Donor breast milk versus infant formula for preterm infants: systematic review and meta-analysis

Catherine A Boyd, Maria A Quigley, Peter Brocklehurst


Breast milk is the recommended form of enteral nutrition for all infants, including those born preterm. Donor breast milk is an alternative form of milk when the mother’s own milk is not available or is in short supply. The advantages of breast milk over infant formulas include:

- the presence of active enzymes that enhance the maturation of the underdeveloped gut;
- earlier tolerance of full enteral feeding;
- anti-infective properties which protect the newborn from infection.

Although the nutrient concentrations in preterm breast milk tend to be either the same as or higher than those in term breast milk, there is concern that breast milk, whether maternal or donated, may be inadequate to support the increased nutritional requirements of the preterm or very low birthweight infant.

The use of donor breast milk varies across the world. Currently in the UK, 17 human milk banks supplying 50–60 neonatal units (Gillian Weaver, UK Association for Milk Banking, personal communication, 2004). In these banks all donor milk is frozen following Holder pasteurisation (heated to 62.5 °C for 30 min). However, this not only inactivates HIV, cytomegalovirus and other viruses, it also affects the nutritional and immunological properties of breast milk.

Donor breast milk is associated with a lower risk of NEC and slower growth in the early postnatal period, but the quality of the evidence is limited. Further research is needed to confirm these findings and measure the effect of fortified or supplemented donor breast milk.

Methods

Search strategy

We carried out standard search strategies using the databases Cochrane, CENTRAL, MEDLINE, EMBASE, CINAHL, and HMIC: DH from their inception to August 2004. Details of the search strategy can be found in the appendix (see http://adc.bmj.com/supplemental). There was no language restriction. There was no systematic attempt to search the “grey” literature although some articles were found in the references for indexed articles.

Selection

We included studies on the basis of study design, population and comparison groups (box 1). All donor breast milk had to be donated from someone other than the infant’s mother and it had to be pasteurised. All clinical outcomes were included.

Abbreviation: NEC, necrotising enterocolitis
**Box 1 Inclusion criteria**

**Study design**
- Randomised controlled trials (RCTs), quasi-RCTs and observational studies.

**Population**
- Preterm (<37 weeks’ gestation) or low birthweight (<2500 g) infants.

**Types of intervention/exposure**
- Sole diet of pasteurised donor milk v sole diet of formula.
- Mother’s own milk supplemented with pasteurised donor milk v mother’s own milk supplemented with formula.
- Fortified, pasteurised donor milk v fortified formula.

**Outcome measures**
- All clinical outcomes were considered. The primary outcomes were necrotising enterocolitis and infection. All other short-term and long-term health and development outcomes including any data on adverse events were considered as secondary outcomes.
- Studies which only assessed the risk of transmissible diseases from milk banks were excluded.

**Data abstraction**
The articles identified by our search strategy were screened (title and abstract) by two independent reviewers (CB and MQ). Then those articles which potentially met the inclusion criteria were critically reviewed. The decision to include or exclude a specific article was made by consensus of the two reviewers. For two studies, information on whether the milk was pasteurised was not available in the published reports but was supplied by the authors of the primary studies.

**Validity assessment**
We assessed all studies for methodological quality in terms of sample size estimation, proportion followed up, blinding of outcome assessment, comparison of baseline variables and assessment of confounding. The RCTs were also assessed for method of randomisation, allocation concealment and blinding of intervention.

**Quantitative data synthesis**
Data were extracted and summarised into evidence tables, which included effect measures with 95% CIs. Where outcome measures were given in different units across studies, these were made consistent where possible. Meta-analyses were planned if there were sufficient data, and it was anticipated that a fixed-effects model would be used unless there was evidence of significant heterogeneity (p<0.10). We conducted and reported this review in accordance with the guidelines set out in the Quality Of Reporting Of Meta-analyses (QUOROM) statement.

**RESULTS**
The search produced 1594 articles which were screened (title and abstract). Of these, 242 potentially addressed the research questions but on reading the articles only 16, arising from 7 studies, met the inclusion criteria (fig 1).

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**Figure 1** Results of search and selection of articles (QUOROM statement flow diagram)

**Study characteristics**
Table 1 provides details of the characteristics of the seven included studies.9–24 The combined sample size of the studies which compared the sole diet of donor breast milk with sole formula was 471 infants. Three of these studies started in the 1970s (in Wales,9 Finland10 and Hungary11) and four in the 1980s (in the USA,12 England,13–22 South Africa23 and France24). One of these studies12–22 (Lucas et al21 will be cited as the primary paper for this study) also compared donor milk with formula, both given as a supplement to mother’s own milk. This study was conducted in England in the 1980s, with a sample size of 343.12 We did not find any other studies comparing donor milk with formula as a supplement to mother’s own milk. No studies were found comparing fortified donor milk with formula.

There was considerable variability between the studies in terms of the type of donor milk (preterm v term; drip v expressed) and formulas used, the feeding regimens and the period of intervention. The study population also varied in terms of mean gestation (range 30.2–33.2 weeks) and mean birth weight (range 1310–1954 g) (table 1).

**Methodological quality of studies**
The methodological quality of the studies is summarised in table 2. Five studies were RCTs, however, only one of these trials13 reported that a sample size estimate had been calculated prior to the trial starting. This study also had adequate methodological quality in terms of allocation concealment and randomisation. None of the remaining four RCTs included a sample size estimate, and two did not specify the method of randomisation.9–11 One of the studies did not specify whether it was randomised.24 One study,23 which was designed as a trial, stopped recruitment in the formula group due to an “outbreak” of NEC, and continued to recruit in the formula group from another hospital. We have only used outcome data from the first hospital.

**Findings of the included studies**
Tables 3–5 present the main results of the seven studies included in the review.

**Effect on mortality**
Mortality was reported in one study13 for both sole diet and supplementary diet comparisons. This study found a lower risk of mortality at ages 9 months and 18 months in the donor milk group compared with the formula group, for both sole and...
Table 1  Summary of the characteristics of the seven included studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Time period</th>
<th>Design</th>
<th>Sample size</th>
<th>DBM group</th>
<th>Formula group</th>
<th>Study inclusion criteria</th>
<th>Baseline data in study population</th>
<th>Feeding regimen</th>
<th>Additional nourishment</th>
<th>Post diet regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Davies (1972-1973)</td>
<td>RCT</td>
<td>68</td>
<td>Term (34)</td>
<td>PTF (34)</td>
<td>28-34&quot;</td>
<td>32.9 19.54</td>
<td>Not stated</td>
<td>0.5 kg/kg increased to 200 mg/kg or until satisfied</td>
<td>Not stated</td>
<td>2 months old</td>
</tr>
<tr>
<td>Raiha et al (1972-1975)</td>
<td>RCT</td>
<td>106</td>
<td>Term (22)</td>
<td>Not stated (84)</td>
<td>28-36 &lt;2100</td>
<td>31-33 16.90</td>
<td>Not stated</td>
<td>Within 24 h of birth</td>
<td>2400 g</td>
<td>Not stated</td>
</tr>
<tr>
<td>Schultz et al (1980)</td>
<td>RCT</td>
<td>20</td>
<td>&quot;Mature&quot; (10)</td>
<td>Not stated (10)</td>
<td>30-37*</td>
<td>&lt;2000* 32.2 16.98</td>
<td>Not stated</td>
<td>Increased to 170 ml/kg/day by 1 week</td>
<td>Not stated</td>
<td>Before 24 h (usually 6-12 h)</td>
</tr>
<tr>
<td>Gross (1980-1982)</td>
<td>RCT</td>
<td>67</td>
<td>Preterm (20)</td>
<td>PTF (46)</td>
<td>27-33</td>
<td>&lt;1600 30.9</td>
<td>Gastric gavage 24 ml/kg/day increased to 180 ml/kg/day</td>
<td>Not stated</td>
<td>Day 1-6 (mean day 3)</td>
<td>1800 g</td>
</tr>
<tr>
<td>Lucas A et al (1982-1984)</td>
<td>RCT</td>
<td>159</td>
<td>&quot;Mainly drip&quot; (83)</td>
<td>PTF (76)</td>
<td>&lt;1850</td>
<td>31.3 1401</td>
<td>Nasogastric tube Up to 300 ml/kg/24 h</td>
<td>In 3 centres all infants received DBM for first 24 h</td>
<td>Median 7 days</td>
<td>2000 g or discharge</td>
</tr>
<tr>
<td>Lucas B et al (1982-1984)</td>
<td>RCT</td>
<td>343</td>
<td>&quot;Mainly drip&quot; (176)</td>
<td>PTF (173)</td>
<td>&lt;1850</td>
<td>31.1 1388</td>
<td>Nasogastric tube Up to 300 ml/kg/24 h</td>
<td>In 3 centres all infants received DBM for first 24 h</td>
<td>Median 7 days</td>
<td>2000 g or discharge</td>
</tr>
<tr>
<td>Cooper et al (1980)</td>
<td>Observational</td>
<td>39</td>
<td>Preterm (34)</td>
<td>PTF (15)</td>
<td>&lt;36</td>
<td>1200-1500 32.3 13.99</td>
<td>Nasogastric tube or bottle</td>
<td>Formula: 1.75 ml/kg/day DBM: 170-200 ml/kg/day</td>
<td>Not stated</td>
<td>When enteral feeding started</td>
</tr>
<tr>
<td>Putet et al (1984)</td>
<td>Study design unclear</td>
<td>12</td>
<td>Not stated (6)</td>
<td>PTF (6)</td>
<td>&quot;VLBW&quot;</td>
<td>30.2 1310</td>
<td>Nasogastric/gavage or breast</td>
<td>Formula: mean 157 ml/kg/day DBM: mean 1.68 ml/kg/day</td>
<td>Parenteral glucose and amino acid solution until oral feeding, all infants initially fed DBM within 24-48 hours until full diet had been reached</td>
<td>Study 1: once full oral feeding attained</td>
</tr>
</tbody>
</table>

DBM, donor breast milk; IV, intravenous; N/A, not applicable as outcomes measured whilst on allocated diet; PTF, premature formula; RCT, randomised controlled study; VLBW, very low birth weight.

*Drip* milk: the milk that drips from one breast while the infant feeds at the other breast.

These were the characteristics of the study sample rather than specific inclusion criteria.

Lucas A and Lucas B refer to the Lucas study trial A (sole diet comparison) and trial B (supplementary diet comparison), respectively.

Initially a quasi-RCT that became observational due to a change in selection criteria and population.

DBM, donor breast milk; IV, intravenous; N/A, not applicable as outcomes measured whilst on allocated diet; PTF, premature formula; RCT, randomised controlled study; VLBW, very low birth weight.
supplementary diet comparisons, but this effect was not statistically significant (table 3).

**Effect on NEC**

In the sole diet comparison, NEC was reported in three studies. In all of these studies, there was a lower risk of NEC in the donor milk group than the formula group but the effect was not statistically significant (table 3). For confirmed cases of NEC, the three studies yielded almost identical measures of effect (risk ratio (RR) 0.21–0.22) with similar 95% CIs (the largest study had a much lower overall risk of NEC and hence had a similar level of precision to the smallest study). In view of the homogeneity of these RR, a fixed-effects meta-analysis and a random-effects meta-analysis gave identical results (combined RR 0.21, 95% CI 0.06 to 0.76, p = 0.017). The combined evidence from these studies suggests that donor milk reduces the risk of NEC by about 79% (95% CI 24% to 94%) (fig 2).

The risk of confirmed NEC in the formula group in these three studies was 5.3%, 11.5% and 20.0%. Each study yielded different estimates of the risk difference (RD) 4.1%, 95% CI −1.4% to 9.6%); 9.2% (95% CI −4.1% to 22.3%); 15.5% (95% CI −5.9% to 37.6%). The combined estimate of the RD, estimated from a random effects meta-analysis, was 5.4% (95% CI 0.5% to 10.3%, p = 0.032). This suggests that in settings in which the risk of NEC in the formula group is about 5–20%, approximately 18.5 preterm infants (95% CI 9.7 to 200) would need to be given donor milk to prevent one case of NEC.

In the supplementary diet comparison, there were more suspected cases of NEC but fewer confirmed cases in the donor milk group than in the formula group but neither effect reached statistically significance (table 3).

**Effect on other perinatal outcomes**

Four studies in the sole diet comparison reported other perinatal morbidity events. Three studies found significantly fewer episodes of feeding intolerance (including NEC) and diarrhoea in the donor milk group compared with the formula group (table 3); in one, infants in the donor milk group were found to tolerate full enteral feeds earlier, another study reported significantly fewer withdrawals due to feeding intolerance (within 9–31 days of starting the intervention) in the donor milk group, and yet another found infants fed donor milk had significantly fewer episodes of mild diarrhoea in the first two weeks after birth. One study reported more withdrawals due to respiratory symptoms within the first few days of starting the intervention in the donor milk group compared with the formula group (12.5% v 6.7%), but this...
effect was not statistically significant. One study found significantly higher levels of plasma bilirubin in the donor milk group on day 4–7 and day 25 in the sole and supplementary diet comparison (data not shown).

**Effect on early postnatal growth**

Many of the outcome measures reported for growth were not standardised across studies. Therefore it was not possible to undertake meta-analysis on these outcomes. The results for days to regain birth weight, weight change from birth to 2 months, and the change in head circumference are given in Table 4. The remaining growth outcomes (other measures of weight, length and skinfold thickness) are available online (see appendix tables B and C at http://adc.bmj.com/supplemental). The donor milk group compared with the formula group in terms of weight gain, increased head circumference and increased skinfold thickness, but no difference in length gain (table 4 and appendix tables B and C at http://adc.bmj.com/supplemental).

**Effect on growth measured at ages 9 months, 18 months and 7.5–8 years**

One study reported several measures of growth at ages 9 months, 18 months and 7.5–8 years (see appendix tables D and E at http://adc.bmj.com/supplemental). The donor milk group and formula group were similar (with no significant differences) at all ages with respect to weight, height, skinfold thickness, body mass index and (at age 7.5–8 years) waist to hip ratio. The differences between donor milk and formula in terms of weight gain and head circumference were greater in the first 2 months of life, but no difference was found in the second year of life.
Effect on developmental status
Child development at age 9 months and 18 months was assessed in one study\(^1\) (table 5). In the sole diet comparison there were fewer neurologically impaired children at age 9 months in the donor milk group compared with the formula group but this effect was not statistically significant (RR = 0.38, 95% CI 0.12 to 1.16), and was even weaker when assessed at age 18 months. There were no significant differences between the two feeding groups with respect to mean developmental quotient at age 9 months (Knobloch index) or 18 months (Bayley index) (table 5).

In the supplementary diet comparison, the proportion of neurologically impaired children at age 9 months and 18 months was similar in the donor milk group compared with the formula group. The donor milk group had significantly lower mean developmental scores than the formula group at age 9 months (Knobloch) but not when assessed at age 18 months (Bayley) (table 5).

Effect on later outcomes
One study measured systolic and diastolic blood pressure at age 7.5–8 years and found no significant differences between the donor milk and formula groups in both the sole and supplementary comparisons (see appendix table F at http://adc.bmj.com/supplemental).\(^2\)

DISCUSSION
Before discussing the results of this review, a number of potential limitations should be considered. First, only seven studies were included and the total sample size for most outcomes was small. Second, these studies started over 20 years ago, and they may no longer be clinically relevant to contemporary practice as survival of preterm and low birth-weight infants has greatly improved\(^3\) and feeding practices have changed. Third, the methodological quality of most of the studies was poor in terms of randomisation, blinding of carers and assessors, and assessment of confounding which may have introduced bias, in particular, for the observational data included. Lastly, substantial heterogeneity between the studies makes it difficult to pool evidence across studies. The studies had different inclusion criteria and varied in terms of the type of donor and formula milk used, and the method, timing, and volume of feeding (table 1). These differences may account for some of the observed differences in effects between the studies.

Since the search was conducted, another trial has been published.\(^4\) This trial, in extremely preterm babies (<30 weeks' gestation), compared fortified donor breast milk with formula, both given as a supplement to mother’s own milk. The trial found no significant difference between the two groups in terms of infection-related events or death. For NEC, there was some protection, but the 95% CI was wide (RR 0.56, 0.20 to 1.58). With regard to growth, the trial revealed no effect on length or head circumference gain, but found significantly poorer weight gain in the donor milk group. This resulted in 21% of the infants randomised to donor milk being given

What is already known on this topic
- Breast milk is the recommended form of enteral nutrition for all infants.
- Pasteurised donor breast milk is an alternative when mother’s own milk is not available.
- Pasteurisation affects the nutritional and immunological properties of breast milk.
- The evidence for the benefits of donor milk compared with formula for preterm infants is limited.

What this study adds
- Donor milk given as a sole diet appears to be associated with a lower risk of NEC but slower growth in the early postnatal period when compared with infant formula.
- The long-term effect of donor milk as compared with formula is unclear.
Donor breast milk for preterm infants

Donor breast milk for preterm infants

formula; this may have diluted the effect of donor milk on outcomes such as NEC.

Our findings, based on 13 cases of NEC in 268 infants, suggest that donor milk given as a sole diet is associated with a lower risk of NEC compared with formula. Although the observed effects were remarkably similar between the three studies (RR 0.21–0.22), true heterogeneity of effect cannot be ruled out because of differences between the studies in terms of the incidence of NEC (5–20%), the type of donor milk and the timing of feeding initiation. Furthermore, one study22 was not randomised, and none of the studies considered blinding of the intervention or outcome. These methodological weaknesses may have biased the observed effects, particularly in the study22 which did not state how NEC was diagnosed; bias due to subjective diagnosis cannot be ruled out. The homogeneous effects found in the three studies reduces the likelihood of a chance finding, and these alternative explanations are unlikely to account wholly for the large effects observed. Moreover, in the study which looked at both sole and supplemented diets,14 the risk of NEC increased as the amount of formula increased from 1.2% (2/167) in infants who received donor milk and mother’s own milk and 1.2% (1/86) in infants who received donor milk only to 2.9% (5/173) in infants who received formula and mother’s own milk and to 5.3% (4/76) in infants who received formula only (p = 0.053 for linear trend). The effect of donor milk on NEC seemed weaker in the study in which donor milk and formula were given as a supplement to mother’s own milk (RR 0.41, 95% CI 0.08 to 2.11), although the study may not have had sufficient power to detect a modest effect for such a rare outcome (incidence of NEC in formula group was 2.9%). In Schanler and colleagues’ recent trial,15 there was a similar suggestion of some protection of fortified donor milk given as a supplement to mother’s own milk.

Breast milk is known to have immune properties as it includes specific immunoglobulin A, lysozyme and lactoferrin.2 Therefore breast milk is thought to protect the preterm infant from bacterial and viral infections. Holder pasteurisation, however, reduces some of the anti-infective properties of breast milk. Infection was not reported as an outcome in any of the studies included in this review, but it was an outcome in the recent Schanler trial,22 although no effect was observed.

The nutrient concentrations in human milk may be inadequate for preterm or extremely low birthweight infants, who may have increased nutritional requirements.2 This may be particularly so for donor milk, as Holder pasteurisation reduces some of the nutritive properties,2 and the composition of donor milk is not the same as that received by a mother’s own infant. This is especially true for drip milk, which was used in one study,13 and term breast milk, which was used in four studies.12 Inadequate nutrition in the early postnatal period is thought to affect growth, bone mineralisation and neurodevelopment. One trial13 excluded infants who developed feed intolerance and NEC after randomisation, which may have exaggerated the increase in short-term growth among infants randomised to formula. Although the evidence suggests that donor milk is associated with slower growth in the early postnatal period, only one study included long-term follow-up.13 Interestingly, this study found no difference between the groups in several growth indices and neurodevelopment at ages 9 months and 18 months, and growth and blood pressure at 7.5–8 years despite observing slower growth in the donor milk group in the short term.

Donor milk given as a sole diet is associated with a lower risk of NEC but slower growth in the early postnatal period. The long-term effect of donor milk as compared with formula is unclear because only one study followed participants into childhood and adulthood. Further research is needed to confirm our findings and measure the effect of donor breast milk that is fortified or given as a supplement to mother’s own milk.

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