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RESEARCH SUMMARY

Breast Milk Exposure is associated with Cortical Maturation in Preterm Infants.
Gemma Sullivan, Kadi Vaher, Manuel Blesa, Paola Galdi, David Q. Stoye, Alan J. Quigley, Michael J. Thrippleton, John Norrie, Mark E. Bastin and James P. Boardman (2023). *Annals of Neurology*, 93(3), 591-603.
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There is a lot of truth behind the well-known aphorism that 'breast is best', and the World Health Organisation's firm recommendation that babies under six months old are exclusively breastfed is based on firm scientific evidence. The advantages of breastfeeding are apparent even when babies are born prematurely; breastfed pre-term infants are known to be less likely to develop neurological problems and to perform better academically. However, little is yet known about the link between exposure to human milk and brain development in these infants.

There are measurable differences in the structure of the cerebral cortex – the outer layer of the brain, which is principally responsible for cognition – between pre-term infants and those born at term, even when measured at equivalent gestational ages. Briefly, a premature infant's cortex is thicker than that of a baby born at term and has a different folding pattern. These differences continue into childhood and adolescence and have been associated with cognitive and behavioural difficulties.

So far, studies of the effect of breast milk on brain development in premature infants have concentrated on the very earliest days, when infants are fed directly into the bloodstream (parenteral nutrition). A group of clinicians and scientists at the University of Edinburgh, Scotland, led by Dr Gemma Sutherland of the MRC Centre for Reproductive Health there have now extended these studies to the next stage, when babies are tube-fed (enteral nutrition) while remaining in a special-care unit. This can be 2-3 months for very pre-term infants, even if they are developing normally. The researchers proposed that, if breast milk was protective against the neurological disadvantage associated with premature birth, the brains of pre-term infants primarily given breast milk throughout their hospital stay would more closely resemble those of infants born at full term.

Sutherland and her colleagues studied 175 infants born before 32 weeks' gestation at the Royal Infirmary of Edinburgh, UK, between February 2017 and December 2020, and 77 infants born at term at the same hospital during the same period. All participating infants were enrolled in the Theirworld Edinburgh Birth Cohort study, which is investigating the effects of premature birth. Feeding data for the premature infants was collected from their hospital records, and they were divided into two groups: those who had received breast milk exclusively on at least 75% of days in the neonatal unit ('high breast milk exposure'; 67 infants) and others ('low breast milk

exposure'; 68 infants). All premature infants received the same iron and vitamin supplements, and parents were encouraged to get involved in the process of their babies' routine care.

Two equivalent MRI scans of the brain of each infant in the study were obtained close to birth for the term-born infants and at term-equivalent age (38-44 weeks after the mother's last period) for the premature ones. Scans were obtained when the babies were sleeping naturally and supervised by experienced clinicians. The scans were combined to obtain a single image of the brain surface and visually inspected for quality control, and then analysed to obtain a set of numerical parameters describing the size and structure of each baby's cortex. These included the cortical grey matter thickness, volume and surface area and the shape of its folds, and parameters related to the ease with which water diffuses through the brain tissue (known as diffusivity).

These brain features were compared between the three groups of infants – pre-term with high breast milk exposure, pre-term with low breast milk exposure, and term – using a statistical technique called ANOVA, after adjusting for gestational age in days at the MRI scan. If this single comparison seemed to show a difference related to breast milk exposure, the data was further adjusted to allow for gestational age at birth and a range of demographic and health characteristics. Then the premature infants were further divided into four equal groups (quartiles) according to breast milk exposure and the analyses were re-calculated to test for a 'dose-response effect' (that is, whether any cortical parameters were dependent on the amount of breast milk given to the babies).

This analysis revealed that the brain structure of the premature infants in the 'high breast milk' group differed significantly from that of the infants in the 'low breast milk' group in specific ways: both the volume and the thickness of their cortical grey matter was reduced – one of the parameters describing the diffusion of water through the brain tissue. This parameter, fractional anisotropy, describes how much the speed of diffusion depends on its direction with respect to brain fibres. In each of these aspects, the brains of the premature infants in the high breastmilk group resembled those of the brains of infants born at term. In fact, there was no statistically significant difference between any of these parameters in term-born infants and in the premature babies in the high breast milk group. Analysis using the breast milk quartiles showed a significant dose-response effect in cortical thickness and in two diffusion-related parameters: fractional anisotropy, and diffusion at right angles to the direction of the fibres of brain tissue (known as radial diffusivity). Again, the higher the breast milk intake, the closer the structure seemed to be to that of a normal term-born infant's brain.

The researchers found that breast milk offered several additional advantages to the pre-term infants. Those in the low breast milk group had, on average, longer hospital stays and were more likely to be diagnosed with a lung condition called bronchopulmonary dysplasia while in hospital. While larger studies will be needed to answer questions such whether maternal milk produces different outcomes from donor milk, it seems clear that, at least in terms of brain development, 'breast is best' for premature infants throughout their time in the special-care baby unit.

Dr Clare Sansom

Policy Implications:
This study indicates an important role for mothers while their infant is in a Special Care Baby Unit. If they are able, then expressing breast milk can help to boost their infant's brain development. SCBU staff should be encouraged to ensure that suitable privacy can be provided for this.

Specialist training of nursing staff who work with premature infants should include as much information as possible about brain development and the relationships between prenatal experiences and subsequent infant development.

Additional financial support may be needed, in addition to maternity pay, to enable mothers of premature infants to be available in or close to the hospital so that breast milk can be made available for their infants.

Breast milk donation takes place but this research highlights why it should be encouraged.

Prof J Barnes