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Bliss Briefings

Bliss for babies born too soon, too small, too sick

Discussion paper on the use of Breast Milk Fortifiers in the Feeding of Preterm Infants

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Introduction

Human milk is considered the optimal feed for preterm babies for both nutritional and non nutritional reasons. The use of unfortified human milk has, however, been associated with poorer rates of growth and bone mineralisation; particularly with very preterm babies. This has lead to the development of Breast Milk Fortifiers (BMF).

BMF has been available in the UK and Ireland since the early 1990s; however, clear guidance on its use is lacking which has led to a wide variation in practice. In addition there has been a build up of misconceptions around its safety. This briefing paper is a review of those misconceptions and the literature that surrounds them.

Rationale

Early preterm expressed breast milk (EBM) is higher in protein and sodium than term milk but levels decline to mature term levels after two-three weeks. At this stage, intakes beyond the tolerance of preterm babies would be needed to provide sufficient nutrients, eg up to 400ml/kg[1]. Most other nutrients are not found in higher levels in preterm milk and are insufficient for preterm babies, the exception being energy. Energy content in expressed human milk is dependent on the fat content which in turn is dependent on expressing technique. If all milk is removed completely from the breast the resulting energy density can be >80kcal/100ml (similar to preterm formula)[2]. This is due to the higher fat content of hind milk which is removed towards the end of an expression as the breast is emptied.

Outcomes

Many studies have shown that a diet of fortified EBM is associated with short term improvement in growth, indicators of bone mineralization, and nitrogen retention compared to unfortified EBM[3].

Concerns

However there have been concerns around the use of BMF which has led to widely differing approaches to its use. It is important to review the evidence, as completely as possible, to avoid restricting use where this is not necessary and to ensure careful use in at-risk groups. The following is an attempt to look at all the available data.

Feed intolerance

A systematic review of randomized controlled trials (RCTs) found there was no significant problem with feed tolerance in babies on fortified breast milk[3].

Most studies have not found BMF to affect gastric emptying[4,5,6]. While there is some evidence that in more immature infants it can be slower than with unfortified EBM[7].

One study found that babies had harder stools on fortified EBM but had no other signs of feed intolerance[8]. The fortifier used was higher in calcium than those commonly used in the UK today, which may have predisposed to the formation of insoluble calcium/fatty acids soaps in the babies' gut[9,10].

Milk curd bolus

Rare examples of obstruction with milk curd bolus in babies fed fortified EBM have been described[11,12,13]. In some the use of BMF containing high levels of calcium may have lead to calcium / fatty acid insoluble soaps[13], as described above. In one study five out of nine babies had had gut surgery prior to developing the milk bolus; this is a known risk factor for milk bolus obstruction[13,14]. In another the infant was also given feed thickener which it was thought led to the lactobezoar[12].

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Osmolality

It has been recommended that the osmolality of enteral feeds be kept below 450 mOsm/kg as higher levels were considered to be associated with an increased risk of necrotising enterocolitis (NEC).[15] In this paper the term *osmolarity* was used and a level below 400 mOsm/l recommended. This is equivalent to an *osmolality* of approximately 450 mOsm/kg. This figure is an arbitrary upper limit based on reports of NEC after use of elemental formulas with osmolality of around 650 mOsm/kg[16]. Thus the upper limits chosen are not based on direct experimental evidence.

In the majority of studies, addition of BMF to EBM causes an early rise in osmolality but it remains below the recommended upper limit of 450 mOsm/kg and continues to remain below this limit after storage for 24 hours[17,18,19,20,21].

Warming previously fortified EBM will cause an additional rise in osmolality following storage. However this has also been shown to remain below the recommended upper limit[22].

The osmolality of other enteral supplements must be taken into account as single doses of some can be far higher than that of EBM plus BMF (e.g. sodium chloride, iron, vitamins)[18].

Necrotising enterocolitis

A systematic review and a randomized study published since the review found no difference in risk between fortified and unfortified EBM[3,23]. However as NEC is a relatively rare complication, a study with much larger numbers would be needed to evaluate risk more accurately.

A recent study looked at babies randomised to a bovine based or a human milk based BMF; if mother's milk was not available the bovine BMF group was supplemented with preterm formula and the other group with donor milk. The bovine based BMF group developed NEC significantly more frequently than the other group. During the course of the study the bovine BMF group received 20 per cent of their feeds as preterm formula. There is no information on the distribution of NEC cases between those who stayed on all mothers milk and those who had to have supplements of preterm formula, thus it is impossible to say whether the increased risk of NEC was due to the fortifier or the formula[24].

Bacterial growth in human milk

Many papers have tested both fresh and previously frozen EBM and found no significant difference in bacterial growth between either milks with or without BMF. Likewise, inhibition of bacterial growth was preserved[25,26,27,28,29]. Where a significantly increased number of colony forming units was found the authors questioned the clinical significance of the difference[17].

Effect on immunological factors in human milk

Levels of TGFalpha and IgA have been found to be unchanged in fortified compared to unfortified EBM.[30,25,17] Addition of formula to EBM has been found to reduce lyzosyme content by ~ 40-70 per cent whereas BMF reduced it by only~20 per cent[25].

Sepsis

In one study of babies randomized to fortified vs unfortified EBM, there was found to be no difference in confirmed sepsis, although there was a significant increase in suspected sepsis[8] (interestingly the babies randomized to BMF had a trend to improved neurodevelopmental outcome). In another no difference in rates of sepsis between groups was found[23]. No difference in late onset sepsis was found when comparing babies on either human milk and bovine protein based fortifier[24].

Allergy

Presumed allergy to fortifiers based on whole cows milk protein have been reported very rarely[31,32]. However, the fortifier used most commonly in the UK is based on a hydrolysed cows milk protein source, and as yet no adverse reactions have been reported with its use; although it is not guaranteed hypoallergenic by the company.

Summary

The minor risks which may be associated with fortifying EBM for preterm babies must be balanced against slower growth and bone mineralisation seen in babies fed unfortified EBM and the alternatives to using a multi-nutrient fortifier which themselves carry risks. Concerns around increased osmolality and bacterial growth may have been over estimated; safety can be maximised by drawing up guidelines for use of BMF using published evidence. Gastrointestinal tolerance may be compromised in very immature babies and those who have previously had gut surgery and this should be taken into account.

Suggested guidelines

The following guidelines are based on available evidence and current practice within the UK and Ireland. As there is insufficient evidence as yet for the development of a national protocol, it is recommended that local guidelines are developed for the use of breast milk fortifiers using these parameters.

Criteria for starting fortification

- All babies <1.5kg birth weight and <34 weeks
- Consider babies 1.5-2kg birth weight and <34 weeks
- Babies >2kg birth weight are unlikely to need BMF

  Plus;
- Receiving ≥ 50 per cent total feeds as breast milk
- Tolerating feed volumes at a minimum of 150 ml /kg/day – preferably 180ml/kg
- Serum urea < 4mmol/l and falling

What to add

- Commercially available fortifier following dose according to manufacturer's instructions

How to add

- Use manufacturers' instructions
- Warm for as brief a period as possible and avoid temperatures >37degC
- Mix well but avoid vigorous shaking
- Fortify the minimum volume possible, and use before fortifying more
- Consider starting at half strength for 24 hours if baby at risk of poor tolerance

Monitoring and additional supplementation

- Weekly weight, length and head circumference
- If growth falters calculate nutrient intake and compare with recommended intakes
- Weekly serum phosphate, calcium, sodium & alkaline phosphatase
- Weekly serum urea taking into account possible increases with dehydration compromised renal function, sepsis, steroid therapy and inadequate non protein energy intake
- If urea within normal range but growth is faltering consider use of hind milk
- Give iron supplement between four to six weeks

Criteria for stopping fortification

- On <50 per cent total feeds EBM and growth satisfactory
- If growth not satisfactory carry on BMF until <25 per cent total feeds EBM
- Able to fully demand breast feed
- At discharge together with satisfactory growth
- Assess babies individually to see if BMF post discharge may be of benefit.

Practical issues

It is a useful practice to label milk sequentially in order of expression so that early milk can be used first. This will not only have a higher protein content but will be higher in immunological compounds[33].

It is recommended that the minimum amount of milk is prepared at a time; this will ensure that EBM is not wasted if a decision is made to stop fortifier or go nil by mouth. It also ensures that any potential disruption of immunological components which has not yet been quantified/investigated is kept to the minimum. Finally should the milk inadvertently be contaminated it would reduce the extent of bacterial growth compared to storage for 24 hours.

It is practice in some units to add fortifier before full enteral feeds has been achieved to prevent faltering growth. However, due to the high levels and variability of early human milk protein levels, early empirical fortification could lead to intakes over 4g/kg/day and may reach 6g/kg/day. These levels are not likely to aid growth and there is the small risk of adverse side effects associated with excessive protein intake.

Contra indications

Current BMFs are not suitable for term babies as they have nutrient profiles designed for the unique needs of the preterm infant.

Breast milk fortifier should never be mixed with infant formula as this practice would increase the calcium content to levels associated with risk of gastrointestinal calcium/milk curd bolus obstruction. Likewise it is advisable neither to exceed manufacturer's instructions for the amount of BMF added to EBM nor to administer additional calcium to already fortified EBM, as this may also exceed safe levels of calcium. Risk of calcium/milk curd bolus formation may also be reduced by the avoidance of BMF and a feed thickener together in the same feed.
If feeding fortified human milk by a continuous infusion there is the risk of incomplete delivery of some minerals[34], and incomplete fat delivery[35]. This risk can be minimised by gently agitating the container before and during feeds and pointing the nozzle of the syringe upwards to allow delivery of the fat-rich milk first.

Conclusion

Fortification of human milk is an effective intervention in the drive to optimise the nutritional status and growth of preterm babies, and may have long term benefits which are beyond the scope of this review to discuss. There may be small risks associated with the use of BMF, however these can be minimized through the development of local guidelines which take into consideration the current evidence base.

It is hoped that a more extensive version of this document will be published in the medical literature in the near future.