Lactoferrin supplementation for very preterm infants

Lactoferrin is a key component of the mammalian innate immune response. Infants born very preterm are relatively deficient in lactoferrin and may benefit from supplementation. Preliminary evidence suggests that bovine lactoferrin supplementation might prevent late-onset invasive infection and its associated mortality and morbidity. In the UK, the ELFIN Trial Investigators Group is undertaking a large, simple and pragmatic randomised controlled clinical trial to test this hypothesis.

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Key points

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1. Invasive infection and necrotising enterocolitis (NEC) are the most common causes of late neonatal death in very preterm infants.
2. Lactoferrin is a natural antimicrobial present in breast milk but very preterm infants are relatively deficient.
3. ELFIN is a large, pragmatic, randomised controlled trial to assess whether enteral supplementation with bovine lactoferrin may help prevent infection and NEC in very preterm infants.
4. Healthcare professionals should be able to discuss research participation with parents to broaden awareness of a research-active unit and promote trial recruitment.

Infection and necrotising enterocolitis

In the UK, almost 2% of infants are born very preterm (<32 weeks' gestation) or with very low birth weight (VLBW, <1,500g). Over the past 30 years, advances in care practices have substantially improved outcomes for this very vulnerable population. In particular, more effective prevention and treatment of respiratory distress syndrome of prematurity means that very preterm or VLBW infants are now more likely to survive beyond the first few days after birth. However, these infants often require several weeks of intensive care and are exposed to invasive procedures that increase their risk of major morbidities. These include late-onset (hospital-acquired) invasive infection and necrotising enterocolitis (NEC). About 20% acquire a serious infection and NEC occurs in about 5% of very preterm or VLBW infants.[1-3] The level of associated mortality is high, especially for Gram negative bacillus or fungal infections and severe NEC that requires surgery, and these conditions are now the most common causes of death beyond the early neonatal period for very preterm infants.[3-5]

Surviving infants have higher likelihoods of developing other problems including chronic lung disease, retinopathy of prematurity (ROP) and neurosensory disability. Furthermore, because very preterm or VLBW infants who acquire infection or NEC spend nearly three weeks longer in hospital, these conditions have important consequences for neonatal care services. By extending the average length of hospital admission, late-onset infection or NEC reduce cot availability in neonatal units and therefore increase the risk of overcrowding and the need for transfer of expectant mothers or their sick or preterm newborn infants to units distant from their homes and families.[6-8] Given this burden of mortality, acute and long-term morbidity, and costs to families and health services, there is a need to develop and assess novel and innovative strategies to prevent late-onset invasive infection and NEC in very preterm or VLBW infants.

- Antimicrobial effects
  - cell membrane disruption
  - iron sequestration
  - inhibition of microbial adhesion to host cells
  - prevention of biofilm formation
- Prebiotic effects
  - promotion of intestinal growth of beneficial bacteria (probiotics)
  - reduction of colonisation with pathogenic species
- Immune-modulatory and anti-inflammatory actions
  - modulation of cytokine expression
  - mobilisation of leucocytes into the circulation
  - activation of T lymphocytes
  - suppression of free radical activity
- Intestinal integrity effects
  - stimulation of differentiation and proliferation of enterocytes
  - promotion of closure of enteric gap junctions
  - increases expression of intestinal digestive enzymes

TABLE 1 Lactoferrin: mechanisms of action.

Lactoferrin

One such promising intervention is enteral supplementation with lactoferrin. Lactoferrin is the major whey protein in the breast milk of all mammals including humans and is also present in tears, saliva, cerebrospinal fluid and other secretions. Lactoferrin has broad antimicrobial actions and is a key component of the mammalian innate response to infection (**TABLE 1**).[9-12] Lactoferrin also has prebiotic properties, creating an enteric environment for the growth of beneficial bacteria and reducing colonisation with pathogenic species.[13]

Enteral lactoferrin supplementation

Given the potential beneficial actions of lactoferrin in a range of inflammatory and infectious conditions, several trials of lactoferrin supplementation have been undertaken over the past 10 years.[14] Although recombinant human lactoferrin is available, it remains very expensive. Most trials have assessed the effect of bovine lactoferrin (processed from cows' milk) which is 70% homologous with human lactoferrin but has higher antimicrobial activity, is inexpensive, and is available commercially as a food supplement in a stable powder form. Bovine lactoferrin has been a component of the human infant diet for thousands of years and is registered 'generally recognised as safe' by the US Federal Drug Administration with no reports of human or animal toxicity.[15] Furthermore, because bovine lactoferrin does not bind strongly to the lactoferrin receptor in the human small intestine, it is not absorbed via the gastrointestinal tract and does not generate hypersensitivity or allergic immunological reactions.[16,17]

Existing evidence

The only existing randomised controlled trial (RCT) of prophylactic lactoferrin supplementation in very preterm infants was conducted in Italy in 2007-8. The investigators found that enteral supplementation with bovine lactoferrin (compared with dextrose placebo) for up to six weeks after birth reduced the incidence of late-onset invasive infection by two-thirds and may have reduced the risk of NEC.[18] The effect size was similar whether infants were fed predominantly with human milk or artificial formula. The incidence of severe ROP was also lower in the lactoferrin group. However, the trial did not find evidence of an effect on all-cause mortality and did not assess any long-term neurodevelopmental outcomes.

Although this trial has provided preliminary evidence that giving very preterm or VLBW infants supplemental bovine lactoferrin may reduce rates of some infections in some infants, this study was not large enough to support adopting this intervention into practice. The current Cochrane review concludes that the effect of bovine lactoferrin supplementation in preventing invasive infection and other morbidity and mortality in very preterm infants 'needs to be confirmed in well-designed, adequately-powered, multi-centre [randomised controlled] trials.'[19]

The ELFIN trial

Several international groups are planning large trials. In the UK, the ELFIN Trial Investigators Group is undertaking a simple and pragmatic RCT with 2,200 very preterm infants, cared for in 30 neonatal units across the UK, being invited to participate (www.npeu.ox.ac.uk/elfin).[20] Parents are offered information about the trial and have up to three days to consider whether they wish their baby to take part. When parents or guardians have provided informed consent, trial investigators in each unit are asked to randomly allocate infants to receive either:

(i) bovine lactoferrin (150mg/kg) mixed with water and a small volume of breast or formula milk or

(ii) sham treatment (placebo).

Treatment with bovine lactoferrin or placebo continues until the infants are no longer at high risk of acquiring serious infections (the equivalent of 34 weeks' gestation). The pre-specified primary outcome is the incidence of late-onset invasive infection. The trial is also powered to assess meaningful effects of bovine lactoferrin supplementation on the:

- risk of other serious morbidities including NEC, chronic lung disease and ROP
- need for infants to receive multiple or prolonged courses of antibiotics (a major cause of antibiotic resistance in neonatal units)
- length of hospital stay.

In addition, the trial team will undertake an economic evaluation to make sure the intervention is cost-effective, that is, assessing not only whether bovine lactoferrin supplementation prevents infection but also that it is the most cost-efficient way of using scarce NHS resources to improve health and care outcomes for very preterm infants.

Delivering ELFIN

During the development of the ELFIN trial, staff have engaged with infant and family representatives experienced in voicing service users' views (principally via Bliss, the special care baby charity) and adhered to INVOLVE good practice guidelines (www.invo.org.uk) to ensure service-user leadership in the delivery and dissemination of the findings.

The ELFIN trial is managed and monitored by a team at the National Perinatal Epidemiology Unit (NPEU) Clinical Trials Unit in Oxford and builds on the expertise, enthusiasm and experience of colleagues in participating neonatal units across the country who have collaborated in the design, development, completion and dissemination of several major multi-centre trials of interventions to prevent morbidity and mortality in very preterm and VLBW infants. This broad and inclusive approach ensures equity of access to participation in high-quality research and therefore increases applicability of the trial findings across the NHS.

In each of the recruiting centres, the key staff needed to ensure trial delivery are dedicated research neonatal nurses or midwives who manage local aspects of the trial including staff education and training, and explaining processes to parents or caregivers. By being responsible for the day-to-day smooth running of the trial in participating sites and the management of administration and data collection in each unit, these staff enhance participation, improve consistency and raise the profile of clinical research within neonatal units. As well as the benefits to this trial, this should enhance the potential of the NHS to undertake future studies and trials which are essential to drive continued improvement in care and outcomes for very preterm or VLBW infants and their families.

Engaging with families

Neonatal nurses and midwives caring for very preterm or VLBW infants are aware that they may venture into emotionally turbulent territory when discussing research and trial participation with parents, especially during the early, difficult days immediately after birth. However, qualitative research indicates that parents value greatly involvement in any process, including research studies that may improve care and outcomes not just for their infants but for future infants.[21-23]

- Giving information
- Exploring understanding
- Assessing capacity
- Ensuring freedom of choice

TABLE 2 The principles of informed consent.[26]

Informed consent

Parents report valuing the informed consent process and the perceived integrity of this process is a key determinant of whether parental permission is given for their infant to participate in a trial (**TABLE 2**).[24-26] The informed consent process continues during and beyond the infant's stay in the neonatal unit and can include frequent discussions or meetings with the research team and with all involved in the ongoing care of the infant[27]: 'informed parental consent reminds the health professional to respect parent autonomy with respect to their infant's health care.'[26]

Parents report that trial participation adds a feeling of security (of "being held") and that being part of a research community brought connection, protection and support.[27] Studies such as ELFIN place the human experience of preterm birth at the heart of the research vision and mission, which is what matters to parents and those who care for preterm infants and their families.

Neonatal nurses and midwives (not just the 'research staff') should feel able and empowered to discuss openly and confidently research participation with parents as part of a remit to broaden awareness of a research-active unit and promote trial recruitment. Qualitative research indicates that parents are concerned most about the way things are said rather than what is said.[28-29] Parents report feeling reassured when all staff are familiar with a trial, which places greater requirement for all unit staff, regardless of grade or discipline, to be involved and enthused by bedside research, even if not actively taking consent. Creating a research-infused workplace culture, reduces the knowledge gap between those who 'do' research and those who watch it going on or read about it.

Simultaneous participation in more than one trial

ELFIN is one of a number of pragmatic neonatal trials being presented to parents in neonatal units around the UK. Some parents will be approached for consent to enroll their infant into more than one (compatible) trial designed to assess the effect of interventions on important outcomes for preterm infants. Although health professionals are often anxious about asking parents to consider consenting for participation of their infants in more than one trial or study, evidence exists that these anxieties are, in general, not shared by parents.[24,29] In order to provide the best care, support and outcomes for mothers and their newborn infants, health professionals – doctors, midwives and nurses working with families and infants – have an important role and responsibility in helping parents understand the implications of research involving their newborn infants. ELFIN is designed to run in parallel with another large UK multicentre trial (SIFT, Speed of Increasing milk Feeds Trial) that aims to assess the effect of different rates of enteral feed advancement on the incidence of invasive infection and NEC in very preterm infants.[30,31]

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The ELFIN trial – general information

Clinical trials unit:	National Perinatal Epidemiology Unit Clinical Trials Unit
Sponsor:	University of Oxford
Funder:	NIHR Health Technology Assessment (HTA) programme
Recruitment target:	2,200 (including pilot phase)
Duration:	March 2013 - December 2017
Inclusion criteria:	Gestational age at birth is less than 32 weeks Infant is less than 72 hours of age Written informed parental consent is obtained
Exclusion criteria:	Infants with a severe congenital anomaly Anticipated enteral fasting of more than 14 days Infants who have no realistic prospect of survival

For further information on the ELFIN trial visit www.npeu.ox.ac.uk/elfin

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