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Promotion of a healthy gut microbiome in elective caesarean section arrivals (PROMESA) by supplementing breastfed newborns with an infant probiotic.

Submission date
09/03/2018

Recruitment status
No longer recruiting

Registration date
13/04/2018

Overall study status
Completed

Last Edited
13/10/2022

Condition category
Digestive System

[_] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
Recent medical discoveries have found that intestinal levels of Bifidobacterium infantis (B. infantis) help to develop a healthy gut in infants and protects against harmful bacteria. Data from around the world point to B. infantis as universally associated with newborn babies, and that this bacteria is naturally introduced to babies who are born vaginally and breastfed. The growth of protective Bifidobacterium strains within the intestine of the breastfed infant is supported by components in breast milk called human milk oligosaccharides (HMO). These HMO feed the bifidobacteria that in turn protect and guide the intestinal health of the developing infant. However, the ever-growing number of deliveries by Caesarean section is resulting in babies with very low levels of intestinal B. infantis. Our goal is to investigate whether short term daily probiotic supplementation (B. infantis) in breastfed babies delivered by Caesarean section promotes a healthy infant faecal microbiome profile that can be maintained by breastfeeding until weaning at 6 months.

Who can participate?
Pregnant women over the age of 18 who are planning to have a Caesarean section birth in addition to breastfeeding their baby for at least 6 months.

What does the study involve?
Approximately 70 women will be recruited to provide vaginal and rectal swabs for baseline assessment of the maternal microbiome before Caesarean section. At postnatal Day 7-9, infants that are eligible to continue in the study (i.e. breastfed and not exposed to antibiotics for > 3 days) will be randomly allocated to receive either a daily supplement of B. infantis or a dummy treatment of lactose in breast milk for 28 days. All women will be contacted regularly by a research midwife trained in lactation support. Infant faecal samples/swabs and mother's breast milk will be collected at regular intervals during the study until 6 months of age. There will be up

to three follow-up visits until 2 years of age. The infant gut microbiome, and other indicators of gut health, will be analysed along with components of the mother's breast milk.
Mothers will complete questionnaires and infant health logs throughout the course of the study.

Added 01/08/2019:
A protocol amendment was made to include a continuation study of 30-40 additional recruits to evaluate immune and inflammation markers in infant participants. Participants who agree to take part in the continuation study will not provide maternal vaginal, rectal, or breast milk samples, but will instead provide a cord blood sample and 2 infant blood samples, one on Day 0-4 of life and another at 3 months (Day 84-104).

What are the possible benefits and risks of participating?
There are no known side-effects to the supplement or placebo. Filling surveys and collecting samples may be time consuming for new mothers. All women will receive regular extra support (e.g. by telephone and hospital or home visit) from a breastfeeding specialist midwife to help establish breastfeeding.

Added 01/08/2019: There are risks associated with infant heel sticks and drawing blood from a vein, which include bruising and short-term pain or soreness, although these are generally considered to be mild and/or rare.

Where is the study run from?
The PROMESA study is taking place at St. Thomas' Hospital.

When is the study starting and how long is it expected to run for?
February 2017 to December 2022

Who is funding the study?
Evolve BioSystems, Inc. (US)

Who is the main contact?
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Public

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Additional identifiers

Integrated Research Application System (IRAS)
221152

Protocol serial number
IRAS# 221152

Study information

Scientific Title
PROMESA: Promotion of a healthy gut microbiome in elective caesarean section arrivals. Can exclusive breastfeeding supplemented with a probiotic promote a sustained healthy gut microbiota in babies born by caesarean section?

Acronym
PROMESA

Study objectives
The principal question is whether short term daily probiotic supplementation in breastfed infants delivered by Caesarean section promotes a healthy infant faecal microbiome profile that can be maintained by breastfeeding until weaning at 6 months.

Added 15/07/2020:
The principal question for the extension study is whether promoting a healthy gut by supplementing breastfed infants delivered by Caesarean section with B. infantis for 3 months will improve the development of the infant immune system and prevent a proinflammatory phenotype at 3 months of age.

Ethics approval required
Old ethics approval format

Ethics approval(s)
London - Camberwell St Giles Research Ethics Committee,10/01/2018, ref:17/LO/0641

Added 15/07/2020:
Extension approved 09/06/2020

Added 17/12/2020:
Amendment approved 19/11/2020

Study design
PROMESA is an interventional single-centre randomized double-blinded placebo-controlled trial of a dietary (probiotic) supplement added to breast milk for the enhancement of the normal neonatal gut microbiome in term babies delivered by Caesarean section.

Added 15/07/2020:
The extension study will be a multi-centre non-randomized study

Primary study design
Interventional

Study type(s)
Other

Health condition(s) or problem(s) studied
Infant gut microbiome

Interventions
Approximately 70 women will be recruited to provide vaginal and rectal swabs for baseline assessment of the maternal microbiome prior to Caesarean section. Newborn infants will be randomised to receive either a daily probiotic supplement (Bifidobacterium longum subsp. infantis EVC001 - 8x10^9 CFU) or placebo mixed with breast milk for 28 days. Infant faecal samples and mother's breast milk will be collected at regular intervals during the study until 6 months of age. Additional infant stool samples will be collected at 12,18 and 24 months. Randomisation will be carried out online via the MedSciNet web portal (www.medscinet.com) and linked to the participant’s initial Subject ID. Allocation will be stored remotely from the main study database, so that members of the study team remain blinded to probiotic/placebo allocation. Recruitment and trial coordinators will not have access to the randomisation sequence. Subjects will be randomized at a 1:1 ratio of intervention to placebo. Minimisation will be based on parity and maternal pre-pregnancy BMI >30.

Added 01/08/2019:
A protocol amendment was made to include a continuation study of 30-40 additional recruits to evaluate immune and inflammation markers in infant participants. Participants who agree to take part in the continuation study will not provide maternal vaginal, rectal, or breast milk samples, but will instead provide a cord blood sample and 2 infant blood samples, one on Day 0-4 of life and another at 3 months (Day 84-104). Randomisation and minimisation will be conducted in the same manner as the original protocol for the same probiotic/placebo interventions.

Added 15/07/2020:
A protocol amendment was made to include an extension study of approximately 52 additional recruits to evaluate the development and function of the immune system in infant participants. The extension study will not be randomized or placebo-controlled. Patients at a 'probiotic' site (St. Thomas' Hospital) will receive a daily supplement of B. infantis in breast milk for approximately 90 days and patients at a 'control' site (Chelsea and Westminster Hospital) will receive no probiotic nor placebo. Participants who agree to take part in the extension study will provide an additional infant blood sample at 1 month (Day 28-34) of life. Participants will collect infant stool samples at only three timepoints (Baseline, Month 1 and Month 3). Infants will not be followed for 2 years, their study involvement will end at the time of the 3 month blood draw. The study will not be randomized, the control group will not receive a placebo and will be enrolled at a hospital separate to the probiotic cohort.

Intervention Type
Supplement

Primary outcome(s)
1.The change in infant faecal microbiota before, during and after probiotic or placebo supplementation by shotgun sequencing or next generation sequencing (NGS, e.g. Illumina MISeq or HiSeq)

Added 01/08/2019:
2. Continuation study: The change in levels of immune cells and markers from baseline (Day 0 – Day 4) to 3 months (Day 84 – Day 104)

Added 15/07/2020:
3. Extension study: The change in infant faecal B. infantis colonization levels from baseline during B. infantis supplementation as measured by quantitative PCR

Key secondary outcome(s))
1.Biochemistry of infant stools by assessing pH levels, HMO and short-chain fatty acids using liquid chromatography-mass spectrometry may be performed on samples collected at Baseline (Day 4-7), 1 month, 3 months, 6 months, 12 months, 18 months and 24 months.
2. Comparison of the composition of the maternal and infant microbiome at baseline using shotgun sequencing or next generation sequencing.
3.Adverse events will be recorded on daily and weekly adverse event logs, as well as infant health surveys, for the duration of the study. Medical records will be reviewed as needed for confirmation.

Added 01/08/2019:
4. Continuation study: The correlation between gut microbiota composition and abundance and levels of immune cells and markers
5. Continuation study: The differences between B. infantis and placebo supplementation on levels of immune cells and markers
6. Continuation study: The differences between B. infantis and placebo supplementation on vaccine response (antibody titres)

Added 15/07/2020:
7. Extension study: The differences between probiotic and control infants with respect to:
7.1. The infant faecal microbiome composition as measured by shotgun metagenomics, and
7.2. Levels of enteric inflammation as measured by inflammatory cytokines in infant stool.

Exploratory Endpoints for the Extension Study Include:
• The differences between treatment and control infants with respect to: Immune and inflammatory responses as measured by calprotectin, lipocalin-2, and soluble faecal IgA and IgG in infant stool
• Immune-sensing of the microbiome as measured by IgA-seq in infant stool
• Stool metabolomics
• The development of immune cell populations in whole blood by mass cytometry
• Plasma proteins by immunoassays
• Transcriptional analysis in whole blood by RNA-Seq
• Plasma metabolomics
• Functional analysis of Peripheral Blood Mononuclear Cells (PBMCs, blood immune cells)
• Transcriptomics of PBMCs and stool

Completion date
20/12/2022

Eligibility

Key inclusion criteria
Current inclusion criteria as of 17/12/2020:

1. Singleton pregnancies (primip or multi)
2. Pregnant women age 18 and above
3. Elective Caesarean section ≥37 weeks gestation
4. Maternal pre-pregnancy BMI < 35kg/m²
5. Intention to exclusively breastfeed for at least 35 days, preferably for 6 months
6. Non-smoker (gave up prior to pregnancy)
7. Intention to exclusively breastfeed for at least 3 months
8. Non-smoker (never smoked or gave up prior to enrolment)

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Previous inclusion criteria:

1. Singleton pregnancies (primip or multi)
2. Pregnant women age 18 and above
3. Elective Caesarean section ≥37 weeks gestation
4. Maternal pre-pregnancy BMI < 35kg/m²
5. Resident in UK for 3 years or more
6. Intention to exclusively breastfeed for at least 35 days, preferably for 6 months
7. Non-smoker (gave up prior to pregnancy)

Added 15/07/2020:
8. Willingness to vaccinate infant with BCG vaccine no later than Day 4
9. Intention to exclusively breastfeed for at least 3 months
10. Non-smoker (never smoked or gave up prior to enrolment)

Participant type(s)
Healthy volunteer

Healthy volunteers allowed

No

Age group
Mixed

Sex
All

Key exclusion criteria
Current exclusion criteria as of 17/12/2020:

At antenatal screening
1. Multiple pregnancy
2. Vaginal deliveries
3. Fetus has a known medical condition that would preclude breastfeeding or alter gut microbiota
4. Maternal breast surgery or injury within the past 5 years that would reduce the likelihood of successful exclusive breastfeeding (not exclusionary if mother can evidence successful breastfeeding of a previous infant after the surgery or injury)
5. Plan to administer non-study probiotics to infant any time throughout the study
6. Plan to apply maternal vaginal swab to infant's mouth
7. Maternal infection with HIV or Hepatitis C or experiencing symptoms of COVID-19
8. Maternal smoking (current)
9. Maternal medication use that may alter infant's gut microbiotia (e.g. daily antibiotics)

At Day 7 postnatal screen, pre-randomization:
1. Infants who have taken antibiotics for more than 3 days
2. Intake of formula within 24 hours of the Postnatal Eligibility Screen
3. Infants born with medical complications such as: respiratory distress syndrome, birth defects, and infection
4. Mothers who experienced medical complications that would preclude them from breastfeeding
5. Infants who had exposure to maternal vaginal microbiome via oral swab
6. Infants who have received the BCG vaccine
7. Infants whose caregivers intend to vaccinate their infant with the BCG vaccine prior to 3 months of life
8. Infants with known exposure to an individual testing positive for, or experiencing symptoms of, COVID-19

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Previous exclusion criteria:

At antenatal screening
1. Multiple pregnancy
2. Recent arrival in UK (< 3 years)
3. Vaginal deliveries
4. Mothers with another child < 14 months of age at recruitment
5. Fetus has a known medical condition that would preclude breastfeeding or alter gut microbiota
6. Maternal breast surgery or injury within the past 5 years that would reduce the likelihood of

successful exclusive breastfeeding (not exclusionary if mother can evidence successful breastfeeding of a previous infant after the surgery or injury)
7. Plan to administer non-study probiotics to infant any time throughout the study
8. Plan to apply maternal vaginal swab to infant's mouth
9. Maternal infection with HIV or Hepatitis C
10. Maternal type 1 or type 2 diabetes (gestational diabetes is not exclusionary)
11. Maternal pre-eclampsia
12. Smoking this pregnancy
13. Plan to leave UK in < 6 months (added 01/08/2019)
14. Maternal medication use that may alter infant's gut microbiotia (e.g. daily antibiotics) (added 01/08/2019)

At Day 7 postnatal screen, pre-randomization:
1. Infants who have taken antibiotics for more than 3 days
2. Intake of formula within 24 hours of the Day 7-9 visit
3. Infants born with medical complications such as: respiratory distress syndrome, birth defects, and infection
4. Mothers who experienced medical complications that would preclude them from breastfeeding
5. Infants who had exposure to maternal vaginal microbiome via oral swab

Date of first enrolment
09/02/2018

Date of final enrolment
02/09/2022

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
St Thomas's Hospital
Guy's and St. Thomas' NHS Foundation Trust
249 Westminster Bridge Road
London
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SE1 7EH

Study participating centre
Chelsea and Westminster Hospital
Chelsea and Westminster Hospital NHS Foundation Trust
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Sponsor information

Organisation
Evolve BioSystems, Inc.

Funder(s)

Funder type
Not defined

Funder Name
Evolve BioSystems, Inc.

Results and Publications

Individual participant data (IPD) sharing plan
Not provided at time of registration

IPD sharing plan summary
Not expected to be made available

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article		13/07/2021	29/12/2022	Yes	No
HRA research summary			28/06/2023	No	No
Protocol file		16/01/2019	01/08/2019	No	No