ISRCTN39133303 https://doi.org/10.1186/ISRCTN39133303

# Sildenafil therapy in dismal prognosis early-onset intrauterine growth restriction

**Submission date**
31/07/2014

**Recruitment status**
No longer recruiting

**Registration date**
31/07/2014

**Overall study status**
Completed

**Last Edited**
03/09/2018

**Condition category**
Pregnancy and Childbirth

[X] Prospectively registered

[X] Protocol

[_] Statistical analysis plan

[X] Results

[_] Individual participant data

## Plain English summary of protocol

Background and study aims
Failure to thrive before birth, also known as intrauterine fetal growth restriction (IUGR), can occur due to a variety of causes. However, the main problem is when fetal growth slows down, or stops altogether, because of a poorly functioning placenta. In a healthy pregnancy, placental cells (trophoblasts) invade the lining (endothelium) of the mothers uterine blood vessels. Normally, this trophoblast invasion should be complete early in pregnancy to enable maternal blood to flow easily to the developing placenta. In IUGR pregnancies, the trophoblast invasion is less effective and this leads to damage of the developing placenta and abnormally slow fetal growth. The earlier this occurs, the more difficult and challenging the treatment options are, including very early preterm birth by caesarean section. Extremely premature babies with low birth weight may suffer from long-term complications. Not only is their early life more traumatic, but there is also increasing evidence that the impact of being within a less nourishing uterus environment persists beyond infancy into adulthood. Fetal growth restriction has been linked with an increased risk of a wide variety of adult diseases which include heart disease and diabetes. Sildenafil citrate (Viagra®) causes the blood vessels supplying the uterus and placenta to relax. This relaxation increases blood flow through the placenta and leads to improved fetal weight gain. Sildenafil has been found to be safe in both pregnant and non-pregnant women and has been used for many years for the treatment of newborns with lung disease. These features suggest that it has the potential to offer a unique treatment for IUGR - a currently untreatable fetal disease.

Who can participate?
Women whose unborn children are failing to thrive due to the poor blood supply to the placenta.

What does the study involve?
Once the patient has agreed to take part and signed the consent form, they will be given medication to take (by mouth) three times a day, from the time they start the study until they reach 32 weeks pregnancy or the baby is born. The patient wont know whether they are taking sildenafil or the placebo (dummy), and neither will the doctor or pharmacist. In addition to the patients regular ultrasound scans the patient will have extra blood tests and more detailed monitoring of their blood pressure. This will be carried out by the hospital doctors or research midwives. Detailed blood pressure monitoring will involve placing a Velcro cuff on the patients

wrist and arm. In some hospitals as part of the study extra monitoring of the patients heart will be carried out. This will depend on the hospital having the appropriate equipment. Heart monitoring is a painless, non-invasive procedure where four stickers are placed on the skin of the patients chest to record the signal from the heart  very similar to routine ECG heart monitoring done in the GP practices. The research team will try to complete these tests during the patients stay in the hospital or during the patients regular hospital appointments, if the patient is monitored from home. Appointments may take a little longer than normal to complete. Patients will also be asked to donate their placenta after the baby is born to study in the laboratory; the placenta is no longer required by the baby and is normally disposed of after birth. If the patient wishes to keep the placenta, it will not be collected.

What are the possible benefits and risks of participating?
We hope that the results of the study overall will show us whether sildenafil helps pregnancies affected by severe IUGR. If our results show it does, we will be able to use this knowledge to improve the care for affected women and their babies. It is possible that sildenafil may not work in the way we intended. This is also very important so we can focus our future efforts on other possible treatments, but they will be tested in the same way we are testing sildenafil. Blood sampling will be carried out by someone who is skilled in taking blood. The patient may have some bruising at the site of blood collection, but this will go after a few days. The studies of sildenafil in animals, non-pregnant adults, pregnant women and unborn babies have not shown harmful effects. Like all medicines, it is not possible to say that sildenafil is 100% safe, but based on what is known it is unlikely that the use of sildenafil in pregnancy will harm the patient or the baby. We know that people receiving sildenafil can have some short-lasting side effects like headache, flushing, blurred vision and indigestion. Sildenafil can cross the placenta and babies may be at risk for some of these side effects which are not permanent. At present we do not know whether these side effects are relevant to a fetus or how they compare to any discomfort experienced by a baby with IUGR. Sildenafil has been used in pregnant women and premature babies previously but none of these side effects have been reported in babies. The long-term consequences, positive or negative, of exposure to sildenafil before birth are not known. This is why we plan to follow the babies after they are born. We will stop the trial medication at 32 weeks and babies born before 32 weeks will not be given the study medication after birth. We do not know the effects of stopping sildenafil that has been given to a fetus, but we will monitor all pregnancies that continue beyond 32 weeks and examine carefully any babies born before 32 weeks.

Where is the study run from?
The study will be carried out in the following 18 large maternity units in England:
1. Liverpool Women's NHS Foundation Trust
2. St. Marys Hospital Manchester
3. University Hospital of North Staffordshire
4. St Georges Hospital
5. Heartlands Hospital, Heart of England NHS Foundation Trust
6. Leicester Royal Infirmary
7. Royal Victoria Infirmary
8. St. Michaels Hospital, University Hospitals Bristol NHS Foundation Trust
9. Birmingham Women's NHS Foundation Trust
10. Queen's Medical Centre (QMC) Nottingham University Hospitals NHS Trust
11. UCL, University College London
12. Leeds Teaching Hospitals NHS Trust, Leeds General Infirmary
13. Norfolk and Norwich University Hospital NHS Foundation Trust
14. John Radcliffe Women's Centre, Oxford University Hospital NHS Trust
15. The Jessop Wing, Sheffield Teaching Hospitals NHS Foundation Trust

16. Maternal Fetal Medicine MRC Centre for Reproductive Health
17. Kings College Hospital NHS Foundation Trust
18. Guys and St Thomas Hospital NHS Foundation Trust

When is the study starting and how long is it expected to run for?
The study starts in August 2014 and will run for two years.

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

Who is the main contact?
Miss Sarah Quinby
s.quinby@liverpool.ac.uk

# Contact information

### Type(s)
Scientific

### Contact name
Miss Sarah Quinby

### Contact details
Liverpool CR-UK Centre - Waterhouse Building
1-3 Brownlow Street
Liverpool
United Kingdom
L69 3GL
-
s.quinby@liverpool.ac.uk

# Additional identifiers

### EudraCT/CTIS number
2013-005398-32

### IRAS number

### ClinicalTrials.gov number

### Secondary identifying numbers
16986

# Study information

### Scientific Title
A randomised controlled trial of sildenafil therapy in dismal prognosis early-onset intrauterine growth restriction

### Acronym

STRIDER

## Study objectives
The STRIDER trial aims to determine whether maternal treatment of oral sildenafil citrate improves perinatal outcomes in pregnancies complicated by severe early-onset IUGR without increasing risk to mother.
Failure to thrive before birth (intrauterine growth restriction (IUGR)) can occur due to a variety of causes such as fetal chromosomal or structural abnormalities. However, the main management issues occur when fetal growth slows down, or stops altogether, because of poorly functioning placenta.
In a healthy pregnancy, placental cells invade the lining of the maternal uterine blood vessels. Women whose unborn children are failing to thrive due to poor blood supply to the placenta will be invited to participate. The trial will be conducted in large maternity units across England. During a 24 month period, all women carrying a fetus diagnosed with severe IUGR before 30+0 weeks of pregnancy will be invited to participate. It is anticipated that around 50% of eligible women will agree to participate and 112 women will be given either oral sildenafil or matching placebo tablets until delivery, or 32+0 weeks of pregnancy, whichever comes first.
It is expected that babies exposed to sildenafil will be delivered one week later compared to those exposed to placebo. This one week increase in maturity is clinically very important.

## Ethics approval required
Old ethics approval format

## Ethics approval(s)
14/NE/0011; First MREC approval date 20/03/2014

## Study design
Randomised; Interventional; Design type: Treatment

## Primary study design
Interventional

## Secondary study design
Randomised controlled trial

## Study setting(s)
Other

## 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
Topic: Reproductive health and childbirth; Subtopic: Reproductive Health and Childb (all Subtopics); Disease: Reproductive Health & Childbirth

## Interventions

Participants are randomised to two arms:
Arm A: Sildenafil tablets 25 mg three times per day from baseline until delivery 31+6 weeks gestation, whichever comes first
Arm B: Placebo tablets 25 mg three times per day from baseline until delivery 31+6 weeks gestation, whichever comes first
Follow-up length: 12 month(s)

## Intervention Type
Other

## Phase
Phase III

## Primary outcome measure
Difference in length of gestation (days):
The primary outcome will be average prolongation of pregnancy for one week i.e. one week difference between two randomised groups in the mean randomisation to birth interval. Gestational age will be determined by early pregnancy dating ultrasound examination. The primary outcome was chosen as a surrogate for long-term morbidity as it has been shown that gestational age at birth remains the most powerful predictor of intact survival in early-onset IUGR cohorts. Recently published data from the 2006 English cohort of babies born between 22 and 26 weeks gestation showed a step increase in survivors without major morbidity ranging from 15% at 23 weeks to 50% at 26 weeks.

## Secondary outcome measures
Fetal outcomes:
1. Abdominal circumference growth velocity defined as increase of abdominal circumference in mm per day
2. Changes in gestational age adjusted Doppler measurements expressed as pulsatility index in the umbilical artery, middle cerebral artery and ductus venosus and uterine arteries
3. Changes in short-term variability of the fetal heart rate recorded by transabdominal cardiotocography

Infant outcomes include:
1. Gestational age at birth (days)
2. Survival to discharge
3. Birth weight centile
4. Length of admission on the Neonatal Intensive Care Unit (days)
5. Bronchopulmonary dysplasia requiring oxygen 36 weeks corrected age
6. Necostising enterocolotos (requiring surgery)
7. Retinopathy of prematurity (requiring treatment such as laser, grade 2/3 or more)
8. Severe central nervous system injury (detected by ultrasound and or MRI) periventricular leucomalacia grade II or more, intracerebral haemorrhage or more or hydrocephalus
9. Confirmed sepsis by positive blood culture
10. Patent ductus arteriosus needing medical or surgical treatment
11. Need for inotropes or vasopressors
12. Number of doses of surfactant
13. Ventilator days
14. Supplemental oxygen days
15. Number of days to full feeds

Maternal safety monitoring including:
1. Mode of delivery
2. Standardised blood pressure and pulse monitoring during treatment
3. Pre-eclampsia
4. Postpartum haemorrhage
5. Recording of the side effects e.g. headache, facial flushing
6. In-patient postnatal stay

### Overall study start date
01/08/2014

### Completion date
31/07/2016

## Eligibility

### Key inclusion criteria
1. Women with singleton pregnancy and fetus diagnosed with severe, early onset intrauterine growth restriction (IUGR) between 22+0 and 29+6 weeks of gestation and clinical decision to manage pregnancy expectantly.
2. IUGR is defined as estimated fetal weight or abdominal circumference <10th centile and absent or reversed end diastolic velocity Doppler in the umbilical artery.
3. 16 years of age or older
4. Consent to take part in the trial

### Participant type(s)
Patient

### Age group
Adult

### Sex
Female

### Target number of participants
Planned Sample Size: 112; UK Sample Size: 112; Description: Accounts for potential 10% drop out (even 100 participants would be able to detect clinically meaningful data) -see IRAS A60

### Key exclusion criteria
1. Multiple pregnancy
2. Known or suspected structural or chromosomal fetal abnormality
3. Maternal illness (e.g., pre-eclampsia) that is expected to require delivery for maternal reasons within the next 72 hours
4. Maternal wish not to have active management of the pregnancy, or to have pregnancy termination weeks
5. Inability to give informed consent
6. Cocaine use
7. Contraindication to sildenafil therapy, e.g., known maternal cardiac disease, left ventricular outflow tract obstruction, concomitant treatment with nitrates or previous allergy to sildenafil

**Date of first enrolment**
01/08/2014

**Date of final enrolment**
31/07/2016

# Locations

**Countries of recruitment**
England

United Kingdom

**Study participating centre**
**Liverpool CR-UK Centre - Waterhouse Building**
Liverpool
United Kingdom
L69 3GL

# Sponsor information

**Organisation**
Liverpool Women's NHS Foundation Trust (UK)

**Sponsor details**
Liverpool Women's Hospital
Liverpool Womens Hospital
Crown Street
Liverpool
England
United Kingdom
L8 7SS

**Sponsor type**
Hospital/treatment centre

**ROR**
https://ror.org/04q5r0746

# Funder(s)

**Funder type**
Government

**Funder Name**
NIHR Evaluation, Trials and Studies Coordinating Centre (UK); Grant Codes: 12/62/109

# Results and Publications

## Publication and dissemination plan
Not provided at time of registration

## Intention to publish date

## Individual participant data (IPD) sharing plan

## IPD sharing plan summary
Not provided at time of registration

## Study outputs

| Output type | Details | Date created | Date added | Peer reviewed? | Patient-facing? |
|---|---|---|---|---|---|
| Protocol article | protocol | 11/03/2014 | | Yes | No |
| Protocol article | protocol | 28/12/2017 | | Yes | No |
| Results article | results | 01/02/2018 | | Yes | No |
| HRA research summary | | | 28/06/2023 | No | No |