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Multicomponent fortified human milk for promoting growth in preterm infants

[Review]

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Outline

Graphics

Abstract

Background: For term infants, human milk provides adequate nutrition to facilitate growth, as well as potential beneficial effects on immunity and the maternal-infant emotional state. However, the role of human milk in premature infants is less well defined as it contains insufficient quantities of some nutrients to meet the estimated needs of the infant. There are potential short term and long term benefits from human milk, although observational studies have suggested that infants fed formula have a higher rate of growth than infants who are breast fed. Commercially-produced multicomponent fortifiers provide additional nutrients to human milk (in the form of protein, calcium, phosphate, and carbohydrate, as well as vitamins and trace minerals).

Objectives: The main objective was to determine if addition of multiple dietary supplements to human milk leads to improved growth, bone metabolism and neurodevelopmental outcomes without significant adverse effects in premature infants.

Search strategy: The standard search strategy of the Neonatal Review Group was used. This includes searches of the Oxford Database of Perinatal Trials, MEDLINE, previous reviews including cross references, abstracts, conferences and symposia proceedings, expert informants, journal handsearching mainly in the English language.

Selection criteria: All trials utilising random or quasi-random allocation to supplementation of human milk with multiple nutrients or no supplementation in premature infants within a nursery setting were eligible.

Data collection and analysis: Data were extracted using the standard methods of the Cochrane Collaboration and its Neonatal Review Group, with separate evaluation of trial quality and data extraction by each author and synthesis of data using relative risk and weighted mean difference.

Main results: Supplementation of human milk with multicomponent fortifiers is associated with short term increases in weight gain, linear and head growth. There is no effect on serum alkaline phosphatase levels. Bone mineral content and nitrogen retention appear to be increased.

There are insufficient data to evaluate long term neurodevelopmental and growth outcomes.

Adverse effects of fortification do not appear to be significantly increased, although the total number of infants studied and the unavailability of results for some infants randomized and subsequently withdrawn reduces confidence in this conclusion. Blood urea levels are increased and blood pH levels minimally decreased, but the significance of this is uncertain.

Conclusions: Multicomponent fortification of human milk is associated with short-term improvements in weight gain, linear and head growth. Despite the absence of evidence of long-term benefit and insufficient evidence to be reassured that there are no deleterious effects, it is unlikely that further studies evaluating fortification of human milk versus no supplementation will be performed. Further research should be directed toward comparisons between different proprietary preparations and evaluating both short-term and long-term outcomes in search of the "optimal" composition of fortifiers.

Background

Human milk is the recommended nutritional source for full-term infants for at least the first six months of postnatal life. It is known that in this group of infants, breast milk supplies adequate substrate to meet the infant's nutritional demands, as well as supplying the infant with other substances that may afford some physiological advantage (for example, immunoglobulins and gastrointestinal hormones). Breast feeding may also contribute to maternal-infant bonding.

However, the role of human milk in premature infants is less well defined. The nutrient content of premature human milk provides insufficient quantities of protein, sodium, phosphate and calcium to meet the estimated needs of the infant. In addition, large fluid volumes may be required to provide sufficient calories to maintain adequate growth.

Observational studies have shown that premature infants fed human milk have lower growth rates than infants fed term or preterm infant formulae. Serum albumin and blood urea nitrogen concentrations may decline in premature infants as a result of inadequate dietary protein intake. Premature infants are born with low skeletal stores of calcium and phosphate, and have very high requirements for these minerals if they are to attain adequate postnatal skeletal growth. Poor radiological bone mineralisation, rickets, and fractures have been described in premature infants receiving inadequate dietary intakes of calcium and phosphate, as may be supplied by breast milk alone.

Despite these apparent inadequacies of human milk, other studies have demonstrated that feeding human milk to premature infants may lead to benefits in both the short-term (for example, a lower risk of necrotising enterocolitis) and long-term (for example, improved neurodevelopmental outcomes).

Commercially-produced multicomponent fortifiers are available for the supplementation of breast milk. These fortifiers provide additional nutrients in the form of protein, calcium, phosphate, and carbohydrate, as well as vitamins and trace minerals. However, many of the nutrients contained within commercial preparations have not been studied either individually or in combination. This review includes trials where infants received more than one nutrient supplement (that is, protein and/or fat and/or carbohydrate and/or minerals). This intervention was prespecified prior to the literature search although it is appreciated that this would lead to a range of potential combined interventions. Other reviews will evaluate the effects of individual components given alone (that is, protein, fat, carbohydrate, or minerals) and the effect of caloric supplementation (regardless of supplement type).

For a detailed discussion of the suitability of human milk for low-birthweight infants, see Schanler 1995.

This review updates the existing review of Multicomponent fortified human milk for promoting growth in preterm infants which was published in The Cochrane Library, Issue 4, 1998 (Kuschel 1998). This update adds additional data from one previously included trial (Polberger 1989).

Objectives

To determine if addition of multiple dietary supplements to human milk leads to improved growth, bone metabolism and neurodevelopmental outcomes without significant adverse effects in premature infants.

Criteria for considering studies for this review

Types of participants

Premature infants receiving care within a nursery setting.

Types of intervention

All randomized controlled trials evaluating the supplementation of human milk with multiple nutrients (more than one of the following components: protein, fat, carbohydrate, or minerals [calcium and/or phosphate]), in which treatment was compared with unsupplemented human milk, are included. Supplementation with electrolytes, vitamins, or trace minerals in addition to only one of the above has not been classified as multicomponent fortification for the purposes of this review.

Types of outcome measures

1. Primary outcomes

a. Growth to discharge

Weight

Length

Head circumference

b. Size at 12-18 months

Weight

Length

Head circumference

c. Bone metabolism

Serum alkaline phosphatase (ALP)

Bone mineral content (BMC)

d. Neurodevelopmental outcomes

Neurodevelopmental outcome at 18 months

2. Secondary Outcomes

a. Bone metabolism

Fractures

b. Nitrogen retention studies

c. Adverse effects

Significant hypercalcemia (>2.85mmol/l)

Gastrointestinal disturbance

Feed intolerance

Diarrhea

Necrotizing enterocolitis (NEC)

Blood pH

Blood urea

Death

Types of studies

Controlled trials utilising either random or quasi-random patient allocation.

Search strategy for identification of studies

Searches of the Oxford Database of Perinatal Trials, Medline, previous reviews including cross references, abstracts, conferences and symposia proceedings, expert informants, journal handsearching mainly in the English language.

Methods of the review

The criteria and standard methods of the Cochrane Collaboration and its Neonatal Review Group were used to assess the methodological quality of the included trials.

Additional information requested from the authors of each trial to clarify methodology and results as necessary.

Each author extracted the data separately, compared data, and resolved differences.

The standard method of the Neonatal Review Group was used to synthesize the data.

Description of studies

Details of the included studies are included in the Table 'Characteristics of Included Studies'. Ten studies met the inclusion criteria (Modanlou 1986, Carey 1987, Gross 1987 (1), Gross 1987 (2), Greer 1988, Pettifor 1989, Polberger 1989, Kashyap 1990, Lucas 1996, Wauben 1998).

The types of human milk fortifier (HMF), as defined in this overview, varied from supplementation with a commercial preparation (containing protein, fat, carbohydrate, minerals, electrolytes, and trace minerals) to supplementation with only two individual components. Modanlou 1986 used a fortifier containing protein, carbohydrate, and minerals (Mead Johnson, preparation not specified). Carey 1987 used HMF containing protein and minerals only, but quantities of these were not specified. Gross 1987 (1) and Gross 1987 (2) used Similac Special Care (Ross Laboratories) preterm formula as supplementation, or a powdered HMF. Greer 1988 used a preparation from Ross Laboratories (powdered fortifier, unspecified), as did Pettifor 1989 (Ross Laboratories Human Milk Fortifier) and Kashyap 1990 (preparation not specified). Polberger 1989 supplemented with both protein and fat, and infants in both the control and treatment arms received mineral supplementation. Lucas 1996 used Enfamil HMF (Mead Johnson). Wauben 1998 used a non-commercial fortifier produced by Wyeth-Ayerst.

There was variation between studies in the entry criteria. All studies based entry on birthweight (generally <1850g), although the limits for these were variable. Almost all studies excluded infants with congenital abnormalities or significant illness. Fortification was commenced in most studies once the infant tolerated a prespecified enteral intake. For almost all studies fortification ceased at a specified weight (generally 1800 to 2000g) or at discharge, although, for some studies, the duration of intervention is unclear.

The daily intakes of the various individual components varied between studies, as did enteral intakes. In some studies, there was little or no difference in caloric intakes between the groups (Gross 1987 (1), Gross 1987 (2), Greer 1988). Details of the individual components are included in the table "Characteristics of Included Studies".

Excluded studies are listed in the Table "Characteristics of Excluded Studies". Ronnholm 1982 included a treatment group that received both protein and fat supplementation, and was therefore eligible for inclusion. However, it was impossible to extract data from the published reports (information has been requested from the author). Boehm 1991 compared a commercial preparation (EOPROTIN) with a control group supplemented with albumin, minerals, and sodium, thereby comparing essentially a different form of protein intake. Moyer-Mileur 1992 compared commercial preparations of fortifier but did not have an unsupplemented control group, as was the case with Metcalf 1994 and Sankaran 1996. McClure 1996 did not report any of the prespecified clinical outcomes. Lucas 1984 was strongly considered for inclusion in this review, particularly as this study was included in a previous systematic review of infant feeding (Sinclair 1992). Although infant nutrition was supplemented, it was by the substitution of insufficient quantities of maternal milk with a preterm formula. This was not felt to represent "fortification" as such.

Methodological qualities of included studies

Eight of the ten studies report results for fewer than 15 infants in each arm. Only Lucas 1996 and Wauben 1998 included sample size estimates as part of the study design.

Pettifor 1989 used quasi-random allocation via maternal hospital number. Other studies used sealed envelopes (Modanlou 1986, Gross 1987 (1), Gross 1987 (2), Polberger 1989, Kashyap 1990, Lucas 1996) or random number tables (Greer 1988). The method of randomisation is unknown for Carey 1987 and Wauben 1998.

Polberger 1989 conducted a double blind study. The assessment of neurodevelopmental and long term growth outcomes for Lucas 1996 was masked, but short-term outcomes were not. In other studies, there was no masking to the intervention (Modanlou 1986, Greer 1988, Wauben 1998) or masking was unknown.

Most studies have focussed on relatively well infants. Infants who developed significant illness were frequently not enrolled or not included in results (Modanlou 1986, Carey 1987, Greer 1988, Gross 1987 (1), Gross 1987 (2), Pettifor 1989, Polberger 1989, Wauben 1998). Polberger 1989 withdrew one control infant for apnoea, and two treatment infants (feed intolerance; apnoea) [additional information provided by author]. In only five studies (Modanlou 1986, Pettifor 1989, Kashyap 1990, Lucas 1996, Wauben 1998) are the outcomes reported for all infants enrolled. In other studies, either the number of infants enrolled or the reasons for withdrawal are unknown. Where infants have been withdrawn because of feed intolerance, NEC, or death, results have been included if possible.

Lucas 1996 supplemented the control group with phosphate and, in both groups, provided premature formula if there was insufficient maternal milk. Similarly, Wauben 1998 supplemented control infants with calcium and phosphate. Polberger 1989, primarily assessing caloric supplementation, provided both treatment and control groups with calcium and phosphate. These interventions in the control groups may reduce any differences attributable to treatment. The results of this overview have been subjected to a sensitivity analysis excluding these studies.

Results

These studies report results for 596 infants. There is significant variability between studies in the outcomes of weight gain and linear growth and blood urea levels (all trials included, but not with the sensitivity analysis), head growth, ALP activity, and BMC. This potentially reflects differences in fortifier composition, study design (for example, exclusion criteria, variable enteral and caloric intakes, duration of intervention), and outcome measures (primarily, timing of outcome measurements).

Short-term growth parameters

All studies evaluated short-term growth, although the weight data from Gross 1987 (1), Gross 1987 (2) and Modanlou 1986 could not be included. The two largest studies (Pettifor 1989, Lucas 1996) did not demonstrate a statistically significant increase in weight gain in the fortification group. Nevertheless, the overall analysis demonstrated greater weight gains in infants receiving fortification (WMD 2.3g/kg/day, 95% CI, 1.7 to 2.9g/kg/day). The difference in daily weight gain remained statistically significant at 3.7g/kg/day (95% CI, 2.7 to 4.7g/kg/day) when the studies where control infants received mineral supplementation are excluded.

Infants receiving fortifier had greater length gain by 0.13cm/week (95% CI, 0.07 to 0.18cm/week). When the sensitivity analysis was performed, the difference in weekly length gain remained statistically significant at 0.18cm/week (95% CI, 0.08 to 0.28cm/week).

Head growth was also greater in those infants receiving HMF (WMD 0.12cm/week, 95% CI 0.07 to 0.16cm/week). The sensitivity analysis did not significantly alter this finding (WMD 0.14cm/week, 95% CI, 0.09 to 0.20cm/week).

Long-term growth parameters

Only one study (Lucas 1996) evaluated long term growth. No difference was found between weight, length, or head circumference at 18 months.

Serum alkaline phosphatase

There was no effect on mean ALP activity in the infants studied. This result did not change with the sensitivity analysis.

Bone mineral content

Modanlou 1986, Gross 1987 (1), and Gross 1987 (2) found that BMC values were not statistically different between control and treatment groups, although no absolute values are available. Wauben 1998 evaluated whole body BMC and found no difference. From the two studies where data are available in the same format (mg/cm), infants receiving HMF had higher BMC than those receiving unsupplemented milk (WMD 8.3mg/cm, 95% CI 3.8 to 12.8mg/cm). This result is heavily influenced by the study by Pettifor 1989 which contributed 59 of the 79 infants. The lack of absolute data from those individual trials where there was no difference between groups considerably reduces the confidence of this result.

Neurodevelopmental outcomes

Only Lucas 1996 evaluated developmental performance at 18 months. There was no statistically significant difference between intervention and control groups.

Fractures

No studies addressed this outcome.

Nitrogen retention studies

Two studies have demonstrated increased nitrogen retention in infants receiving HMF containing protein (WMD 66mg/kg/day, 95% CI 35 to 97mg/kg/day). Sensitivity analysis does not significantly change this result.

Hypercalcemia

Although most studies evaluated serum calcium levels, only Lucas 1996 and Wauben 1998 evaluated absolute hypercalcemia (>2.85mmol/l and >2.7mmol/l, respectively). There was no difference between the treatment and control groups, although both studies supplemented the control groups with minerals.

Feed intolerance

Many studies withdrew infants with feed intolerance and did not report results. Modanlou 1986 and Lucas 1996 both evaluated feed intolerance, finding no difference between the groups, but the outcomes could not be numerically analysed. On the basis of the small number of infants for whom this outcome is reported, there is a non-significant trend towards an increased risk of feed intolerance in fortified infants (RR 2.85, 95% CI 0.62 to 13.1).

Diarrhea

No study specifically addressed this outcome. Lucas 1996 found that infants receiving HMF were more likely to have "hard stools" than the control group.

Necrotizing enterocolitis

There is no significantly increased risk of NEC in infants receiving fortified human milk (RR 1.44, 95% CI 0.68 to 3.07). Sensitivity analysis does not significantly alter this result.

Blood pH

Lucas 1996 demonstrated a statistically significant reduction in pH in infants receiving HMF (pH 7.33, vs. pH 7.34 in controls - WMD -0.01, 95%CI -0.02 to -0.00) which is unlikely to have any clinical significance. Wauben 1998 withdrew one control infant because of metabolic acidosis.

Further information has been requested from other authors.

Blood urea

Urea levels are significantly increased in infants receiving HMF (WMD 0.27mmol/l, 95% CI 0.14 to 0.40mmol/l). When the studies evaluating mineral supplementation are excluded, this difference is increased (0.96mmol/l, 95% CI 0.56 to 1.36mmol/l).

Death

Death as a specific outcome is reported by Pettifor 1989 and Lucas 1996. Other studies studied relatively well infants. There does not appear to be any increased risk of death associated with fortification of human milk (RR 1.48, 95% CI 0.66 to 3.34), although all infants who died in one study (Pettifor 1989) were assigned fortifier. Sensitivity analysis, excluding Lucas 1996, results in inclusion of Pettifor's study only with a trend towards increased risk of death (RR 13.3) but with very wide confidence intervals (95% CI, 0.78 to 227). Further information has been requested from other authors.

Discussion

This overview has demonstrated that fortification of human milk with more than one nutritional supplement (caloric and/or mineral) results in small but statistically significant increases in weight gain, linear growth, and head growth over the short term study periods evaluated. No long term advantage has been shown in terms of either growth or neurodevelopmental outcome, although this has been addressed by only one study (Lucas 1996).

Short-term growth is a difficult outcome to assess - particularly if the first two weeks of life, when weight loss is common, are included in the overall weight gain results. Although the differences for these outcomes are small, the effect of these small increases in growth over the short term is cumulative. For prolonged hospital stays, a small advantage in weight gain or head or linear growth may have a significant impact on growth parameters at discharge or even age at discharge. However, these outcomes were not evaluated in this review. Two studies reported these outcomes (Modanlou 1986, Wauben 1998) and found no difference between the groups.

Fortification of human milk may improve BMC but has no effect on ALP levels. Fractures have not been reported as an outcome in any study. Nitrogen retention has been examined in two studies and is significantly increased in infants receiving fortifier.

Adverse effects of fortification do not appear to be significantly increased, although the total number of infants studied and the unavailability of results for some infants randomized and subsequently withdrawn makes it difficult to be confident of this finding. There is no evidence of a significantly increased risk of NEC. Urea levels are higher and pH levels lower in infants receiving fortification, but the clinical significance of this is not clear. The increased urea levels in the fortifier group are not above the accepted range of normal - if anything, excluding Lucas 1996, those in the control group are low and the higher levels in fortified infants may reflect improved dietary protein intake. There are insufficient data to evaluate other potential adverse effects.

Conclusions

Implications for practice

There is sufficient evidence to demonstrate that fortification of human milk with more than one nutritional component is associated with short-term improvements in weight gain, linear and head growth. Bone mineral content may also increase. However, there is not yet any evidence that this short-term gain leads to any demonstrable long-term benefit in growth or neurodevelopmental outcomes, although this may well be related to the absence of follow-up in almost all studies. There does not appear to be any increase in clinically significant adverse effects in supplemented infants, although the total number of infants studied is small and the abstractable data from the published studies is limited.

Implications for research

Fortification of human milk has become common practice, based largely on metabolic studies evaluating the composition of human milk and the nutritional requirements of preterm infants. There is an absence of evidence of long-term benefit, and insufficient evidence to be reassured that there are no deleterious effects. Despite this, it is unlikely that further studies evaluating fortification of human milk versus no supplementation will be performed. Indeed, Lucas 1996 felt that it was not ethical to withhold phosphorus supplementation in control infants.

Most commercially available fortifiers contain varying amounts of protein, carbohydrate, calcium, phosphate, other minerals (zinc, manganese, magnesium, and copper), vitamins, and electrolytes. The benefits of many of these individual components have not been evaluated in a controlled manner. Further research should be directed toward comparisons between different proprietary preparations and evaluating both short-term and long-term outcomes and adverse effects, in search of the "optimal" composition of fortifiers. This has, in part, been addressed by studies excluded from this overview (Moyer-Mileur 1992, Metcalf 1994, Sankaran 1996). The number of study subjects required to adequately evaluate these outcomes would be extremely large.

Internal sources of support to the review

* National Women's Hospital, Auckland NEW ZEALAND
* University of Auckland, Auckland NEW ZEALAND
*

External sources of support to the review

* None on file
*

Potential conflict of interest

None known.

Synopsis

Multicomponent fortified breast milk for promoting growth in preterm infants

Babies born at full term (40 weeks) get all their nutrition and immunity needs from breast milk. Babies born early (preterm), have different needs and may need extra nutrition supplements to meet these needs. However, preterm babies have quicker growth rates when fed baby or preterm formula than when fed breast milk and may need extra supplements. The review of trials found evidence that adding nutritional components to breast milk leads to short term improved growth and possibly also bone formation. The review found no evidence of long-term benefit or adverse effects.

Citation

Kuschel CA, Harding JE. Multicomponent fortified human milk for promoting growth in preterm infants (Cochrane Review). In: The Cochrane Library, Issue 3, 2002. Oxford: Update Software.

Contribution of Reviewer(s)
Most recent changes
Issue protocol first published

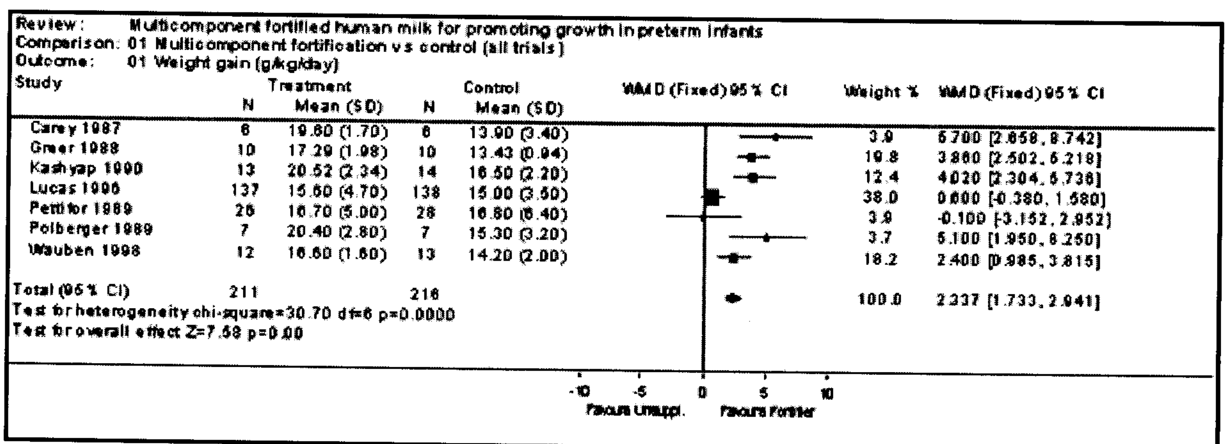
1997 Issue 3

Issue review first published

1998 Issue 4

Date new studies sought but none found
Date new studies found but not yet included or excluded
Date new studies found and included or excluded
Date reviewers' conclusions section amended
Table of comparisons

Fig 01 MULTICOMPONENT FORTIFICATION VS CONTROL (ALL TRIALS)

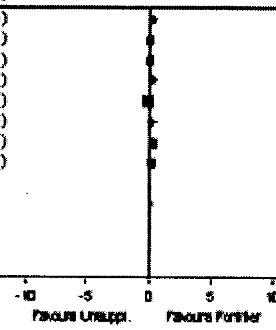


01.01.00 Weight gain (g/kg/day)

Review: Multicomponent fortified human milk for promoting growth in preterm infants
Comparison: 01 Multicomponent fortification vs control (all trials)
Outcome: 02 Length gain (cm/week)

Study	Treatment N	Treatment Mean (SD)	Control N	Control Mean (SD)	WMD (Fixed) 95% CI	Weight %	WMD (Fixed) 95% CI
Greer 1989	10	1.13 (0.23)	10	0.77 (0.24)		8.3	0.360 [0.154, 0.566]
Gross 1987 (1)	10	0.89 (0.19)	10	0.81 (0.22)		10.9	0.080 [-0.100, 0.260]
Gross 1987 (2)	8	0.86 (0.23)	9	0.79 (0.12)		11.2	0.070 [-0.108, 0.248]
Kashyap 1990	13	1.27 (0.48)	14	0.91 (0.21)		4.4	0.360 [0.077, 0.643]
Lucas 1996	137	0.93 (0.41)	138	0.96 (0.41)		37.5	-0.030 [-0.127, 0.067]
Modanlou 1986	8	0.99 (0.40)	10	0.81 (0.44)		2.3	0.180 [-0.209, 0.569]
Polberger 1989	7	1.20 (0.17)	7	0.83 (0.17)		11.1	0.370 [0.192, 0.548]
Wauben 1998	12	1.10 (0.20)	13	0.90 (0.20)		14.3	0.200 [0.043, 0.357]
Total (95% CI)	205		211			100.0	0.125 [0.066, 0.184]

Test for heterogeneity chi-square=26.30 df=7 p=0.0004
Test for overall effect Z=4.12 p=0.00

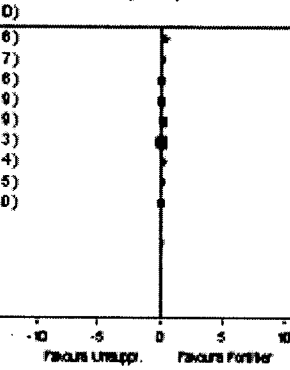


01.02.00 Length gain (cm/week)

Review: Multicomponent fortified human milk for promoting growth in preterm infants
Comparison: 01 Multicomponent fortification vs control (all trials)
Outcome: 03 Head growth (cm/week)

Study	Treatment N	Treatment Mean (SD)	Control N	Control Mean (SD)	WMD (Fixed) 95% CI	Weight %	WMD (Fixed) 95% CI
Carey 1987	6	1.10 (0.27)	6	0.70 (0.36)		1.5	0.400 [0.040, 0.760]
Greer 1988	10	1.05 (0.16)	10	0.80 (0.17)		9.2	0.250 [0.105, 0.395]
Gross 1987 (1)	10	0.92 (0.09)	10	0.83 (0.16)		14.8	0.090 [-0.024, 0.204]
Gross 1987 (2)	8	0.84 (0.14)	9	0.84 (0.09)		14.9	0.000 [-0.113, 0.113]
Kashyap 1990	13	1.20 (0.18)	14	1.00 (0.19)		9.8	0.200 [0.060, 0.340]
Lucas 1996	137	1.01 (0.41)	138	0.95 (0.33)		24.8	0.060 [-0.028, 0.148]
Modanlou 1986	8	1.09 (0.07)	10	0.82 (0.24)		7.8	0.270 [0.114, 0.426]
Polberger 1989	7	1.11 (0.13)	7	0.94 (0.25)		4.4	0.170 [-0.039, 0.379]
Wauben 1998	12	1.00 (0.10)	13	0.90 (0.20)		12.8	0.100 [-0.023, 0.223]
Total (95% CI)	211		217			100.0	0.118 [0.074, 0.162]

Test for heterogeneity chi-square=16.88 df=8 p=0.0313
Test for overall effect Z=5.29 p=0.00

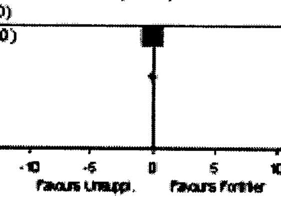


01.03.00 Head growth (cm/week)

Review: Multicomponent fortified human milk for promoting growth in preterm infants
Comparison: 01 Multicomponent fortification vs control (all trials)
Outcome: 04 Weight at 18 months (kg)

Study	Treatment N	Treatment Mean (SD)	Control N	Control Mean (SD)	WMD (Fixed) 95% CI	Weight %	WMD (Fixed) 95% CI
Lucas 1996	125	10.05 (1.34)	120	10.09 (1.10)		100.0	-0.040 [-0.346, 0.266]
Total (95% CI)	125		120			100.0	-0.040 [-0.346, 0.266]

Test for heterogeneity chi-square=0.00 df=0 p=0.0000
Test for overall effect Z=-0.26 p=0.80



01.04.00 Weight at 18 months (kg)

Review: Multicomponent fortified human milk for promoting growth in preterm infants
Comparison: 01 Multicomponent fortification vs control (all trials)
Outcome: 05 Length at 18 months (cm)

Study	Treatment N	Treatment Mean (SD)	Control N	Control Mean (SD)	WMD (Fixed) 95% CI	Weight %	WMD (Fixed) 95% CI
Lucas 1996	125	80.00 (3.35)	120	80.10 (3.29)		100.0	-0.100 [-0.932, 0.732]
Total (95% CI)	125		120			100.0	-0.100 [-0.932, 0.732]

Test for heterogeneity chi-square=0.00 df=0 p=0.0000
Test for overall effect Z=-0.24 p=0.80

-10 -5 0 5 10
Favours Unsuppl. Favours Fortifier

01.05.00 Length at 18 months (cm)

Review: Multicomponent fortified human milk for promoting growth in preterm infants
Comparison: 01 Multicomponent fortification vs control (all trials)
Outcome: 06 Head circumference at 18 months (cm)

Study	Treatment N	Treatment Mean (SD)	Control N	Control Mean (SD)	WMD (Fixed) 95% CI	Weight %	WMD (Fixed) 95% CI
Lucas 1996	125	48.10 (1.12)	120	48.10 (1.10)		100.0	0.000 [-0.278, 0.278]
Total (95% CI)	125		120			100.0	0.000 [-0.278, 0.278]

Test for heterogeneity chi-square=0.00 df=0 p=0.0000
Test for overall effect Z=0.00 p=0.00

-10 -5 0 5 10
Favours Unsuppl. Favours Fortifier

01.06.00 Head circumference at 18 months (cm)

Review: Multicomponent fortified human milk for promoting growth in preterm infants
Comparison: 01 Multicomponent fortification vs control (all trials)
Outcome: 07 Serum alkaline phosphatase (IU/l)

Study	Treatment N	Treatment Mean (SD)	Control N	Control Mean (SD)	WMD (Fixed) 95% CI	Weight %	WMD (Fixed) 95% CI
Carey 1987	8	356.00 (65.00)	8	375.00 (96.00)		19.0	-19.000 [-98.099, 60.099]
Greer 1988	10	446.00 (112.00)	10	382.00 (122.00)		11.3	64.000 [-38.649, 166.649]
Kashyap 1990	13	448.00 (271.00)	14	503.00 (253.00)		3.0	-55.000 [-253.158, 143.158]
Lucas 1996	137	539.00 (243.00)	138	506.00 (210.00)		41.2	33.000 [-20.698, 86.698]
Modanlou 1986	7	790.00 (202.00)	9	1075.00 (434.00)		1.2	-285.000 [-605.612, 35.612]
Pettifor 1989	29	483.00 (162.00)	30	843.00 (514.00)		3.2	-360.000 [-552.072, -167.928]
Wauben 1998	12	388.00 (99.00)	13	371.00 (92.00)		21.1	17.000 [-58.092, 92.092]
Total (95% CI)	214		222			100.0	4.238 [-30.241, 38.717]

Test for heterogeneity chi-square=20.13 df=6 p=0.0026
Test for overall effect Z=0.24 p=0.80

-10 -5 0 5 10
Favours Fortifier Favours Unsuppl.

01.07.00 Serum alkaline phosphatase (IU/l)

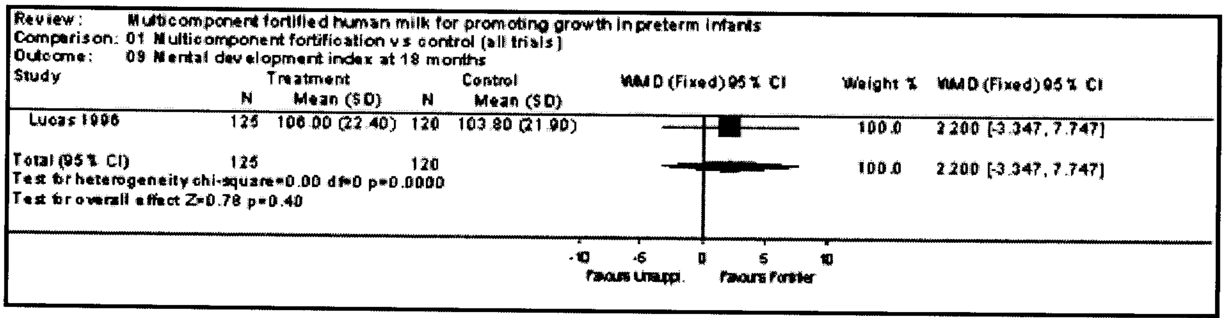
Review: Multicomponent fortified human milk for promoting growth in preterm infants
Comparison: 01 Multicomponent fortification vs control (all trials)
Outcome: 08 Bone mineral content (mg/cm)

Study	Treatment N	Treatment Mean (SD)	Control N	Control Mean (SD)	WMD (Fixed) 95% CI	Weight %	WMD (Fixed) 95% CI
Greer 1988	10	39.30 (9.30)	10	36.70 (6.70)		39.4	2.600 [-4.504, 9.704]
Pettifor 1989	29	59.00 (13.00)	30	47.00 (9.00)		60.6	12.000 [6.276, 17.724]
Total (95% CI)	39		40			100.0	8.300 [3.843, 12.757]

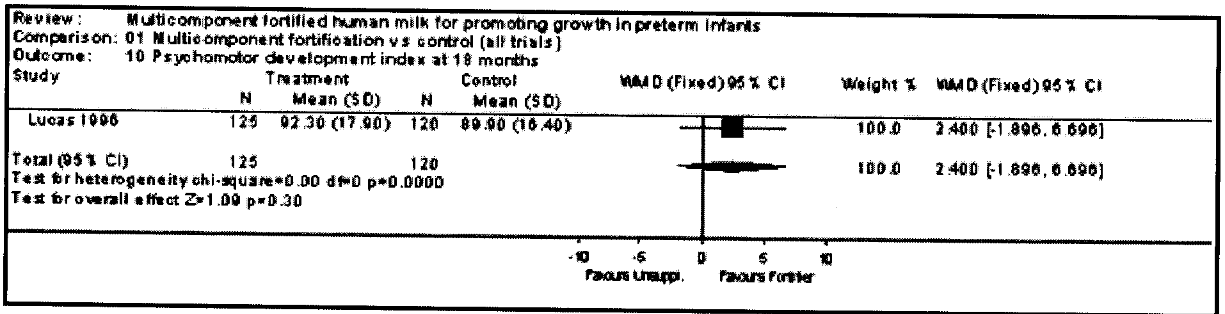
Test for heterogeneity chi-square=4.08 df=1 p=0.0434
Test for overall effect Z=3.65 p=0.00

-10 -5 0 5 10
Favours Unsuppl. Favours Fortifier

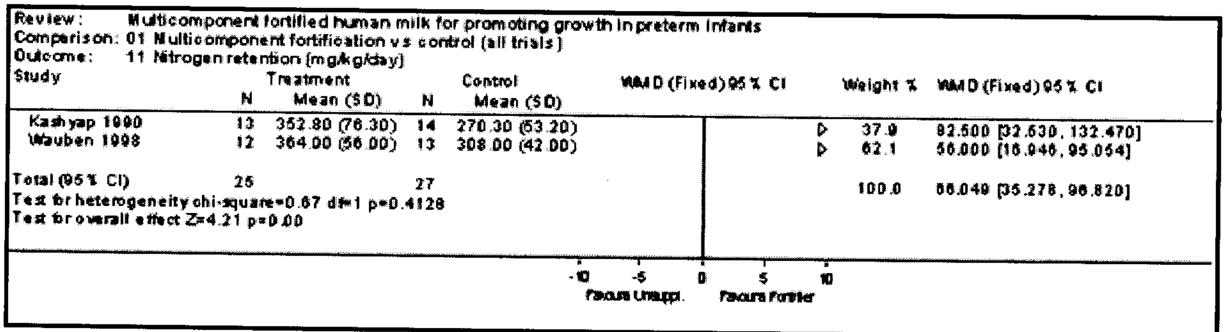
01.08.00 Bone mineral content (mg/cm)



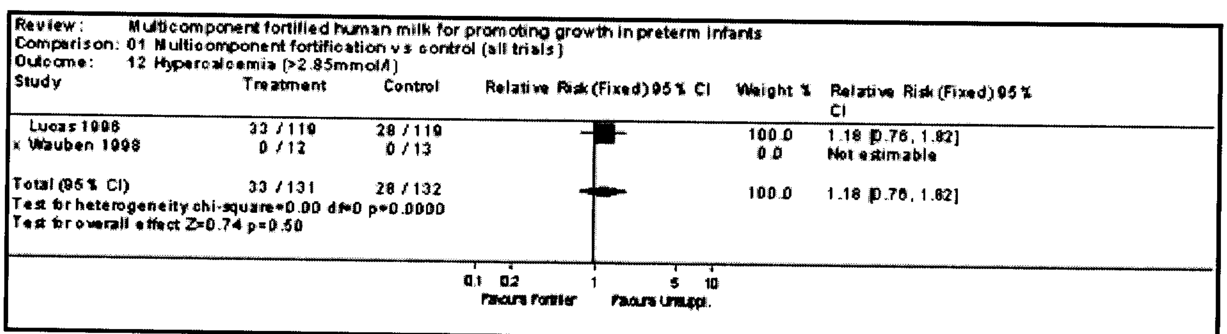
01.09.00 Mental development index at 18 months



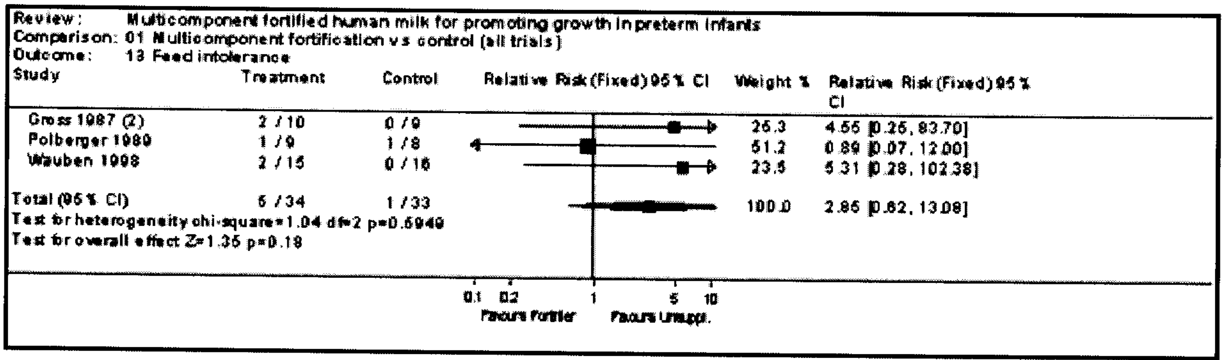
01.10.00 Psychomotor development index at 18 months



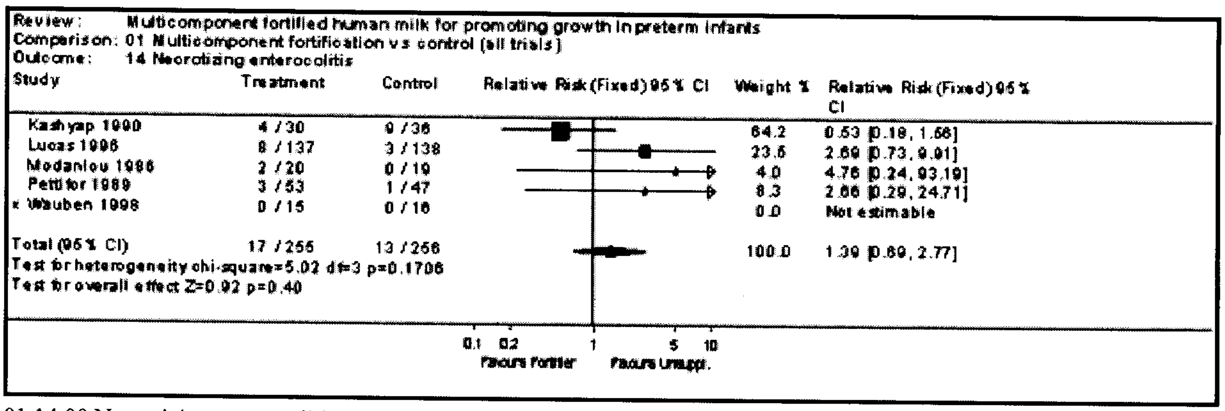
01.11.00 Nitrogen retention (mg/kg/day)



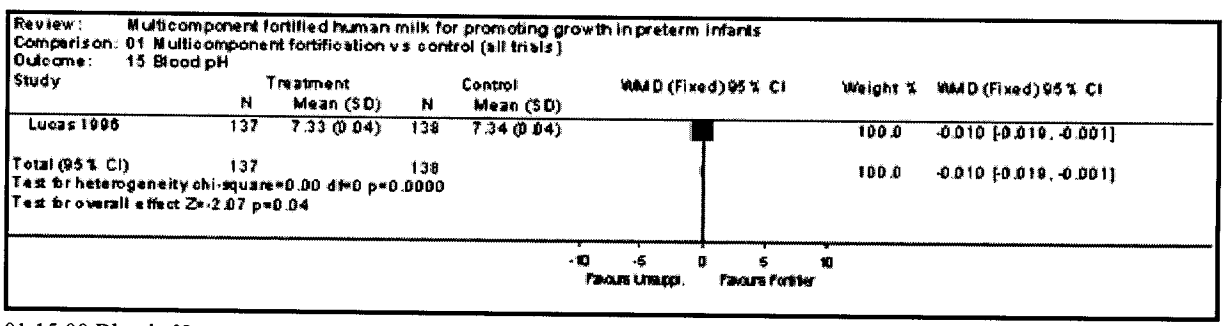
01.12.00 Hypercalcemia (>2.85mmol/l)



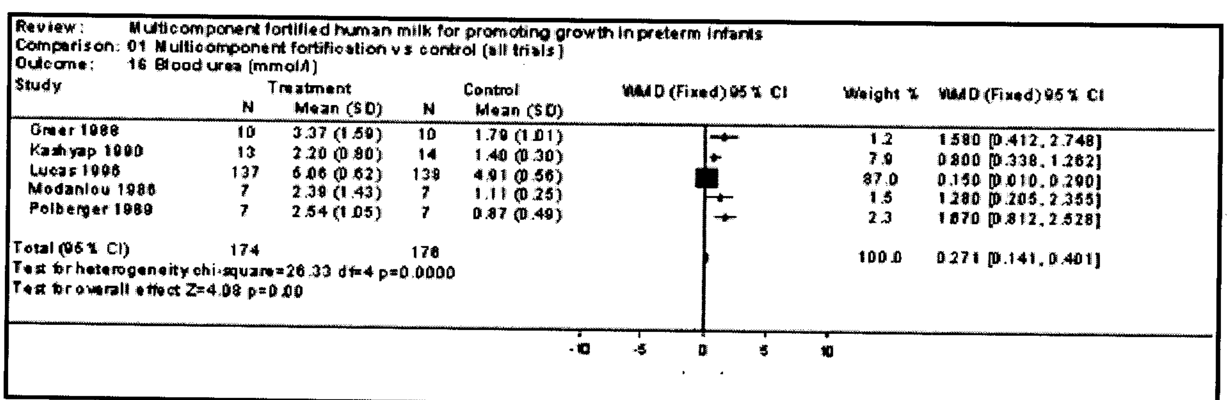
01.13.00 Feed intolerance



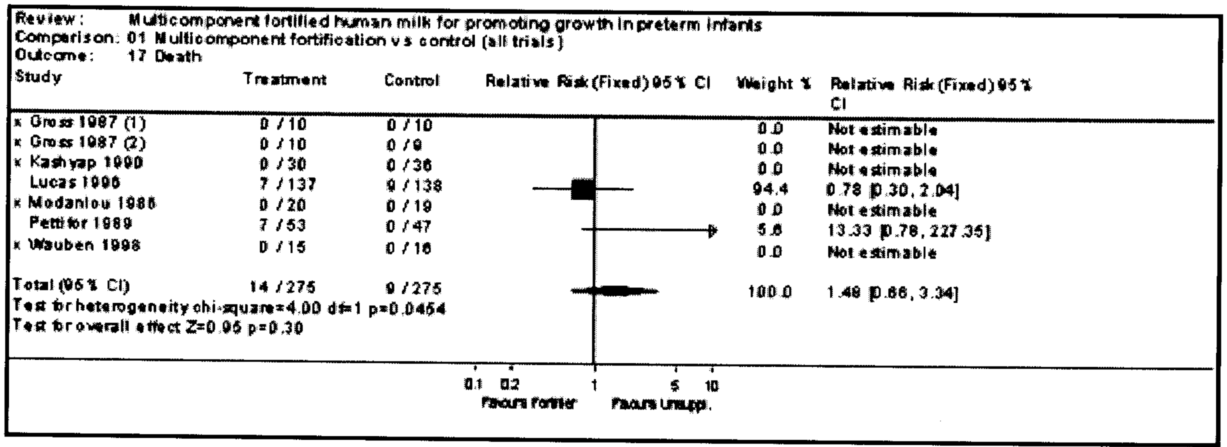
01.14.00 Necrotizing enterocolitis



01.15.00 Blood pH



01.16.00 Blood urea (mmol/l)



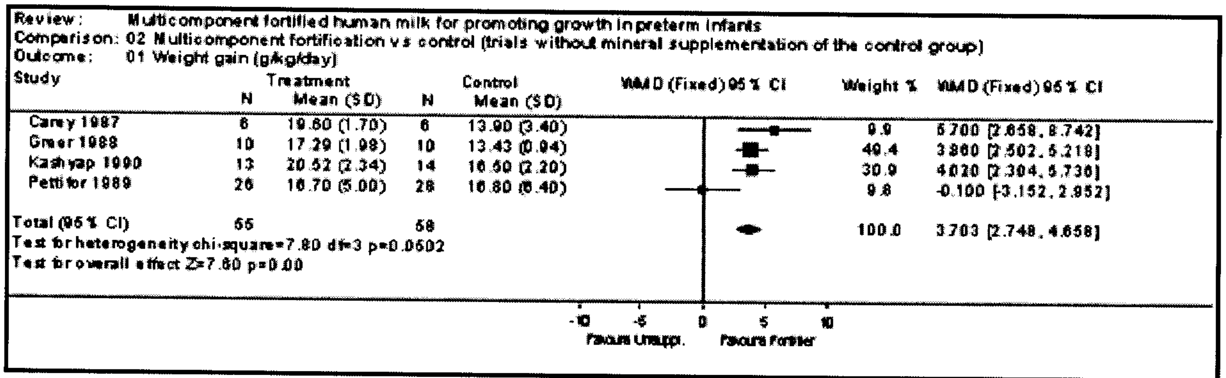
Review: Multicomponent fortified human milk for promoting growth in preterm infants
Comparison: 01 Multicomponent fortification vs control (all trials)
Outcome: 17 Death

Study	Treatment	Control	Weight %	Relative Risk (Fixed) 95% CI
x Gross 1987 (1)	0 / 10	0 / 10	0.0	Not estimable
x Gross 1987 (2)	0 / 10	0 / 9	0.0	Not estimable
x Kashyap 1990	0 / 30	0 / 36	0.0	Not estimable
Lucas 1996	7 / 137	9 / 138	94.4	0.78 [0.30, 2.04]
x Modanlou 1986	0 / 20	0 / 19	0.0	Not estimable
Pettifor 1989	7 / 53	0 / 47	5.6	13.33 [0.78, 227.35]
x Wauben 1998	0 / 15	0 / 16	0.0	Not estimable
Total (95% CI)	14 / 275	9 / 275	100.0	1.49 [0.66, 3.34]

Test for heterogeneity chi-square=4.00 df=1 p=0.0454
Test for overall effect Z=0.95 p=0.30

01.17.00 Death

Fig 02 MULTICOMPONENT FORTIFICATION VS CONTROL (TRIALS WITHOUT MINERAL SUPPLEMENTATION OF THE CONTROL GROUP)

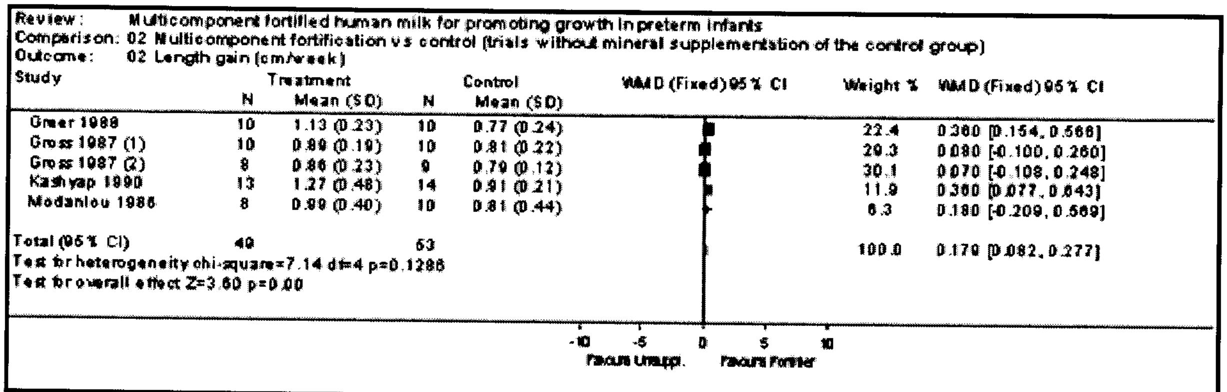


Review: Multicomponent fortified human milk for promoting growth in preterm infants
Comparison: 02 Multicomponent fortification vs control (trials without mineral supplementation of the control group)
Outcome: 01 Weight gain (g/kg/day)

Study	Treatment N	Treatment Mean (SD)	Control N	Control Mean (SD)	Weight %	WMD (Fixed) 95% CI
Carey 1987	6	19.60 (1.70)	6	13.90 (3.40)	9.9	5.700 [2.658, 8.742]
Greer 1988	10	17.29 (1.98)	10	13.43 (0.94)	49.4	3.860 [2.502, 5.218]
Kashyap 1990	13	20.52 (2.34)	14	16.50 (2.20)	30.9	4.020 [2.304, 5.736]
Pettifor 1989	26	16.70 (5.00)	28	16.80 (6.40)	9.8	-0.100 [-3.152, 2.952]
Total (95% CI)	55		58		100.0	3.703 [2.748, 4.658]

Test for heterogeneity chi-square=7.80 df=3 p=0.0502
Test for overall effect Z=7.60 p=0.00

02.01.00 Weight gain (g/kg/day)

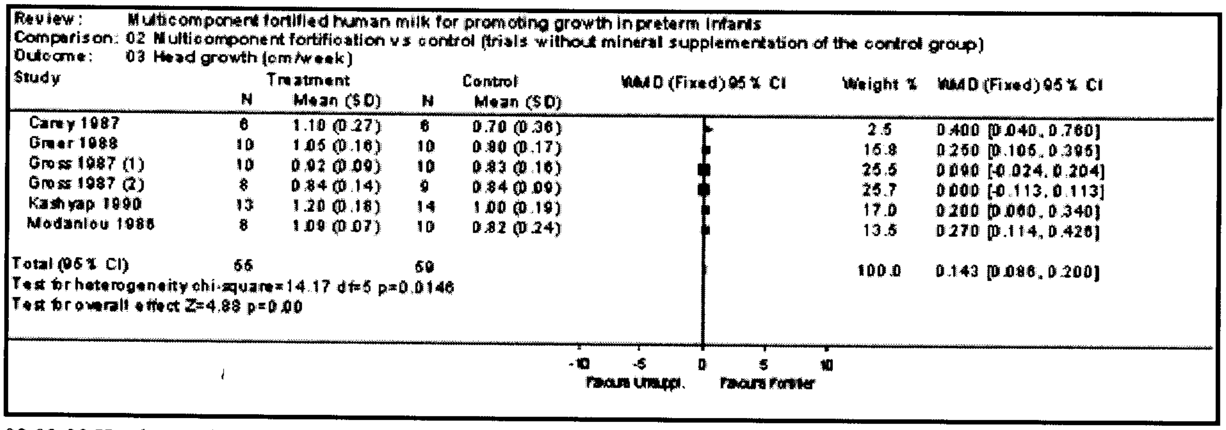


Review: Multicomponent fortified human milk for promoting growth in preterm infants
Comparison: 02 Multicomponent fortification vs control (trials without mineral supplementation of the control group)
Outcome: 02 Length gain (cm/week)

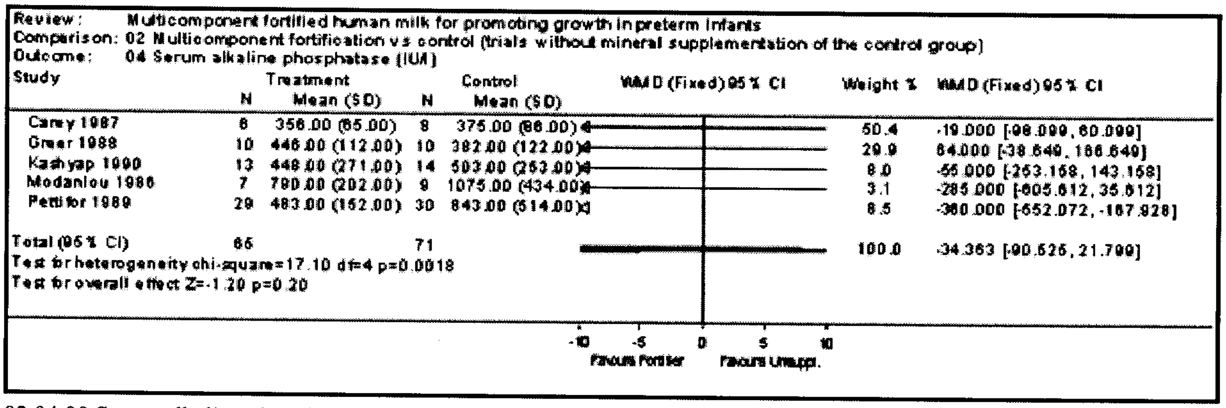
Study	Treatment N	Treatment Mean (SD)	Control N	Control Mean (SD)	Weight %	WMD (Fixed) 95% CI
Greer 1988	10	1.13 (0.23)	10	0.77 (0.24)	22.4	0.360 [0.154, 0.566]
Gross 1987 (1)	10	0.89 (0.19)	10	0.81 (0.22)	29.3	0.080 [-0.100, 0.260]
Gross 1987 (2)	8	0.86 (0.23)	9	0.79 (0.12)	30.1	0.070 [-0.108, 0.248]
Kashyap 1990	13	1.27 (0.48)	14	0.91 (0.21)	11.9	0.360 [0.077, 0.643]
Modanlou 1986	8	0.99 (0.40)	10	0.81 (0.44)	6.3	0.180 [-0.209, 0.569]
Total (95% CI)	49		53		100.0	0.179 [0.082, 0.277]

Test for heterogeneity chi-square=7.14 df=4 p=0.1285
Test for overall effect Z=3.60 p=0.00

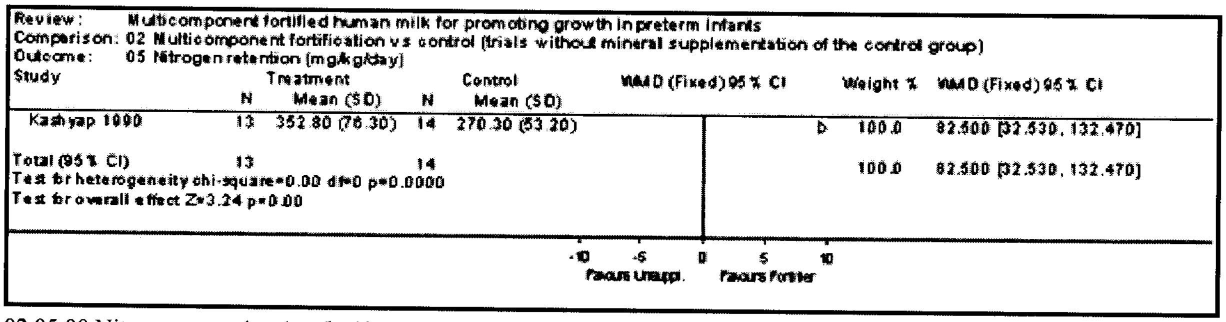
02.02.00 Length gain (cm/week)



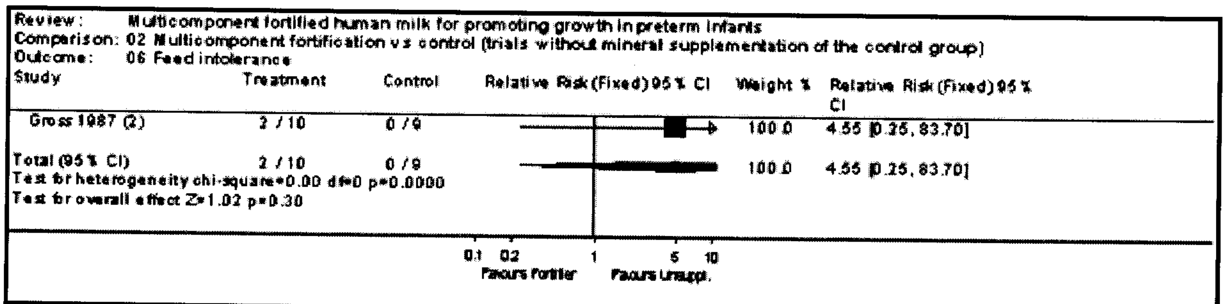
02.03.00 Head growth (cm/week)



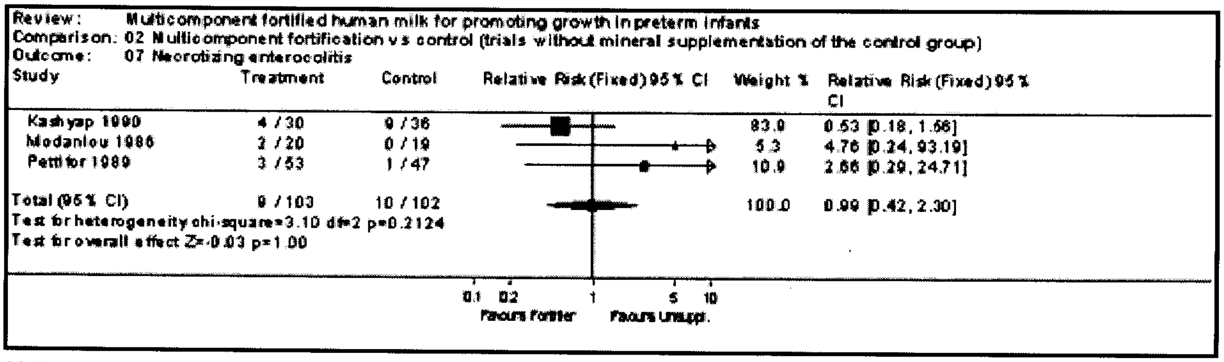
02.04.00 Serum alkaline phosphatase (IU/l)



02.05.00 Nitrogen retention (mg/kg/day)



02.06.00 Feed intolerance

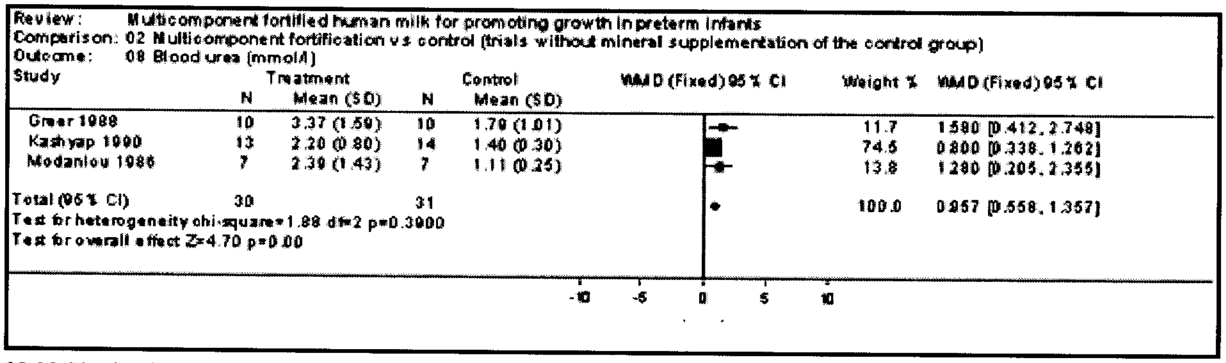


Review: Multicomponent fortified human milk for promoting growth in preterm infants
Comparison: 02 Multicomponent fortification vs control (trials without mineral supplementation of the control group)
Outcome: 07 Necrotizing enterocolitis

Study	Treatment	Control	Weight %	Relative Risk (Fixed) 95% CI
Kashyap 1990	4 / 30	9 / 36	83.9	0.53 [0.18, 1.56]
Modanlou 1986	2 / 20	0 / 19	5.3	4.76 [0.24, 93.19]
Pettifor 1989	3 / 53	1 / 47	10.9	2.66 [0.29, 24.71]
Total (95% CI)	9 / 103	10 / 102	100.0	0.99 [0.42, 2.30]

Test for heterogeneity chi-square=3.10 df=2 p=0.2124
Test for overall effect Z=-0.03 p=1.00

02.07.00 Necrotizing enterocolitis

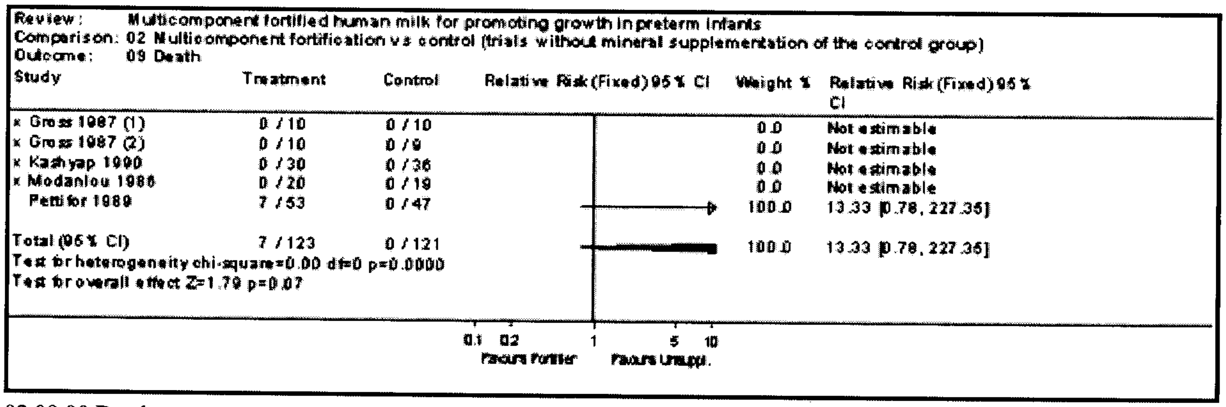


Review: Multicomponent fortified human milk for promoting growth in preterm infants
Comparison: 02 Multicomponent fortification vs control (trials without mineral supplementation of the control group)
Outcome: 08 Blood urea (mmol/l)

Study	Treatment N	Treatment Mean (SD)	Control N	Control Mean (SD)	Weight %	WMD (Fixed) 95% CI
Greer 1988	10	3.37 (1.59)	10	1.79 (1.01)	11.7	1.580 [0.412, 2.748]
Kashyap 1990	13	2.20 (0.80)	14	1.40 (0.30)	74.5	0.800 [0.338, 1.262]
Modanlou 1986	7	2.39 (1.43)	7	1.11 (0.25)	13.8	1.280 [0.205, 2.355]
Total (95% CI)	30		31		100.0	0.957 [0.558, 1.357]

Test for heterogeneity chi-square=1.88 df=2 p=0.3900
Test for overall effect Z=4.70 p=0.00

02.08.00 Blood urea (mmol/l)



Review: Multicomponent fortified human milk for promoting growth in preterm infants
Comparison: 02 Multicomponent fortification vs control (trials without mineral supplementation of the control group)
Outcome: 09 Death

Study	Treatment	Control	Weight %	Relative Risk (Fixed) 95% CI
x Gross 1987 (1)	0 / 10	0 / 10	0.0	Not estimable
x Gross 1987 (2)	0 / 10	0 / 9	0.0	Not estimable
x Kashyap 1990	0 / 30	0 / 36	0.0	Not estimable
x Modanlou 1986	0 / 20	0 / 19	0.0	Not estimable
Pettifor 1989	7 / 53	0 / 47	100.0	13.33 [0.78, 227.35]
Total (95% CI)	7 / 123	0 / 121	100.0	13.33 [0.78, 227.35]

Test for heterogeneity chi-square=0.00 df=0 p=0.0000
Test for overall effect Z=1.79 p=0.07

02.09.00 Death

Characteristics of Included Studies

Study: Carey 1987
Method: Randomized study, single centreSample size estimate: NoRandomization method: Not statedBlinding of randomization: Can't tellComplete follow-up: NoBlinding of outcome measure: Can't tell
Participants: Birthweight <1500gExclusions: significant illness and congenital malformationEnteral feeds of 150ml/kg/day for 48 hoursNumber of Treatment Infants Randomized: UnknownNumber of Control Infants Randomized: Unknown
Interventions: Maternal milk supplemented with Protein, Calcium, and Phosphate (exact quantities not specified) vs. unsupplemented maternal milk.Intervention ceased at approximately 4.5 weeks.No information about supplemental vitamins.

Outcomes: Short term growthBiochemical indices of bone metabolismSerum protein levels
Notes: Some results expressed as means for the number of observations, rather than individuals.Some infants excluded from results because of missing data.
Allocation concealment: B
Study: Greer 1988
Method: Randomized study, single centreSample size estimate: NoMethod of randomization: Random number tableBlinding of randomization: Can't tellBlinding of intervention: NoComplete follow-up: NoBlinding of outcome measurements: Can't tell
Participants: Infants <32 weeks GA or <1600gExclusions: major congenital abnormalities, congenital intrauterine infection, significant gastrointestinal disease, or seizures requiring anticonvulsant therapy.Study commenced once infants tolerating full oral feeds.Number of Treatment Infants Randomized: UnknownNumber of Control Infants Randomized: Unknown
Interventions: Maternal milk supplemented with (per 100ml) 0.85g Protein, 90mg Calcium, and 45mg Phosphorus (Ross Laboratories) vs. unsupplemented maternal milk Enteral intake >120ml/kg/day and <200ml/kg/day - varied according to weight gain, appetite, and tolerance.All infants received Vitamin D 400IU/day.
Outcomes: Short term growthBMCBiochemical indices of bone metabolismUreaTotal protein
Notes: The fortified group received significantly less milk (152 vs. 180 ml/kg/day) than the unsupplemented group. There was no significant difference in caloric intake.Of 176 eligible infants, only 10 in the HMF arm and 10 in the unsupplemented arm completed the study.
Allocation concealment: B
Study: Gross 1987 (1)
Method: Randomized study, single centre.Sample size estimate: NoRandomization method: Sealed envelopesBlinding of randomization: Can't tellComplete follow-up: NoBlinding of outcome measures: Can't tellTwo phase trial, referred to as Gross 1987 (1) and Gross 1987 (2)
Participants: Birthweight <1600g, AGAFree from congenital anomalies and major disease, no supplemental oxygen, enteral feeds begun within one week of birth.Number of Treatment Infants Randomized to Phase 1: 10Number of Control Infants Randomized to Phase 1: 10Number of Treatment Infants Randomized to Phase 2: 10Number of Control Infants Randomized to Phase 2: 9
Interventions: Phase 1: Maternal or donor milk mixed ml-for-ml with Similac Special Care (Ross Laboratories) vs. unsupplemented human milk.Phase 2: Maternal or donor milk with powdered HMF (Ross Laboratories) providing (per 100ml) 0.9g protein, 87mg Calcium, and 50mg Phosphorus, and electrolytes vs. unsupplemented human milk.Enteral intake 180ml/kg/day, adjusted according to weight gains.Intervention ceased at a weight of 1800-2000g.All infants received supplemental vitamins (including Vitamin D 400IU/day).
Outcomes: Short term growthGrowth at 44 weeks postconceptional ageBMCBiochemical indices of bone metabolism
Notes: Phase 2 compared HMF to unsupplemented human milk, as well as a group who received preterm formula as in Phase 1. Only the control group and the group receiving powdered fortifier have been included in this review.Results of short-term weight gain could not be included as they were expressed in g/day. Information has been requested from the author.4 infants in the phase 2 study were withdrawn post-randomization because of feed intolerance (2 each from the HMF and formula supplementation arms).
Allocation concealment: B
Study: Gross 1987 (2)
Method: See Gross (1)
Participants: See Gross (1)
Interventions: See Gross (1)
Outcomes: See Gross (1)
Notes: See Gross (1)

Allocation concealment: B
Study: Kashyap 1990
Method: Randomized study, single centreSample size estimate: NoRandomization Method: Sealed envelopeBlinding of randomization: AdequateBlinding of intervention: Can't tellComplete follow-up: NoBlinding of outcome measurement: Can't tell
Participants: Birthweight 900-1750gNumber of Treatment Infants Randomized: 30Number of Control Infants Randomized: 36
Interventions: Intervention commenced once infants enterally feeding.Maternal milk supplemented with (per kg/day) with 1.1g Protein, 3.7mmol Calcium, 2.11mmol Phosphate, and Sodium (Ross Laboratories) vs. unsupplemented maternal milk.Feeds maintained at 180ml/kg/dayOutcomes assessed at 2200g.All infants received supplemental Vitamin D (400 iU/day)
Outcomes: Short term growthBiochemical indices of bone metabolismNitrogen retentionUrea
Notes: High attrition from both unsupplemented (22 of 36) and fortified (17 of 30) groups. Reasons included NEC, PDA, and insufficient maternal milk. Some of these infants were placed into a third, non-random arm of the study in which they received supplemented term human milk. This arm has not been included in this review.Other outcomes included plasma amino acid levels and skinfold thickness.
Allocation concealment: A
Study: Lucas 1996
Method: Randomized trial, two centresSample size estimate: Yes - neurodevelopmental outcomeMethod of randomization: Sealed opaque envelope, stratified by birthweight (<1200 and >1200g)Blinding of randomization: YesBlinding of intervention: NoComplete follow-up: YesBlinding of outcome measurement: Yes (neurodevelopmental outcome)
Participants: <37 weeks and <1850gSurvival to 48-72 hoursExclusions: major congenital abnormalities affecting neurodevelopmental outcomes, non-resident in UKNumber of Treatment Infants Randomized: 137Number of Control Infants Randomized: 138
Interventions: Maternal milk supplemented with (per 100ml) 0.7g Protein (bovine), 2.73g Carbohydrate, 0.05g Fat, 90mg Calcium, and 45mg Phosphate, and electrolytes (Enfamil, Mead Johnson), vs. maternal milk supplemented with 15mg/100ml Phosphate.Enteral intake 180ml/kg/day.Intervention ceased at discharge or 2000g.All infants received vitamins (including Vitamin D 260 IU/100ml).Infants whose mothers could not provide sufficient milk were supplemented with a premature formula and not excluded from the analysis.
Outcomes: Neurodevelopmental outcome at 9 and 18 months.Short term growth.Growth to 9 and 18 months.Serum indices of bone metabolismUrea
Notes: The authors felt it was not ethical to provide totally unsupplemented human milk so added 15mg Phosphate/100ml in control infants.A large proportion of infants in both groups were supplemented with a premature formula when there was insufficient maternal milk.Linear and head growth have been converted from mm/day to cm/week.
Allocation concealment: A
Study: Modanlou 1986
Method: Randomized study, single centreSample size estimate: NoRandomization Method: Sealed envelopesBlinding of randomization: AdequateBlinding of intervention: NoComplete follow-up: YesBlinding of outcome measurement: No
Participants: 1000-1500g AGA infants.Exclusions: Ventilatory assistance >1 week, oxygen >10 days, diuretic therapy >3 days, not enterally fed by 14 daysNumber of Treatment Infants Randomized: 20Number of Control Infants Randomized: 19
Interventions: Maternal milk supplemented with (per 100ml) 0.7g Protein, 2.7g Carbohydrate, "trace" Fat, 60mg Calcium, and 33mg Phosphate, trace minerals, and electrolytes (preparation not specified), vs. unsupplemented maternal milk.Enteral intake approximately 135-140ml/kg/day.Intervention ceased at discharge or 1800g.Vitamin D supplementation unknown.

Outcomes: Short term growthIndices of bone metabolismBMCUreaSerum proteins
Notes: A third arm of the study evaluated infants receiving a premature formula (not analysed in this review).9 infants in the control arm and 10 in the HMF arm were withdrawn for insufficient maternal milk. 2 infants in the HMF arm were withdrawn for suspected NEC.Infants whose mothers could not provide sufficient milk were supplemented with a term infant formula and not excluded from the analysis unless formula intake was >10% of weekly total.
Allocation concealment: A
Study: Pettifor 1989
Method: Quasi-randomized trial, single centre.Sample size estimate: NoMethod of randomization: Allocation by maternal hospital numberBlinding of randomization: NoBlinding of intervention: Can't tellComplete follow-up: NoBlinding of outcome measurement: Can't tell
Participants: 1000-1500g birthweightNo major congenital abnormalities, no ventilator requirement, no serious infection, no major metabolic disturbance, and enteral intake at least 45ml/kg/day on Day 4Number of Treatment Infants Randomized: 53Number of Control Infants Randomized: 47
Interventions: Maternal milk supplemented with (per 100ml) 0.05g Protein, 1.1g Carbohydrate, 0.26g Fat, 72.3mg Calcium, and 34mg Phosphate, and electrolytes and vitamins (HMF, Ross Laboratories) vs. unsupplemented maternal milk.Maximal enteral intake 200ml/kg/dayIntervention ceased at approximately 1800g.All infants received additional Vitamin D 750IU/day.
Outcomes: Short term growthBMCSerum indices of bone metabolismSerum albumin
Notes: 41 of 100 infants enrolled were withdrawn - 13 for insufficient maternal milk, 16 for significant illness [2 NEC, 11 respiratory causes, and 3 others], and 7 died. 5 others were excluded for incomplete data.
Allocation concealment: C
Study: Polberger 1989
Method: Randomized trial. Single centreMethod of randomization: Sealed envelopesBlinding of randomization: AdequateBlinding of intervention: AdequateComplete follow-up: No
Participants: AGA preterm infants <1500gEnteral intake 170ml/kg/dayExclusions: major illness, requirement for supplemental oxygenNumber of Treatment Infants Randomized: 9Number of Control Infants Randomized: 8
Interventions: Maternal or donor milk supplemented with (per 100ml) 1.0g human milk protein and 1.0g human milk fat vs. unsupplemented human milk.Intervention ceased at 2200g or when breast fed.All infants were supplemented with vitamin E, folic acid, multivitamins, and extra Vitamin D (to a total of 1200 IU/day). All infants received Calcium (30mg/kg/day) and Phosphate (20mg/kg/day) from day 5.2mg elemental iron per kg per day given from 4 weeks.
Outcomes: Short term growthPlasma protein levels
Notes: This study is included in the multicomponent review because of the two nutritional supplements. This study had four arms - unsupplemented, vs. supplemented with protein, vs. supplemented with fat, vs. supplemented with fat and protein. Supplementation with fat alone and protein alone is discussed in separate reviews. 34 infants were enrolled in all four study groups, but six infants were excluded following randomization (reasons discussed in separate reviews). Results were reported for only 7 infants in each group.Ultrafiltration of human milk to obtain protein may result in additional calcium being provided to the fortifier group.There were large fluctuations in the energy intake for all four groups across the study.Other outcomes, not included in the review, included plasma and urine amino acid levels.
Allocation concealment: A
Study: Wauben 1998
Method: Randomized trial. Single centreMethod of randomization: Block randomization, random number tablesBlinding of randomization: YesBlinding of intervention: NoComplete follow-up: NoSample size estimate: Yes (BMC at term corrected)

Participants: AGA preterm infants <1800g, greater than 1 week oldEnteral intake 160ml/kg/dayExclusions: Gastrointestinal disease, major congenital anomaliesNumber of Treatment Infants Randomized: 15Number of Control Infants Randomized: 16
Interventions: Commenced when maternal milk providing >80% of enteral intakeMaternal supplemented with (per 100ml) 0.37g human milk protein, 3.47g carbohydrate, 61mg Calcium, 44mg Phosphorus, as well as electrolytes, other minerals, and vitamins (including Vit D 472IU/day) (Wyeth-Ayerst, Toronto) vs. unsupplemented human milk.Mean fluid intakes significantly greater in the control group (177 vs. 164ml/k/day).Intervention ceased at discharge or 38 weeks corrected GA, whichever occcured later.Control infants supplemented with vitamin D (600IU/day) whilst receiving supplements. All infants received "standard" vitamin supplementation following discharge.
Outcomes: Short term growthBiochemical indices of bone metabolismBMC (whole body) Nitrogen retention
Notes: 6 infants (3 in each group) were withdrawn - 2 in the HMF group for feed intolerance (defined as abdominal distension - personal communication, Dr S Atkinson), and 1 for insufficient maternal milk. 2 infants in the control group developed chronic lung disease, and 1 developed a metabolic acidosis. These infants' results are not included in the paper.A third arm of the study (not analysed in this review) evaluated infants who received a preterm formula.Infants in the control arm were significantly lighter at birth, and significantly lighter and shorter at study entry and exit than the group receiving HMF.Nutrient intakes were also measured.
Allocation concealment: A

Characteristics of Excluded Studies

Study: Boehm 1991
Reason for exclusion: No unsupplemented control group. The interventions contrasted were multicomponent fortifier (EOPROTIN) versus supplementation with human albumin, minerals, and sodium.
Study: Lucas 1984
Reason for exclusion: Infants received a preterm formula or donor term human milk as a substitute for maternal milk. The supplements were given in varying amounts, with the median intake 42%. Over a third of mothers provided less than 20% of their infant's intake.
Study: McClure 1996
Reason for exclusion: Did not include any prespecified outcomes of this review.
Study: Metcalf 1994
Reason for exclusion: Comparison of multicomponent fortifiers.
Study: Moyer-Mileur 1992
Reason for exclusion: Comparison of multicomponent fortifiers.
Study: Ronnholm 1982
Reason for exclusion: Unable to abstract data for those infants supplemented with fat and protein together against those who were unsupplemented.
Study: Sankaran 1996
Reason for exclusion: Comparison of multicomponent fortifiers.

References to studies included in this review

Carey 1987 (*published data only*)

Carey DE, Rowe JC, Goetz CA, Horak E, Clark RM, Goldberg B. Growth and phosphorus metabolism in premature infants fed human milk, fortified human milk, or special premature formula. Use of serum procollagen as a marker of growth. Am J Dis Child 1987;141:511-515. [Medline Link] [Context Link]

Greer 1988 (*published and unpublished data*)

Greer FR, McCormick A. Improved bone mineralization and growth in premature infants fed fortified own mother's milk. milk. J Pediatr 1988;112:961-969. [Medline Link] [Context Link]

Gross 1987 (1) *(published data only)*

Gross SJ. Bone mineralization in preterm infants fed human milk with and without mineral supplementation. J Pediatr 1987;111:450-458. [Medline Link] [Context Link]

Gross 1987 (2) *(published data only)*

Gross SJ. Bone mineralization in preterm infants fed human milk with and without mineral supplementation. J Pediatr 1987;111:450-458. [Medline Link] [Context Link]

Kashyap 1990 *(published and unpublished data)*

Kashyap S, Schulze KF, Forsyth M, Dell RB, Ramakrishnan R, Heird WC. Growth, nutrient retention, and metabolic response of low-birth-weight infants fed supplemented and unsupplemented preterm human milk. Am J Clin Nutr 1990;52:254-262. [Medline Link]Kashyap S, Schulze KF, Ramakrishnan R, Dell RB, Forsyth M, Zucker C, Heird WC. Growth, nutrient retention and metabolic response of low birth weight (LBW) infants fed human milk (HM). Pediatr Res 1988;23:486A. [Context Link]

Lucas 1996 *(published and unpublished data)*

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*Food, Fortified; Growth; Human; *Infant Nutrition; Infant, Newborn; Infant, Premature; *Milk, Human

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