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Chronic Hypertension and l-citrulline study

Submission date
18/09/2017

Recruitment status
No longer recruiting

Registration date
20/09/2017

Overall study status
Completed

Last Edited
04/10/2023

Condition category
Pregnancy and Childbirth

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

Plain English summary of protocol

Background and study aims
Chronic hypertension (high blood pressure) affects 2% of pregnancies and is associated with significant risks for both mother and baby. There is a 1 in 4 chance that complications will arise in pregnancy (pre-eclampsia (diabetes during pregnancy) and/or fetal growth restriction) requiring a preterm delivery. Oral L-citrulline is an amino acid supplement which has been associated with an improvement in blood pressure and blood vessel function. In a phase I study of 24 obese pregnant women, three weeks treatment of L-Citrulline (3g/day) was associated with a significant reduction in blood pressure, which persisted after the treatment had ceased until the end of pregnancy. There was also a marked change in factors involved in blood vessel function, which are altered in pregnancies complicated by placental dysfunction, at several time points over pregnancy. This suggests a potential beneficial effect of oral L-citrulline on placental and/or vessel function. The potential use of an amino acid supplement, which is safe, readily available and of relatively low-cost, represents an appealing intervention for the long-term management of chronic hypertensive diseases, especially in pregnancy where the number of treatment options might be more limited, and non-pharmacological interventions are more acceptable. At present, there is no information regarding either the efficacy or acceptability of L-citrulline supplementation to modulate cardiovascular function in women with chronic hypertension in early pregnancy. The aim of this study is to assess the acceptability and feasibility of using L-citrulline supplements for women with chronic hypertension to then plan a larger study, which to determine whether oral L-citrulline treatment is cost-effective for the treatment of chronic hypertension.

Who can participate?
Women aged 18 and older who are 12-16 weeks pregnant who have high blood pressure.

What does the study involve?
Participants are randomly allocated to one of two groups. Those in the first group receive a supplement with amino acid L-citrulline twice per day for a maximum of 10 weeks around 14-22 weeks of pregnancy. Those in the second group receive a placebo (dummy) supplement for 10 weeks around 14-22 weeks of pregnancy. Participants are follow up until 12 weeks post giving birth to measure their blood pressure.

What are the possible benefits and risks of participating?
Participation in this study could help lower blood pressure in hypertensive pregnant women. There are no risks associated with participation.

Where is the study run from?
1. St Mary's Hospital Manchester (UK)
2. St Thomas's Hospital London (UK)

When is the study starting and how long is it expected to run for?
September 2012 to January 2019

Who is funding the study?
National Institute for Health Research (UK)

Who is the main contact?
Miss Sophie Hennessy
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Contact information

Type(s)
Public

Contact name
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Additional identifiers

EudraCT/CTIS number
2015-005792-25

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
35351

Study information

Scientific Title
CHronic HypERtension and L-citRulline studY: Feasibility study on the effects of L-citrulline on uteroplacental and cardiovascular function in hypertensive pregnant women

Acronym
CHERRY

Study objectives
Study aims:
The aims of the present study are
1. Determine the effect of L-citrulline supplementation on maternal blood pressure in women with chronic hypertension
2. Determine whether L-citrulline supplementation can improve uterine blood flow and other markers associated with adverse pregnancy outcomes

Hypothesis:
The hypothesis that tight blood pressure control in early pregnancy has a favourable impact on placental development such that the risk of subsequent placental dysfunction is lower. In addition, the beneficial effects on the vascular endothelium of L-Citrulline may impact on the interaction between the placental trophoblast cells and the maternal spiral arteries improving invasion and ultimately placentation.

Ethics approval required
Old ethics approval format

Ethics approval(s)
North West Haydock REC, 14/09/2016, ref: 16/NW/0557

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

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Home

Study type(s)
Treatment

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

Health condition(s) or problem(s) studied

Specialty: Reproductive health and childbirth, Primary sub-specialty: Reproductive and Sexual Medicine; UKCRC code/ Disease: Reproductive Health and Childbirth/ Respiratory and cardiovascular disorders specific to the perinatal period

Interventions
Treatment across arms are double blinded with only the trial pharmacist at site and randomising statistician being unblinded. Randomisation is done via a secure web based system and is performed by a member of the research team at site. Once randomisation has occurred an automated blinded email is sent to all relevant members of the research team and an unblinded email is sent to the pharmacist.

Group 1: Participants receive supplementation with the amino acid L-citrulline (3g twice per day) from 14±/-2 to 22±/-2 weeks' gestation (maximum of 10 weeks treatment duration).
Group 2: Participants receive supplementation with the placebo from 14±/-2 to 22±/-2 weeks' gestation (maximum of 10 weeks treatment duration).

The women are followed up until 12 weeks post-delivery to measure blood pressure.

Intervention Type
Other

Phase
Phase II

Primary outcome measure
1. Recruitment rate is measured by number of women recruited and completing study per month
2. Change in diastolic blood pressure (from baseline to 8 weeks post randomisation following L-citrulline supplementation, compared with placebo – Change in clinic diastolic BP (average of 3 readings) will be calculated at baseline and week 8

Secondary outcome measures
1. Acceptability of intervention in pregnant women with chronic hypertension is measured by number of women completing treatment and completion of participant questionnaire at end of the treatment period
2. The following results are compared within treatment groups only (paired analysis) as the study is not sufficiently powered to identify a difference between randomised groups:
2.1. Average day and night time Ambulatory Blood Pressure Measurements (ABPM.) ABPM measurements will be downloaded from the software (SpaceLabs) and the day and night time averages calculated by the software.
2.2. Pulse wave velocity measurements will be exported from the Tensioclinic software. Vascular compliance measurements including central BP, pulse wave velocity, augmentation index will be compared within groups.
2.3. Peripheral vascular resistance measurements obtained from the NICOM. Measurements of cardiac output, cardiac index, SVI and TPRI will be compared within groups.
2.4. Uteroplacental blood flow measurements: uterine artery resistance index (RI) and pulsatility index (PI), presence/absence of notching
2.5. Plasma ADMA/arginine concentrations
2.6. Change in antihypertensive therapy

Overall study start date

12/09/2012

Completion date
04/01/2019

Eligibility

Key inclusion criteria
1. Viable singleton pregnancy
2. Gestation: 12+0 to 16+0 weeks
3. Aged 18 years or over
4. Able to provide informed consent
5. Diastolic BP of ≥90 mmHg (average of two clinic readings) OR ≥80 mmHg if taking antihypertensive medication OR PWV ≥9m/s before 16 weeks' gestation
6. Serum creatinine <120 mmol/l at booking

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Female

Target number of participants
Planned Sample Size: 42; UK Sample Size: 42

Total final enrolment
36

Key exclusion criteria
There is no exclusion criteria.

Date of first enrolment
04/07/2017

Date of final enrolment
01/03/2018

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
St Mary's Hospital Manchester
Oxford Road
Manchester
United Kingdom
M13 9WL

Study participating centre
St Thomas's Hospital London
Westminster Bridge Road
Lambeth
London
United Kingdom
SE1 7E

Sponsor information

Organisation
Central Manchester University Hospitals NHS Foundation Trust

Sponsor details
Trust Headquarters
Cobbett House
Manchester Royal Infirmary
Oxford Road
Manchester
England
United Kingdom
M13 9WL

Sponsor type
Hospital/treatment centre

ROR
https://ror.org/00he80998

Funder(s)

Funder type
Government

Funder Name
National Institute for Health Research

Alternative Name(s)
National Institute for Health Research, NIHR Research, NIHRresearch, NIHR - National Institute for Health Research, NIHR (The National Institute for Health and Care Research), NIHR

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Funder Name
Wellcome Trust

Alternative Name(s)

Funding Body Type
Private sector organisation

Funding Body Subtype
International organizations

Location
United Kingdom

Results and Publications

Publication and dissemination plan
Planned publication in a peer-reviewed high impact journal.

Intention to publish date
04/01/2020

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

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Basic results			17/06/2020	No	No
HRA research summary			28/06/2023	No	No
Results article		03/10/2023	04/10/2023	Yes	No