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Effects of in-hospital breast feeding on brain function development in preterm infants in China: study protocol for a prospective longitudinal cohort study

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ABSTRACT

Introduction Due to immature brain development, preterm infants are more likely to develop neurological developmental defects compared with full-term infants. Most preterm infants without neurodevelopmental damage can eventually reach the same scholastic level as their same-age peers; however, some show persistent impairment. Breast feeding (BF), which is an important public health measure, is of great significance for preterm infants. Various active substances in breast milk promote the development of the brain and central nervous system in premature infants. We present a protocol for a prospective longitudinal cohort study to explore the effect of in-hospital BF on brain development in preterm infants and possible influencing factors.

Methods and analysis This study will enrol 247 Chinese preterm infants (gestational age: 30–34 weeks) delivered in Women's Hospital School of Medicine, Zhejiang University, and transferred to the neonatal intensive care unit. Demographic, clinical and in-hospital BF data will be collected through electronic medical records. Moreover, follow-up data will be obtained by telephone, interview or online. Measurements will be obtained using the Breastfeeding Self-Efficacy Scale-Short Form, neuroimaging with functional near-infrared spectroscopy, extrauterine growth restriction and the Ages and Stages Questionnaire. Follow-up will be performed at 3, 6 and 12 months after birth.

Ethics and dissemination This study has been approved by the Women's Hospital School of Medicine Zhejiang University Medical Ethics Committee (2019-058). The study results are expected to be published in peer-reviewed journals and reported at relevant national and international conferences.

Trial registration number ChiCTR1900027648; Pre-results.

Strengths and limitations of this study

► This study will adopt a large-scale prospective study design and will be, to the best of our knowledge, the first to be conducted in the Chinese population.
► Neuroimaging assessment in this study will involve functional near-infrared spectroscopy with whole-brain coverage.
► The study is not designed as a randomised controlled trial because of ethical considerations.
► The study follow-up time can be extended with additional research funding and sufficient staff.

Approximately 1 million children die each year due to preterm birth complications and many who survive present permanent disabilities, including learning disabilities, as well as vision and hearing problems.[3]

China has the second-highest number of preterm births worldwide with an incidence of about 7.0%. Further, preterm birth has become the most common cause of infant death in China. The perinatal mortality rate among preterm infants is four to six times higher than that among normal term infants. Multicentre studies have reported an increase in the survival rate of preterm infants; however, the incidence of complications for these children remains higher than that in developed countries.[3–6] If effective and comprehensive interventions are not taken promptly, the growth, development and nutritional status of preterm infants will lag behind those of normal-term infants.[7]

Compared with full-term infants, preterm infants are more likely to develop neurological developmental defects due to immature brain development.[8–10] According to the American Agency for Healthcare Research and Quality, about 50% of very-low-birth-weight (preterm infants with a weight <1500 g or gestational age <32 weeks) preterm infants develop at least one

INTRODUCTION

According to the WHO as of February 2018, 15 million infants are born prematurely every year worldwide, which means that more than one premature birth occurs in every ten newborns.[1] Premature birth, that is, birth prior to gestational age of 37^{+0} weeks, is the leading mortality cause among children aged under 5 years worldwide.[2]

significant neurodevelopmental defect. Most preterm infants without neurodevelopmental damage can reach the same development level as term infants of the same age; however, some become permanently impaired.[11] Stunted growth and poor neurodevelopmental prognosis associated with preterm infants have become new problems in global public health. The peak period of rapid growth of brain tissue and medullary synapse formation is 34–36 weeks of gestation. Preterm birth occurs during this period, which places preterm infants at a higher risk of neurodevelopmental dysfunction.[12 13] Late preterm infants, birth between gestational ages 34 and 36^{+9} weeks, have only 65% of the brain volume in full-term infants with the remaining 35% growing postnatally.

In the critical period of brain development, especially during white matter development, preterm infants are exposed to the extrauterine environment earlier due to their preterm birth. As a result, the brain lacks the rapid accumulation and support of important nutrients, and consequently misses the golden opportunity for development. Compared with the brain volume at birth, the cerebellum of preterm infants grows fastest after birth with a weekly growth rate of 22%, which is equivalent to an absolute volume increase of 1.76 mL/week.[14] The early postnatal birth environment is critical for neurodevelopment in preterm infants.

Breast milk is rich in various nutrients that play an important role in brain development in preterm infants. Neurotrophic factors in breast milk, including long-chain polyunsaturated fatty acids, cholesterol, sialic acid, taurine, hormones and growth factors, as well as neuroprotective factors, including glutamic acid, probiotics and oligosaccharides, may play an important role in nervous system development and cannot be substituted by other dairy products. The benefits of breast milk for preterm infants may occur through the direct and indirect mechanisms of nutrition, antioxidants, immune regulation, neuroprotection and reduced complications.[15–17]

Studies have reported a dose-dependent relationship of breast milk intake with IQ and the entire adolescent brain volume; further, it is positively correlated with the volume of the hippocampus and deep grey matter nuclei.[18 19] Belfort et al[20] evaluated 180 breastfeeding (BF) preterm infants for 28 days after birth and found that when breast milk intake exceeded 50% of enteral nutrition, the BF duration extended by 1 day and the baby's IQ increased by 0.5 points. When the breast milk intake increased by 10 mL/(kg/day), IQ scores increased by 0.7 points. Lenehan et al[21] reported a significant positive relationship of BF with compound and non-verbal IQ scores at 5 years of age. Further, Belfort et al[20] analysed the relationship between BF and neurological developmental outcomes at 7 years of age and observed a positive correlation of breast milk intake with intelligence, memory, motor function and academic achievement. In addition, they reported that the advantages of breast milk for neurodevelopment can continue into old age, which is particularly reflected in speech reasoning ability.[22]

The aforementioned literature indicates a positive correlation between breast milk and brain development. However, there are currently no prospective longitudinal follow-up studies confirming the effect of breast milk on neuronal development in preterm infants. It is necessary to conduct such a study in the Chinese population who has never undergone such research due to different genetic backgrounds, living environments and ethnic groups. Further, there is a need to clarify the association between BF and brain development in preterm infants and identify the key factors that may be involved.

Given that hospital-provided BF information is objective and accurate, in addition to ensuring the consistency of the preterm infants' early postpartum environment, this proposed prospective longitudinal cohort study will evaluate the effect of in-hospital breast milk on brain development in preterm infants and its associated influencing factors.

Study aims

This cohort study aims to investigate the correlation between the proportion of breast milk intake and brain development in Chinese preterm infants, as well as its main influencing factors, by performing the following:

1. Exploring the correlation between different proportions of breast milk consumption and brain function/development in preterm infants.
2. Follow-up of preterm infants to explore the correlation between different proportions of breast milk consumption and long-term development of cognitive outcome in preterm infants.

METHODS
Study design

This prospective longitudinal cohort study aims to explore the effect of breast milk on brain development in preterm infants. Enteral feeding of preterm infants is recorded during in-patient care in the neonatal intensive care unit (NICU); further, demographic and clinical characteristics of preterm infants and their mothers are collected. The outcome indicators are collected and analysed according to the study protocol. Figure 1 shows the study flowchart, while table 1 shows the schedule of study enrolment and assessments.

Study setting and location

Participant recruitment was started in January 2020 and this study is currently being conducted in the level 3 NICU of Women's Hospital School of Medicine Zhejiang University, which has 105 available beds and a staff of more than 100 paediatricians and nurses. Approximately 800 early-to-moderate preterm infants were hospitalised in this NICU in the first half-year of 2019. Participant recruitment has been interrupted due to the COVID-19 epidemic. Recruitment will continue after government restrictions permit continuance.
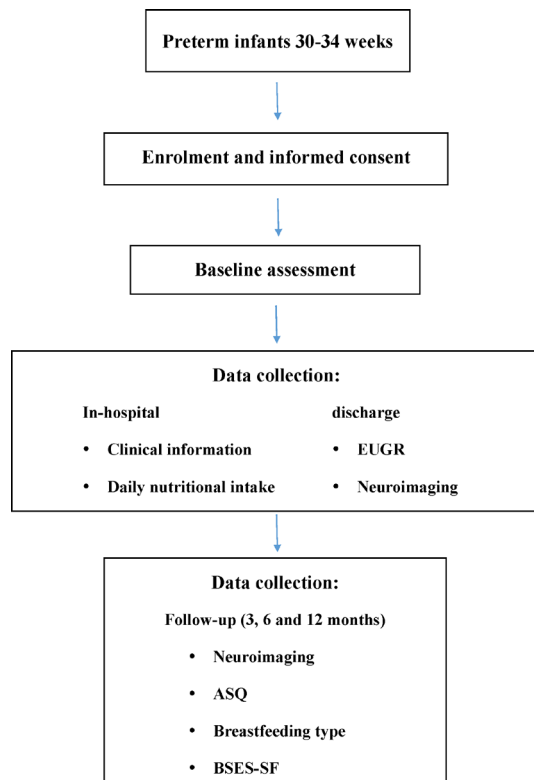
Figure 1 Study flowchart. ASQ, Ages and Stages Questionnaire; BESE-SF, Breastfeeding Self-Efficacy Scale Short Form; EUGR, extrauterine growth restriction.

Table 1	Schedule overview of participants				
	Time points				
Measures	**t_1**	**t_2**	**t_3**	**t_4**	**t_5**
Enrolment					
Eligibility screen	X				
Informed consent	X				
Data collection					
Demographic information of preterm infants and mothers	X				
Daily nutrition intake collection	X				
Head circumference	X	X	X	X	X
fNIRS scan		X			
EUGR		X			
ASQ			X	X	X
Breastfeeding type information collection			X	X	X
BSES-SF			X	X	X

t1=during hospitalisation, t2=the day of discharge or the day before, t3=3 months after discharge, t4=6 months after discharge and t5=12 months after discharge.
ASQ, ages and stages questionnaire; BESE-SF, breastfeeding self-efficacy scale short form; EUGR, extrauterine growth restriction ; fNIRS, functional near-infrared spectroscopy.

Participants

This study considers the proportion of breast milk consumption in preterm infants during their hospitalisation as a continuous variable; consequently, there is no control group. Studies have reported a positive correlation of the corrected gestational age with the total amplitude-integrated electroencephalogram (aEEG) score and the scores of various parameters in preterm infants. Maturity of brain development is directly measured by the aEEG, which is indicated by graph continuity, a more obvious sleep–wake cycle, a gradual increase in the lower bound amplitude of the narrow band and a narrower bandwidth. The bandwidth change is not obvious in preterm infants aged <30 gestational weeks; however, it rapidly increases in infants aged 30–34 gestational weeks.[23 24] Therefore, this study population is comprised of preterm infants aged 30–34 gestational weeks.

In a pilot study, preterm infants with breast milk exposure >80% and <20% scored 47.00±10.10 and 35.91±16.25, respectively, at the corrected age of 6 months in the personal–social section of the ASQ-3. Using a one-way analysis of Variance (ANOVA) at a significance level of 5% and a statistical power of 80%, each group was found to require 70 participants. This study will analyse three interval groups based on UNICEF's definition of BF types; thus, a total of 210 participants are required. Based on a dropout rate of 15%, this longitudinal cohort study is expected to include 247 participants. Preterm infants delivered in Women's Hospital School of Medicine Zhejiang University are transferred to the NICU. Preterm infants who satisfy the inclusion criteria will be enrolled.

Inclusion criteria:
1. Gestational age between 30 and 34 weeks.
2. Apgar scores at 1 and 5 min ≥7.

Exclusion criteria:
1. Parents with a history of depression or mental illness.
2. Parents with a history of congenital brain development disorders.
3. Congenital malformations.
4. Chromosomal abnormalities.
5. Moderate-to-severe hypoxic-ischaemic encephalopathy.[25]
6. Grade IV periventricular/intraventricular haemorrhage.[26]
7. Cystic periventricular leukomalacia.
8. Congenital genetic metabolic disease.

Data collection

In-hospital breast milk intake

Colostrum is recommended to be given as soon as it becomes available. Breast milk is the preferred nutrition source when the mother expresses breast milk and delivers it to the NICU. Standardised feeding guidelines will be used with the addition of human milk fortifier when preterm infants reach 80 mL/kg/day of enteral feeds. The daily nutritional intake in the NICU is recorded through electronic medical records. The proportion of breast milk consumption is defined as breast milk

Table 2 Definition of BF type

Categories	Proportions*			
	100	80	20	0
Full BF				
Exclusive BF	=			
Almost exclusive BF†	≈			
Partial BF				
High proportion BF	<	≥		
Medium proportion BF		<	≥	
Low proportion BF			<	>
Token BF‡				≈

*Breast milk as a percentage of total infant food intake.
†Infants are also given vitamins, water and juice for no more than one to two times a day and no more than one to two mouthfuls each time in addition to breast milk.
‡Breast milk intake that provides almost no calories.
BF, breast feeding.

intake as a percentage of total enteral nutrition during hospitalisation.

Out-of-hospital breast milk intake

The Breastfeeding Self-Efficacy Scale-Short Form (BSES-SF) measures the degree of confidence a woman has in her ability to adhere to BF by self-reporting. The BSES-SF is an important factor for BF and has been translated into multiple versions and is widely used worldwide, including in China, with good reliability and validity.[27–30] The BSES-SF has 14 entries with each using a 5-point Likert Scale and a high score indicating better BF self-efficacy.

Out-of-hospital feeding type is divided into the following six categories according to the definition proposed by the UNICEF[31] (the definitions are shown in table 2): exclusive BF, almost exclusive BF, high proportion BF, medium proportion BF, low proportion BF and token BF.

Development of brain function

Brain activity is accompanied by changes in cerebral blood flow. Moreover, these optical tissue changes can be detected using functional near-infrared spectroscopy (fNIRS), which can be used to test neurovascular coupling in humans, including preterm infants.[32 33] Neuroimaging with fNIRS is practical and appropriate for detecting brain development in preterm infants since it is non-invasive, portable and sensitive.[34–37] Data are collected using NirSmart (Huichuang Medical Technologies, LLC, Jiangsu province, China), which is a 56-channel portable instrument with 24 emission and 16 detection probes, and therefore covers the prefrontal, occipital and bilateral motor areas, as well as the bilateral temporal lobes. Quiet and low-to-no light conditions are required for minimal environmental impact.

Extrauterine growth restriction (EUGR)

EUGR is defined as the measured growth value (weight, length or head circumference) at the time of discharge of preterm infants at-or-below the 10th percentile of the predicted value according to Clark *et al*.[38] EUGR affects recent growth and development, as well as disease recovery, of preterm infants; moreover, it affects long-term neurological development, including retardation, cognition, sensory development and poor school performance.[39 40]

Growth and development evaluation

The Ages and Stages Questionnaire (ASQ) is revised by the Human Development Center of the University of Oregon, which covers children aged from 1 to 66 months. The ASQ is a screening scale for social and emotional development, as well as the mental health of infants and young children, and is filled in by parents or primary caregivers. The consistency of the ASQ and the Bayley Scales of Infant Development—3rd Edition—Screening Test is positively correlated with age (the correlation coefficient increased from 0.55 at 8 months to 0.75 at 30 months); moreover, the consistency in preterm infants is higher than that in full-term infants.[41 42] Compared with the Gesell Developmental Schedules, the ASQ has a sensitivity of 87.74% and a specificity of over 85%.[43]

The ASQ contains 20 age groups with each having 30 questions that evaluate five areas: individual-social, rough movements, fine movements, problem solving and communication skills, which should be completed within 12–18 min. Infants or children with scores higher than the threshold (defined in the questionnaire description) are considered normal, those with scores close to the threshold are considered marginal, and those with scores below the threshold are considered impaired with further diagnostic testing required.[44] The ASQ has been translated into several languages and is widely used worldwide with high applicability and internal consistency.[45 46] It can be used to screen developmental behaviours of children in regions with low economic levels[47 48]; moreover, the average ASQ scores in European, American and Asian populations are relatively consistent. China has introduced and developed a Chinese version of the normal ASQ model, which has proven reliable.

Procedures

Preterm infants who satisfy the inclusion criteria will be included in the cohort after being transferred to the NICU. Clinical information will be collected including gestational age, gender, weight, height, head circumference, Apgar score (1′, 5′), delivery type, parity, congenital birth defects, causes of premature birth and mothers' age and education. Fenton preterm growth charts will be used to monitor the growth of preterm infants. Nurses will ask whether the mother is willing to her milk (MOM) and accept donor human milk (DHM) if MOM is unavailable or insufficient. The order of the preferred enteral nutrition source is as follows: MOM, DHM and infant formula. The type and volume of each nutritional intake will be regularly recorded through electronic medical records. A BF handbook for preterm infants will be provided

for every family with preterm infants hospitalised in the NICU. Mothers of preterm infants will start expressing milk within 1–6 post-delivery hours at a frequency of at least eight times a day. Breasts, nipples and hands would be washed with water before expressing breast milk and keep the breast surface dry. The hospital does not provide a breast pump; however, the handbook provides recommendations for using and cleaning breast pumps. Breast pump instructions should be read carefully before use. All accessories in contact with breasts or breast milk should be disassembled, submerged in water and boiled for 5–10 min before first use and between each use.

We will evaluate EUGR and brain function development in preterm infants using fNIRS on the day of discharge or the previous day. Preterm infants will be brought to a quiet and low-light room near the NICU. Data will be collected after setting up the device and the preterm infant adapts to the environment and is calm (ie, falling asleep without major movements). Here, time nurses will observe the vital signs of preterm infants.

Online inquiries and regular telephone contact will be maintained during their out-of-hospital times. At 3, 6 and 12 months after the birth of preterm infants, trained medical staff will use the ASQ to assess the infants' growth and development, as well as the BSES-SF to assess the mothers' BF self-efficacy. Trained researchers will perform fNIRS scans to assess brain function. Additionally, out-of-hospital BF-type data will be collected through interviews for local participants or by telephone inquiries and online communication. The definitions of BF type will be explained before each inquiry. All data will be transcribed into an electronic form.

Data analysis
Participants will be divided into several groups based on the proportion of BF consumption. Demographic data will be collected as descriptive statistics. ANOVA and Duncan's multiple range test will be used for between-group comparisons with a significance level of $p<0.05$. The correlation between different BF proportions and brain function connections in preterm infants will be investigated using an ANOVA with covariates, including the length of hospital stay and birth weight. Data analysis will be implemented using statistical software SPSS V.22.0 (IBM SPSS Statistics, IBM Corporation).

Patient and public involvement
There is no patient or public involvement in the design or the implementation of the study; moreover, no patient or public will be involved in the subsequent reporting and dissemination of the study.

DISCUSSION
Breast milk is the first choice for enteral feeding of preterm infants. Studies have confirmed that the breast milk composition of preterm mothers differs from that of full-term mothers and is characterised by increased protein content, reduced fat and lactose content and elevated peptides and hormones that promote gastrointestinal maturity.[49]

Breast milk has advantages over artificial formula.[50] Breast milk can improve digestion and absorption in preterm infants, meet their nutritional needs and promote rapid growth and development. Premature breast milk can help regulate immune function and improve the long-term health of preterm infants. The exclusive BF rate and BF duration in hospitalised preterm infants are significantly lower than those in full-term newborns.[51–54] Preterm infants are transferred to the NICU immediately after birth for disease observation, diagnosis and treatment, which results in separation of mother and child, leading to insufficient lactation, an important factor that affects BF in preterm infants.[55] BF impacts the health economics of developing countries, improves the health of mothers and infants and reduces social inequities while reducing the incidence of infectious diseases, especially for disadvantaged children in poor areas.[56–59]

This study explores the association of different proportions in breast milk exposure with brain development in preterm infants. The proportion of breast milk exposure may be a cost-effective neurodevelopment predictor in preterm infants. Our findings could be used to evaluate the proportion of in-hospital breast milk feeding for preterm infants to identify preterm infants requiring monitoring of their neurodevelopment. This could allow early measures for reducing neurodevelopment complications. For underdeveloped areas, an appropriate increase in breast milk exposure is an important health measure for improving the neurodevelopmental outcomes of preterm infants. Additionally, this study is expected to determine whether exclusive breast milk feeding can be achieved and the proportion of breast milk exposure that can better promote the development of preterm infants. This study may provide recommendations regarding the proportion of breast milk exposure for individuals presenting difficulty in achieving exclusive BF.

Limitations
This study type has several limitations. First, we could not apply a randomised controlled trial (RCT) design due to ethical considerations and research budget constraints. Therefore, this study aims to collect reliable data to provide basic support for subsequent RCT research. Second, this study contains a 12-month follow-up period for preterm infants, which can be extended if the study budget and time are increased. Another limitation of this study is the lack of objective measurement tools for the infant feeding type.

Dissemination
This is the first large-scale study of in-hospital BF and brain development in preterm infants in China. The study results are expected to be published in peer-reviewed journals and reported at relevant national and international conferences.

Ethics approval

The study is currently ongoing and is in the recruitment phase. This study protocol was approved by Women's Hospital School of Medicine Zhejiang University Medical Ethics Committee (2019-058).

All participants will receive a detailed explanation regarding the study contents from a researcher. Written informed consent will be obtained from all participants at the time of inclusion in the study. The families of all participants can withdraw from the study at any time without any explication to researchers or any impact on the infant's care. The researchers and staff of Women's Hospital School of Medicine Zhejiang University are not incentivised nor disincentivised to retain study participants.

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