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PREvention of Preterm birth with Oral Probiotics

Submission date	Recruitment status	[X] Prospectively registered
11/03/2021	No longer recruiting	[ ] Protocol
Registration date	**Overall study status**	[ ] Statistical analysis plan
31/03/2021	Ongoing	[ ] Results
Last Edited	**Condition category**	[ ] Individual participant data
09/08/2023	Pregnancy and Childbirth	[ ] Record updated in last year

Plain English summary of protocol

Background and study aims
Approximately 15 million babies are born too soon every year, and over 1 million of them die. Those that survive sometimes need ongoing medical care throughout their lives into adulthood. The emotional burden for families and their babies is substantial, and healthcare costs extend into billions every year. Nearly half of all preterm births happen because the microbes that usually maintain a healthy environment in the vagina become diminished or replaced by unhealthy microbes. This leads to inflammation in the vagina, which triggers preterm birth. The aim of this research study is to identify whether providing healthy microbes in an oral probiotic supplement during pregnancy improves vaginal health and reduces preterm birth in women at high risk of having a preterm baby.

Who can participate?
Women attending the preterm birth surveillance clinic at the National Maternity Hospital, Ireland, will be invited to take part in this research. The women attending this clinic are considered to be at risk of preterm birth.

What does the study involve?
Participants will be allocated to one of two groups, with an equal chance of being in either group (like tossing a coin). Participants and researchers will not have a choice in the treatment given and will not know which treatment participants have received during the study. The participants in the first group will receive a probiotic capsule and the second group of participants will receive an identical-looking capsule with no active medicine. Both groups of participants will take the capsules between around 12 weeks gestation until 1 month postpartum.

Data and samples will be collected from women attending the preterm birth surveillance clinic for routine visits. At the 12 and 24 week visits, participants will complete study questionnaires (e. g. lifestyle questionnaire), cervical length ultrasound assessment, vaginal microbiology swabs, vaginal pH, blood samples, and stool samples. At the 36-week visit, participants will provide vaginal microbiology and pH, blood samples, and stool samples. At the time of birth, an umbilical cord blood sample will be collected. At 1 month after birth participants will complete study questionnaires and provide vaginal microbiology swabs, a breast milk sample, and a baby stool sample.

What are the possible benefits and risks of participating?
There will be no clear benefits for mothers or babies in the trial. However, the information gained from this research may benefit babies, children, and adults in the future by contributing to advances in medical knowledge and health care. Additionally, studies have shown that probiotic supplementation is safe and well-tolerated during pregnancy, and many women consume probiotics as part of their daily diet. Mild discomfort may arise from providing stool or blood samples, though experienced clinical personnel will be looking after trial participants and any discomfort will be minimised.

Where is the study run from?
The National Maternity Hospital (Ireland) and the UCD Perinatal Research Centre (Ireland)

When is the study starting and how long is it expected to run for?
December 2020 to March 2026

Who is funding the study?
Investigator initiated and funded

Who is the main contact?
Prof Fionnuala McAuliffe, fionnuala.mcauliffe@ucd.ie

Contact information

Type(s)
Scientific

Contact name
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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
Nil known

Study information

Scientific Title
A randomised controlled trial investigating the impact of oral probiotic supplementation on the microbiome in pregnant women at high risk of preterm birth

Acronym
PRE POP

Study objectives
Oral probiotic supplementation will increase the relative abundance of Lactobacillus crispatus in pregnant women at high risk of preterm birth compared to a placebo

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 14/12/2020, The National Maternity Hospital Research Ethics Committee (Research Ethics Committee, The National Maternity Hospital, Holles Street, Dublin 2, D02 YH21; +353 (01) 6373155; ethicsresearch@nmh.ie) ref: EC37.2020

Study design
Double-blind placebo-controlled randomized trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Prevention

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

Health condition(s) or problem(s) studied
Pregnant women at high risk of preterm birth

Interventions
Study randomisation will be conducted by a research statistician not involved in the trial. Using computer software, the statistician will generate three blocks of randomly allocated sequential

study numbers for the two groups of capsules. Participants will be assigned to receive either intervention (probiotics) and placebo (control). Participants randomised to the intervention arm will be asked to take two capsules (each containing 5 billion CFU) orally, once daily. This is a total daily dose of 10 billion CFU. Participants randomised to the control arm will be asked to take two capsules (containing no probiotics) orally, once daily. Study capsules will be packed based on group allocation, with only the study number denoted on the plain packaging. Participants will be consecutively assigned to each study number upon recruitment. Neither investigators nor participants will know the study group designation, thus ensuring the trial is double-blinded. Study supplements will be provided to the participant in clinic upon successful recruitment and randomisation to the study. Identical capsules containing either the intervention (a total of 10 billion colony forming units of Lactobacillus crispatus LBV 88, Lactobacillus jensenii LBV116, Lactobacillus gaseseri LBV 150N and Lactobacillus rhamnosus LBV96 per capsule) or placebo (maltodextrin and no probiotics) will be supplemented throughout pregnancy from recruitment (at around 12 weeks gestation) until 1 month postpartum.

Intervention Type
Supplement

Primary outcome measure
Current primary outcome measure as of 26/07/2023:
Increase in the percentage of women with detectable Lactobacillus crispatus in the vaginal microbiome by 25% measured using shotgun metagenomic sequencing after at least twelve weeks of oral supplementation with commercial LBV product which contains Lactobacillus crispatus

Previous primary outcome measure:
25% increase in the relative abundance of L. Crispatus measured using high-throughput DNA sequencing and/or qPCR after at least 12 weeks of oral supplementation

Secondary outcome measures
Current secondary outcome measure as of 26/07/2023:
1. Cervical length at 24 weeks gestation measured using transvaginal ultrasound after at least 12 weeks of oral supplementation
2. Compliance with the intervention measured by counting remaining capsules at 1 month postpartum
3. Preterm premature rupture of membranes measured from patient notes at the time of birth
4. Histological chorioamnionitis measured using placental histopathology at the time of birth
5. Gestational age at delivery measured from patient notes at the time of birth
6. NICU admissions measured from patient notes at 1 month postpartum
7. Neonatal complications measured from patient notes at 1 month postpartum

Previous secondary outcome measure:
1. Cervical length at 26-34 weeks gestation measured using transvaginal ultrasound after at least 12 weeks of oral supplementation
2. Compliance with the intervention measured by counting remaining capsules at 1 month postpartum
3. Preterm premature rupture of membranes measured from patient notes at the time of birth
4. Histological chorioamnionitis measured using placental histopathology at the time of birth
5. Gestational age at delivery measured from patient notes at the time of birth
6. NICU admissions measured from patient notes at 1 month postpartum
7. Neonatal complications measured from patient notes at 1 month postpartum

Overall study start date
14/12/2020

Completion date
31/03/2026

Eligibility

Key inclusion criteria
1. Previous preterm birth (<34 weeks gestation)
2. Previous second-trimester loss (14-24 weeks gestation)
3. ≥2 large loop excision of the transformation zone (LLETZ) procedures
4. ≥1 cone biopsy
5. Uterine anomaly

Participant type(s)
Patient

Age group
Adult

Sex
Female

Target number of participants
150

Key exclusion criteria
1. Aged <18 years
2. Does not speak English and a suitable interpreter is unavailable
3. Cannot provide informed consent due to lack of understanding
4. Having a condition or taking medication, dietary supplement or food product that the investigators believe will interfere with the trial objectives

Date of first enrolment
01/04/2021

Date of final enrolment
31/03/2025

Locations

Countries of recruitment
Ireland

Study participating centre
The National Maternity Hospital
Holles St

Saint Peter's
Dublin
Ireland
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Sponsor information

Organisation
University College Dublin

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UCD Health Sciences Centre
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Sponsor type
University/education

Website
https://www.ucd.ie/medicine/research/researchcentres/ucdclinicalresearchcentre/

ROR
https://ror.org/05m7pjf47

Funder(s)

Funder type
Other

Funder Name
Investigator initiated and funded

Results and Publications

Publication and dissemination plan
All results from the trial are intended for publication in high-impact international peer-reviewed journals.

Intention to publish date
31/03/2027

Individual participant data (IPD) sharing plan
The data sharing plans for the current study are unknown and will be made available at a later date

IPD sharing plan summary
Data sharing statement to be made available at a later date