# Chronic Hypertension and l-citrulline study

Submission date	Recruitment status  No longer recruiting	Prospectively registered		
18/09/2017		☐ Protocol		
Registration date 20/09/2017	Overall study status Completed	Statistical analysis plan		
		[X] Results		
Last Edited	Condition category	[] Individual participant data		
04/10/2023	Pregnancy and Childbirth			

## 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 Lcitrulline 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 cherry.trial@liverpool.ac.uk

## Contact information

## Type(s)

**Public** 

#### Contact name

Miss Sophie Hennessy

#### Contact details

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## Additional identifiers

Clinical Trials Information System (CTIS)

2015-005792-25

Protocol serial number

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

## Study type(s)

Treatment

### 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  $14\pm/-2$  to  $22\pm/-2$  weeks' gestation (maximum of 10 weeks treatment duration). Group 2: Participants receive supplementation with the placebo from  $14\pm/-2$  to  $22\pm/-2$  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(s)

- 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

## Key secondary outcome(s))

- 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

## 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** 

## Healthy volunteers allowed

## Age group

Adult

## Lower age limit

18 years

#### Sex

Female

## 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

**United Kingdom** 

England

## 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

#### **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**

## 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?
Results article		03/10/2023	04/10/2023	Yes	No
Basic results			17/06/2020	No	No
HRA research summary			28/06/2023		No
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes