preterm, a pragmatic decision to include the trial was made. Two infants in the early feeding group were excluded from the trial post-randomisation because of protocol violation. |

#### Risk of bias

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors’ judgement</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allocation concealment?</td>
<td>Yes</td>
<td>A - Adequate</td>
</tr>
</tbody>
</table>

#### Khayata 1987

| Methods | Blinding of randomisation: unclear.  
|         | Blinding of intervention: no.  
|         | Complete follow-up: yes.  
|         | Blinding of outcome measurement: no. |
| Participants | Very low birth weight infants. |
| Interventions | Delayed introduction of enteral feeds (ten days after birth; N = 7) vs. earlier introduction (within four days; N = 5). Infants received standard calorie formula milk. Volumes and rates of advancement were the same in both groups. |
| Outcomes | Growth during the first six weeks of postnatal life. |
Khayata 1987  (Continued)

| Notes | This trial has been reported as an abstract only. Further (unpublished) methodological or outcome data were not available. |

**Risk of bias**

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors’ judgement</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allocation concealment?</td>
<td>Unclear</td>
<td>B - Unclear</td>
</tr>
</tbody>
</table>

Ostertag 1986

| Methods | Blinding of randomisation: unclear.  
Blinding of intervention: no.  
Complete follow-up: yes.  
Blinding of outcome measurement: no. |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>Very low birth weight infants assessed to be at “high risk” of developing necrotising enterocolitis based on a risk assessment score.</td>
</tr>
</tbody>
</table>
| Interventions | Delayed introduction of enteral feeds (day 7 after birth; N = 22) vs. earlier introduction (day 1; N = 19).  
Infants received feeds by continuous intragastric infusion starting initially with sterile water, then progressing to 2.5% dextrose, diluted formula, then full-strength standard calorie formula milk. Volumes and rates of advancement were the same in both groups: constant infusion at 1ml/hour for seven days then daily increments of 10ml/kg/day. |
| Outcomes | Incidence of necrotising enterocolitis, mortality. |
| Notes | Further details received from Dr La Gamma (March 2009). |

**Characteristics of excluded studies**  [ordered by study ID]

<table>
<thead>
<tr>
<th>Study</th>
<th>Reason for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glass 1984</td>
<td>Infants were allocated alternately to either early (first day after birth) or delayed transpyloric enteral feeding. The delayed feeding group commenced enteral nutrition when assessed to be “clinically stable” but this included initiation within the first four days after birth.</td>
</tr>
<tr>
<td>Higgs 1974</td>
<td>Infants in the delayed progressive enteral feeds group received total parenteral nutrition as a co-intervention.</td>
</tr>
<tr>
<td>LaGamma 1985</td>
<td>Although not clearly stated in the title or abstract, this was not a randomised controlled trial.</td>
</tr>
<tr>
<td>Wilson 1997</td>
<td>Infants in the delayed progressive enteral feeds group also received delayed advancement of parenteral nutrition as a co-intervention.</td>
</tr>
</tbody>
</table>
### Characteristics of ongoing studies  [ordered by study ID]

**ADEPT**

<table>
<thead>
<tr>
<th>Trial name or title</th>
<th>Abnormal Doppler Enteral Prescription Trial (ADEPT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methods</td>
<td></td>
</tr>
<tr>
<td>Participants</td>
<td>Preterm infants who of birth weight below 10th percentile and who have Doppler evidence of absent or reversed end diastolic flow velocities in the umbilical arteries.</td>
</tr>
<tr>
<td>Interventions</td>
<td>Delayed introduction of progressive enteral feeds (commencing on day six after birth) versus early introduction (day two).</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Time to establish full enteral nutrition. Incidence of necrotising enterocolitis.</td>
</tr>
<tr>
<td>Starting date</td>
<td>January 2005</td>
</tr>
<tr>
<td>Contact information</td>
<td><a href="mailto:adept@npeu.ox.ac.uk">adept@npeu.ox.ac.uk</a></td>
</tr>
<tr>
<td>Notes</td>
<td></td>
</tr>
</tbody>
</table>
## Data and Analyses

### Comparison 1. Delayed versus early introduction of progressive enteral feeding

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Necrotising enterocolitis</td>
<td>2</td>
<td>101</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>1.27 [0.54, 3.00]</td>
</tr>
<tr>
<td>2 Mortality prior to discharge</td>
<td>2</td>
<td>101</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.87 [0.34, 2.28]</td>
</tr>
<tr>
<td>3 Weight gain (g/kg/week)</td>
<td>1</td>
<td>12</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>-1.0 [-127.37, 125.37]</td>
</tr>
<tr>
<td>4 Duration of hospital admission (postmenstrual weeks at discharge)</td>
<td>1</td>
<td>60</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>0.90 [-1.21, 3.01]</td>
</tr>
</tbody>
</table>

### Analysis 1.1. Comparison 1 Delayed versus early introduction of progressive enteral feeding, Outcome 1 Necrotising enterocolitis.

#### Review: Delayed introduction of progressive enteral feeds to prevent necrotising enterocolitis in very low birth weight infants

#### Comparison: Delayed versus early introduction of progressive enteral feeding

#### Outcome: 1 Necrotising enterocolitis

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Delayed</th>
<th>Early</th>
<th>Risk Ratio M-H/Fixed, 95% CI</th>
<th>Weight %</th>
<th>Risk Ratio M-H/Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Davey 1994</td>
<td>4/31</td>
<td>2/29</td>
<td>27.8 %</td>
<td>1.87 [0.37, 9.46]</td>
<td></td>
</tr>
<tr>
<td>Oster tag 1986</td>
<td>6/22</td>
<td>5/19</td>
<td>72.2 %</td>
<td>1.04 [0.38, 2.86]</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>53</td>
<td>48</td>
<td>100.0 %</td>
<td>1.27 [0.54, 3.00]</td>
<td></td>
</tr>
</tbody>
</table>

Total events: 10 (Delayed), 7 (Early)

Heterogeneity: $\chi^2 = 0.37$, df = 1 ($P = 0.54$); $I^2 = 0.0$

Test for overall effect: $Z = 0.54$ ($P = 0.59$)
Analysis 1.2. Comparison 1 Delayed versus early introduction of progressive enteral feeding, Outcome 2 Mortality prior to discharge.

Review: Delayed introduction of progressive enteral feeds to prevent necrotising enterocolitis in very low birth weight infants

Comparison: 1 Delayed versus early introduction of progressive enteral feeding

Outcome: 2 Mortality prior to discharge

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Delayed</th>
<th>Early</th>
<th>Risk Ratio</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H,Fixed,95% CI</td>
<td>M-H,Fixed,95% CI</td>
</tr>
<tr>
<td>Davey 1994</td>
<td>0/31</td>
<td>1/29</td>
<td>22.4 %</td>
<td>0.31 [ 0.01, 7.38 ]</td>
</tr>
<tr>
<td>Oster tag 1986</td>
<td>6/22</td>
<td>5/19</td>
<td>77.6 %</td>
<td>1.04 [ 0.38, 2.86 ]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>53</td>
<td>48</td>
<td>100.0 %</td>
<td>0.87 [ 0.34, 2.28 ]</td>
</tr>
</tbody>
</table>

Total events: 6 (Delayed), 6 (Early)

Heterogeneity: Chi² = 0.51, df = 1 (P = 0.47); I² =0.0%

Test for overall effect: Z = 0.28 (P = 0.78)

Analysis 1.3. Comparison 1 Delayed versus early introduction of progressive enteral feeding, Outcome 3 Weight gain (g/kg/week).

Review: Delayed introduction of progressive enteral feeds to prevent necrotising enterocolitis in very low birth weight infants

Comparison: 1 Delayed versus early introduction of progressive enteral feeding

Outcome: 3 Weight gain (g/kg/week)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Delayed</th>
<th>Early</th>
<th>Mean Difference</th>
<th>Weight</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N Mean(SD)</td>
<td>N Mean(SD)</td>
<td>IV,Fixed,95% CI</td>
<td>IV,Fixed,95% CI</td>
<td></td>
</tr>
<tr>
<td>Khayata 1987</td>
<td>7 70 (113)</td>
<td>5 71 (108)</td>
<td>-1.00 %</td>
<td>-1.00 [-127.37, 125.37 ]</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>7</td>
<td>5</td>
<td>100.0 %</td>
<td>-1.00 [-127.37, 125.37 ]</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: not applicable

Test for overall effect: Z = 0.02 (P = 0.99)
Analysis 1.4. Comparison 1 Delayed versus early introduction of progressive enteral feeding, Outcome 4
Duration of hospital admission (postmenstrual weeks at discharge).

Review: Delayed introduction of progressive enteral feeds to prevent necrotising enterocolitis in very low birth weight infants

Comparison: Delayed versus early introduction of progressive enteral feeding

Outcome: 4 Duration of hospital admission (postmenstrual weeks at discharge)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Delayed</th>
<th>early</th>
<th>Mean Difference</th>
<th>Weight</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Davey 1994</td>
<td>31</td>
<td>29</td>
<td>0.90 [ -1.21, 3.01 ]</td>
<td>100.0 %</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>31</td>
<td>29</td>
<td>0.90 [ -1.21, 3.01 ]</td>
<td>100.0 %</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: not applicable
Test for overall effect: Z = 0.83 (P = 0.40)

WHAT'S NEW

Last assessed as up-to-date: 19 March 2009.

9 March 2009  New search has been performed  This updates the review “Delayed introduction of progressive enteral feeds to prevent necrotising enterocolitis in very low birth weight infants” (Bombell 2008), published in the Cochrane Database of Systematic Reviews, Issue 2, 2008. This update contains a trial that has been included following receipt of further methodological details from the principal investigator (Ostertag 1986).

HISTORY

Review first published: Issue 4, 1998

13 February 2008  New citation required but conclusions have not changed  New authorship: Bombell S, McGuire W

2 February 2008  New search has been performed  This updates the review “Early versus delayed initiation of progressive enteral feedings for parenterally fed low birth weight or preterm infants” published in the Cochrane Database of Systematic Reviews, Issue 1, 2000 (Kennedy 2000). The title has been modified to read “Delayed introduction of progressive enteral feeds to prevent necrotis-
ing enterocolitis in very low birth weight infants” and has a new authorship of Sarah Bombell and William McGuire. Changes made to the original protocol are outlined below:

1. Introduction of progressive enteral feeds is defined as feed volumes more than 24 ml/kg/day (1 ml/kg/hour).
2. The population has been restricted to very low birth weight and very preterm infants
3. Subgroup analyses of extremely low birth weight and extremely preterm infants, and infants with evidence of intrauterine growth restriction or absent or reversed end-diastolic flow velocities in Doppler studies of the fetal aorta or umbilical artery were prespecified.

Search updated December 2007. No new trials were included, but one on-going trial was identified. The findings and implications for practice and research of the review have not changed overall.

11 January 2008 Amended Converted to new review format.

CONTRIBUTIONS OF AUTHORS

William McGuire and Sarah Bombell independently assessed the methodological quality of the included trials, extracted the relevant information and data, and completed the final review.

DECLARATIONS OF INTEREST

None

INDEX TERMS

Medical Subject Headings (MeSH)

*Infant, Low Birth Weight; Enteral Nutrition [*methods]; Enterocolitis, Necrotizing [*prevention & control]; Infant, Newborn; Infant, Premature; Parenteral Nutrition; Time Factors
MeSH check words

Humans