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Interactions between diet and gut microbes in preterm infants

Submission date	**Recruitment status**	[X] Prospectively registered
24/07/2017	No longer recruiting	[_] Protocol
Registration date	**Overall study status**	[_] Statistical analysis plan
24/07/2017	Completed	[X] Results
Last Edited	**Condition category**	[_] Individual participant data
02/03/2023	Neonatal Diseases	

Plain English summary of protocol

Background and study aims
Around 10% of babies are premature (born before 37 weeks), but feeding them is complex. Mothers own breast-milk (MOM) is best and results in better outcomes such as fewer infections, but many mothers do not produce enough milk so either donor human milk (DHM) or a cow's milk derived formula are used to make up the 'shortfall'. Current feeding practices in the UK vary as there is no clear evidence which is best, but both MOM and DHM require fortification with additional nutrients in order to support optimal growth. This currently requires the use of a ‘fortifier’ derived from cow’s milk, but new milk supplements made only from donor human milk are now used in US and Europe. The pattern of gut bacteria in early life is linked to outcomes including infections and allergies, and this is especially important in preterm infants. The aim of this study is to compare two diets in very preterm infants and study the effect on the pattern of gut bacteria and chemicals (metabolites) in stool and urine, as well as growth and body composition.

Who can participate?
Preterm infants born below 29 completed weeks of gestation

What does the study involve?
Babies are randomly allocated to either the standard diet group or the intervention group. To make up any shortfall in MOM, the standard diet group receive a cow's milk formula designed for preterm babies and a fortifier derived from cow's milk, and the intervention group receive DHM and a fortifier derived from human milk. Stool and urine samples are collected to look at patterns of gut bacteria and metabolites, and body composition is measured using an MRI scan.

What are the possible benefits and risks of participating?
There are not enough data to know whether there is any clear advantage to either diet. All babies who participate receive the same level of care regardless of being in the study. There are therefore no clear benefits to babies and parents of taking part, although the information collected may help improve care in the future. This is a dietary study and there are no known risks. Use of any human derived product carries a potential risk of side effects but this has not been reported so far with Prolacta products. The collection of samples for analysis is not associated with any risk.

Where is the study run from?
1. Newcastle Hospitals NHS Foundation Trust (UK)
2. Chelsea and Westminster Hospital (UK)

When is the study starting and how long is it expected to run for?
July 2017 to February 2020

Who is funding the study?
Prolacta Biosciences US

Who is the main contact?
Dr Nicholas Embleton

Contact information

Type(s)
Scientific

Contact name
Dr Nicholas Embleton

ORCID ID
http://orcid.org/0000-0003-3750-5566

Contact details
Ward 35 Neonatal Unit
Royal Victoria Infirmary
Richardson Road
Newcastle upon Tyne
United Kingdom
NE1 4LP

Additional identifiers

EudraCT/CTIS number

IRAS number
215037

ClinicalTrials.gov number

Secondary identifying numbers
CPMS 34886; IRAS Project ID: 215037; NuTH (Sponsor) Protocol number: NuTH 8360

Study information

Scientific Title
Interactions between the diet and gut microbes and metabolism in preterm infants (INDIGO study)

Acronym
INDIGO

Study objectives
To evaluate in very preterm infants whether an exclusive human milk diet compared with exposure to cow's milk-based products results in differences in gut bacteria (types and diversity, stool and urine metabolites and body composition.

The primary hypotheses are that there are differences in the pattern of gut microbes and in body composition between the two groups. This is determined by looking at the pattern of gut bacterial DNA using a methodology called 16s which is widely used, and MRI. The study is powered to detected a difference in the presence or absence of key bacterial groups (taxa), as well as overall diversity (Shannon diversity).

Ethics approval required
Old ethics approval format

Ethics approval(s)
North East - Tyne & Wear South Research Ethics Committee, 29/06/2017, ref: 17/NE/0169

Study design
Randomised; Interventional; Design type: Treatment, Prevention, Process of Care, Dietary

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use the contact details to request a patient information sheet

Health condition(s) or problem(s) studied
Digestive health of preterm infants

Interventions
All mothers are encouraged and supported to provide as much of their own breast milk ('Mothers Own Milk', MOM) as they wish to. When there is insufficient MOM to meet the infants needs this is called a 'shortfall'. Infants will be enrolled in the first 2 days after birth and before they need any other milks to make up any shortfall in MOM. Parents of infants will be consented and the infants randomised to one of two dietary strategies with equivalent nutrient intakes but where the source of milk differs. Infants will be randomised using a secure online web randomisation programme (www.sealedenvelope.com) with a 30% chance of simple random allocation and include 3 strata: hospital site, gestation <=24+6 weeks gestation or 25-28 weeks,

and multiple status (twin etc). Infants will stay on their assigned diet until 34 weeks corrected gestation when the intervention completes, although infant data will be recorded until discharge home, or until the MRI scan is complete in those infants who receive it (those recruited in Imperial College London). This will mean they are part of the study for between 5-12 weeks.

1. Standard treatment arm consists of MOM with formula milk to make up shortfall, and use of a standard bovine milk derived fortifier to provide additional nutrients.
2. Intervention treatment arm consists of MOM with donor human milk to make up shortfall, and use of a human donor milk derived fortifier to provide additional nutrients.

The study is not blinded as this would be impractical given the dietary regimens. However, the analyses of stool, urine and body composition will be conducted by teams who are blind to trial intervention so there is limited, if any, possibility of researcher bias.

All infants will be routinely monitored as is standard of care on a neonatal unit. It is routine nursing practice to record the amount of milk a baby receives, their clinical condition, their weight (3-7 times per week), length and head size (once/week), whether they are tolerating their feeds or not, and whether they are unwell in any way. Clinical staff and bedside clinical nurse perform routine weight/head/length and record status continuously whilst in intensive and high dependency care. The babies will all receive the same amounts of milk and other nutrients as for standard care. In addition, as part of the study a nurse will collect a daily samples of stool from the nappy, as well as urine collected using cotton wool balls that are squeezed out. These samples will only be analysed after the study completes. In addition the laboratories will be asked to store any blood that is left over after routine tests are complete rather than being discarded. On two occasions (at full feeds and at the end of the study) the trialists will ask the parents' permission to take an extra 1mL (less than half teaspoon) of blood when the baby needs a blood test for other medical reasons. For the infants enrolled in Chelsea & Westminster body composition will be measured using whole body magnetic resonance imaging (MRI) at around 37-42 weeks gestation when the baby is ready to go home or shortly after discharge home. Infants will be accompanied by a neonatal nurse at all times and be monitored using pulse oximetry (oxygen saturation level). The scan takes around 30 minutes. No sedation is used as babies usually sleep during the procedure especially if it is done after a feed. There are no implications for the care of babies after the study completes.

Intervention Type
Other

Primary outcome measure
1. Gut microbiota bacterial diversity and proportions of specific taxa. Stool samples are collected daily and measured on <5 occasions in each infant using 16s RNA on MiSeq at 5 time points from enrolment until trial completion: days 2/3, ~7-10 (at full feeds but prior to fortifier), 10-12 (48 hours following fortifier introduction), day 21-28 and at 34 weeks corrected age (prior to trial cessation)
2. Gut microbiota derived and other metabolites by measuring stool Volatile Organic Compounds using Gas Chromatography Mass Spectrometry (MS), and urine using 1H NMR and /or Liquid Chromatography MS on >=2 occasions between enrolment until trial completion (days 10-12 full feeds) and day 28
3. Body composition by assessing adipose tissue mass and non-adipose tissue mass using whole body magnetic resonance imaging (MRI) at term (37-42 weeks postmenstrual age)

Secondary outcome measures
1. Feeding related outcomes: total number of days on which feeds were withheld on any occasion after trial enrolment; age when enteral feeds ≥150ml/kg/day maintained for at least 3 days (coded as first day achieved); total days exposed to MOM prior to 34 weeks; feeding mode at discharge (breast, formula or mixed). Measured once using clinical records and recorded prior to hospital discharge.
2. Healthcare resource use: total length of stay (days); postmenstrual age at discharge; days in intensive, high-dependency and low-dependency care according to national definitions (BAPM), recorded once at discharge using medical records
3. Survival to discharge; Retinopathy of Prematurity, maximum stage and intervention; Necrotising Enterocolitis requiring surgery or leading to death; blood-culture positive sepsis; total days when any antibiotic administered; chronic lung disease (oxygen requirement or need for any pressure support at 36 weeks postmenstrual age), peri-ventricular haemorrhage (PVH) and/or presence of parenchymal damage. These will all be determined using established national definitions (National Neonatal Audit Programme), and informed using recently completed studies on NEC and agreed by investigator end-point review committee. Measured using clinical records and total morbidities confirmed prior to hospital discharge.
4. Growth and body composition including adipose tissue volume and distribution (MRI at 37-42 weeks gestation) and weight, head circumference and length measured on a weekly basis from enrolment to discharge

Overall study start date
01/07/2017

Completion date
28/02/2020

Eligibility

Key inclusion criteria
Current inclusion criteria as of 11/03/2021:
1. Preterm infants born below 30 completed weeks of gestation (<=29 weeks and 6 days)
2. Written informed consent from parents
3. Has not received any milk other than MOM

Previous inclusion criteria:
1. Preterm infants born below 29 completed weeks of gestation (<=28 weeks and 6 days)
2. Written informed consent from parents
3. Has not received any milk other than MOM

Participant type(s)
Patient

Age group
Neonate

Sex
Both

Target number of participants

Planned Sample Size: 100; UK Sample Size: 100

Total final enrolment
128

Key exclusion criteria
1. Major congenital or life threatening abnormalities
2. Inability to randomise within 48 hours of birth
3. Exposure to bovine milk product prior to randomisation
4. Likelihood of transfer to another hospital before 34 weeks postmenstrual age

Date of first enrolment
20/08/2017

Date of final enrolment
31/08/2019

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
Newcastle Hospitals NHS Foundation Trust
Royal Victoria Infirmary
Richardson Road
Newcastle upon Tyne
United Kingdom
NE1 4LP

Study participating centre
Chelsea and Westminster Hospital
369 Fulham Road
Chelsea
London
United Kingdom
SW10 9NH

Sponsor information

Organisation

The Newcastle Upon Tyne Hospitals NHS Foundation Trust

Sponsor details
Freeman Hospital
Freeman Road
High Heaton
Newcastle-Upon-Tyne
England
United Kingdom
NE7 7DN

Sponsor type
Hospital/treatment centre

ROR
https://ror.org/05p40t847

Funder(s)

Funder type
Industry

Funder Name
Prolacta Biosciences US

Results and Publications

Publication and dissemination plan
The trialists will publish the study protocol in 2019 and the results in Q4 2020, as well as present data at international conferences.

Intention to publish date
01/05/2022

Individual participant data (IPD) sharing plan
The datasets generated and/or analysed during the current study during this study will be included in the subsequent results publication.

IPD sharing plan summary
Other

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article		01/03/2023	02/03/2023	Yes	No
HRA research summary			28/06/2023	No	No