STRIDER: A Randomised Controlled Trial of Sildenafil Therapy In Dismal Prognosis Early-Onset Intrauterine Growth Restriction

End of Study Clinical Trial Report

Chief Investigator:	Professor Zarko Alfirevic, University of Liverpool
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IMP:	Sildenafil citrate 25mg
Protocol:	SSSTR_PROTOCOL.4.1, 24-NOV-2016

Trial Summary

Full Study Title:	**STRIDER**: A Randomised Controlled Trial of **S**ildenafil **T**he**r**apy **I**n **D**ismal Prognosis **E**arly-Onset Intrauterine Growth **R**estriction
Short Title:	STRIDER: Sildenafil for Early-Onset IUGR
Study Acronym:	STRIDER
Protocol Number:	4.1
EudraCT Number:	2013-005398-32 **ISRCTN Number:** ISRCTN391333031

Aim: The overarching aim of the STRIDER trial was to determine whether maternal treatment with oral sildenafil citrate improved perinatal outcomes in pregnancies complicated by severe early-onset intrauterine growth restriction (IUGR) without increasing risks to the mother.

Outcomes data was collected at hospital discharge.

Study Design: Randomised, double blind, placebo controlled trial of 135 women with a diagnosis of severe early-onset IUGR.

Diagnosis and Inclusion / Exclusion Criteria: All legally adult women with a diagnosis of pregnancy affected by severe early-onset IUGR between 22+0 and 29+6 weeks gestation were considered for randomisation.

Inclusion criteria:

- Singleton pregnancy with severe early-onset IUGR between 22+0 and 29+6 weeks gestation **AND** a clinical decision to manage expectantly
- IUGR defined by the presence of two criteria:
  - **I.** an Estimated Fetal Weight <10th centile **OR** Abdominal Circumference <10th centile

    AND

  - **II.** absent or reversed end-diastolic flow in the umbilical artery
- Sixteen years of age or older

Exclusion criteria:

- Multiple pregnancy,
- Known or suspected structural or chromosomal fetal abnormality,
- Maternal illness (such as pre-eclampsia) which is expected to require delivery for maternal reasons within 72 hours,
- Maternal wish not to have active management of the pregnancy, such as a decision to have a termination of pregnancy,
- Inability to give informed consent,
- Cocaine use in the current pregnancy, and
- Contraindication to sildenafil therapy, e.g. known maternal cardiac disease, left ventricular outflow tract obstruction, concomitant treatment with nitrates or previous allergy to sildenafil.

Description of IMP, Dose and Mode of Administration: Sildenafil 25mg 3 times per day or matching placebo administered orally until 31+6 weeks gestation or delivery, whichever came first.

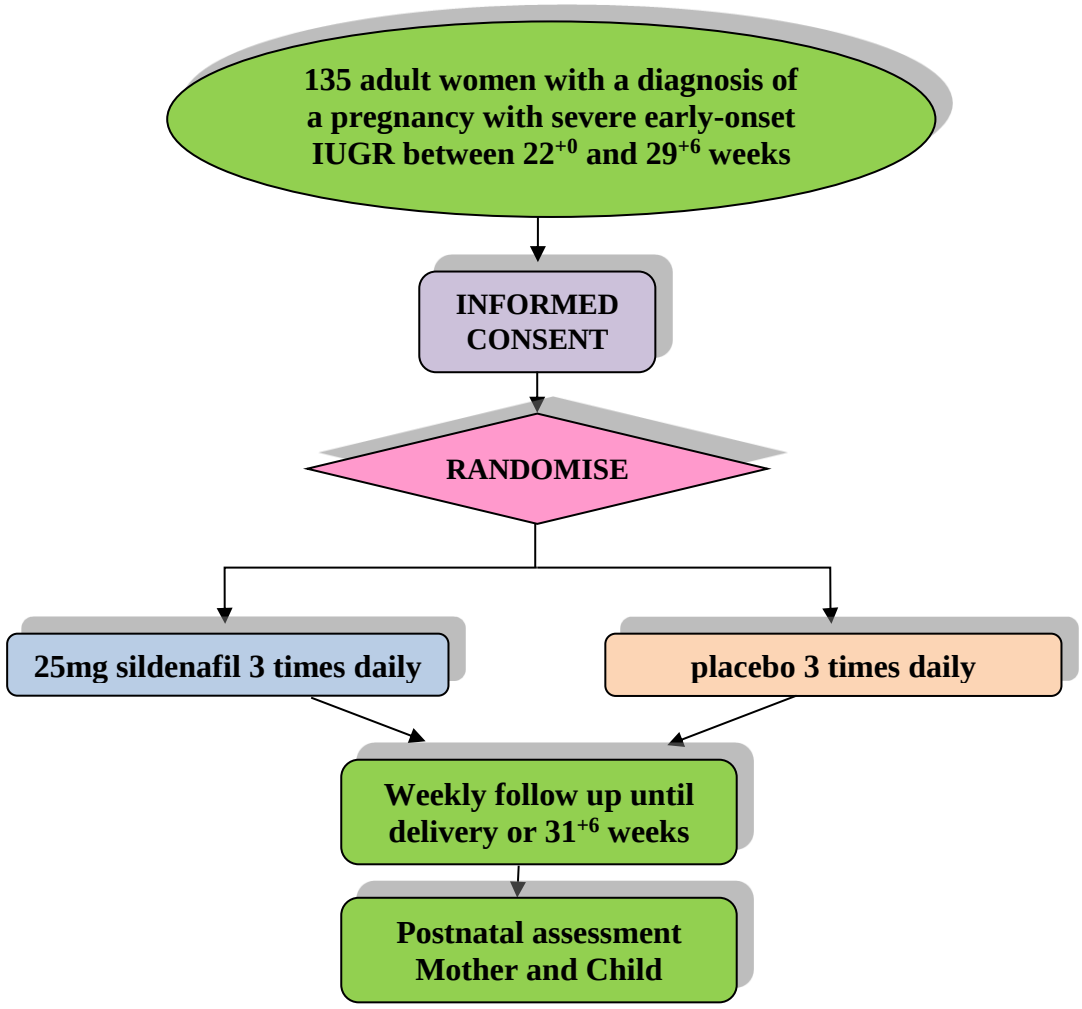
Setting: The study was co-ordinated from the University of Liverpool and conducted in hospitals within the UK. Participant recruitment was from tertiary level fetal medicine units within these hospitals.

Duration of Treatment and Participation: The first study treatment was administered shortly after randomisation, between 22+0 and 29+6 weeks gestation. The last treatment was administered at 31+6 weeks gestation or delivery, whichever came first.

Criteria for Evaluation: All participants randomly assigned to one of the treatment arms were analysed together, regardless of whether or not they completed or received that treatment, on an intention to treat (ITT) basis.

Clinical Phase:	3
Number of Participants:	135
Number of Research Sites:	19
Study Start:	November 2015
First Participant:	21-NOV-2015
Last Participant:	06-JUL-2016

Trial Schematic:



Abbreviations

BMI	Body-mass Index
CI	Confidence Interval
CTA	Clinical Trial Authority
CTU	Clinical Trials Unit
eCRF	electronic Case Report Form
EudraCT	European Clinical Trials
GCP	Good Clinical Practice
GTN	Glyceryl Trinitrate
IMP	Investigational Medicinal Product
IPD	Individual Participant Data
IQR	Interquartile Range
ISDMC	Independent Safety and Data Monitoring Committee
ISRCTN	International Standard Randomised Controlled Trials Number
ITT	Intention To Treat
IUGR	Intrauterine Growth Restriction
LCTU	Liverpool Clinical Trials Unit
$MgSO_4$	Magnesium Sulphate
MHRA	Medicines and Healthcare Products Regulatory Agency
MRC	Medical Research Council
MRI	Magnetic Resonance Imaging
NICU	Neonatal Intensive Care Unit
NIHR	National Institute of Healthcare Research
NO	Nitric Oxide
PI	Pulsatility Index
REC	Research Ethics Committee
RR	Relative Risk

SD	Standard Deviation
TSC	Trial Steering Committee
UKCRC	UK Cancer Research Centre

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1. Abstract

Background: Severe early-onset intrauterine growth restriction (IUGR) can lead to a range of adverse outcomes including fetal or neonatal death, neurodisability and lifelong risks to the health of the affected child. Sildenafil, a phosphodiesterase type 5 inhibitor, potentiates the actions of nitrous oxide, which leads to vasodilation of the uterine vessels and might improve fetal growth.

Methods: The STRIDER trial is a superiority, double-blind placebo controlled randomised trial that was carried out in 19 fetal medicine units in the UK. Random computer allocation (1:1) was used to assign women with singleton pregnancies between 22+0 and 29+6 weeks gestation and severe early-onset IUGR to receive either sildenafil 25mg three times daily or placebo until 31+6 weeks gestation or delivery. Mothers were stratified by site and their gestational age at randomisation (before 26+0 or at 26+0 weeks or later). IUGR was defined as a combination of estimated fetal weight or abdominal circumference below the tenth percentile and absent or revered end diastolic blood flow in the umbilical artery on Doppler velocimetry. The primary outcome was the time from randomisation to delivery, measured in days.

Results: Between 21st November 2014 and 6th July 2016 a total of 135 women were recruited to the study, of these 70 were randomly assigned to receive sildenafil and 65 to placebo. No difference was found in the median randomisation to delivery interval between women assigned to the sildenafil arm (17 days [IQR 7-24]) and women assigned to the placebo arm (18 days [8-28], p=0.23). Live births (relative risk [RR] 1.06, 95% CI 0.84 to 1.33; p=0.62) fetal deaths (0.89, 0.54 to 1.45; p=0.64), neonatal deaths (1.33, 0.54 to 3.28; p=0.53), and birthweight (-14g, -100 to 126; p=0.81) did not differ between the treatment arms and no differences were found for any other secondary outcomes. Eight Serious Adverse Events (SAEs) were reported during the course of the study (six in the placebo group and two in the sildenafil group); none of these were attributed to sildenafil.

Conclusion: Sildenafil did not prolong pregnancy or improve pregnancy outcomes in severe early-onset IUGR and therefore should not be prescribed for this indication outside of research studies with explicit participants' consent.

2. Background

Early-onset IUGR most commonly occurs when the placental transfer of nutrients and oxygen is impaired due to an inadequate placental implantation. The resulting fetal malnutrition and hypoxia are considered untreatable in utero. The only current option is an elective preterm delivery in order to rescue the baby from an adverse intrauterine environment. IUGR and the associated indicated preterm birth expose the fetus and neonate to significant mortality and morbidity. This diagnosis causes an important management dilemma: early delivery causes extreme prematurity with all its sequelae while delivering the baby too late risks intrauterine death or morbidity secondary to critical fetal hypoxia.

Sildenafil potentiates the effect of nitric oxide (NO) and thus may cause vasodilatation of vessels responsive to NO. The incomplete remodelling of maternal spiral arteries in IUGR results in vessels with intact or partially intact muscular layers, which remain responsive to regional vascular control. Sildenafil has the potential to increase uteroplacental circulation and perfusion resulting in improved gaseous and nutrient exchange and improved fetal growth and well-being.

Use of sildenafil in an obstetric population has been limited, but several case reports and small studies now exist. Sildenafil has been used in selected cases for the treatment of maternal pulmonary arterial hypertension where there is growing data on both its safety and efficacy to improve both maternal and fetal outcomes. There is also limited data suggesting that sildenafil has the potential to increase fetal weight.

3. Study Design and Description

3.1 Study Design and Participants

The STRIDER study was a phase III clinical trial to quantify the effects of administration of sildenafil on pregnancy outcome in severe early-onset IUGR. A total of 135 women with affected pregnancies were recruited and randomised to receive one of two treatment arms, sildenafil or placebo. The study received funding from the National Institute of Healthcare research (NIHR) and Medical Research Council (MRC). It was co-sponsored by the University of Liverpool and Liverpool Women's NHS Foundation Trust and co-ordinated through the Liverpool Clinical Trials Unit (LCTU, which is part of the Liverpool Trials Collaborative, UKCRC Registration 12).

All participants were recruited from one of the 19 STRIDER research sites located in the UK. All sites were leading obstetric units within the UK and successfully completed site feasibility during the green light phase of the trial set-up. Suitable collaborating sites and investigators were therefore assessed on the level of fetal medicine and neonatal service they provide and their ability to conduct the trial. In advance of the trial starting at a site the Principal Investigators were required to agree to adhere to the Good Clinical Practice (GCP) Guidelines. In addition, all relevant regulatory and ethics approvals were required.

The study was designed as a randomised double blind, placebo-controlled trial with sildenafil or placebo prescribed orally at a dose of 25mg 3 times per day. This dosage regime was based on previous studies[1,2] by the collaborators on the project. All participants recruited had a singleton pregnancy between 22+0 weeks gestation and 29+6 weeks gestation with a diagnosis of IUGR and had agreed to expectant management. For the purpose of the study, IUGR was defined as a fetus with an Estimated Fetal Weight or Abdominal Circumference below the tenth centile using local charts and absent or reversed end-diastolic flow in the umbilical artery on Doppler velocimetry.

Gestational age was confirmed by first trimester ultrasound and in each case, the diagnosis of severe early-onset IUGR was confirmed by a fetal medicine expert having excluded fetal anatomical abnormalities. Following diagnosis and informed consent, a full history, measurements of maternal cardiovascular parameters (blood pressure and pulse rate), fetal biometry and Doppler velocimetry were taken. Maternal venepuncture for angiogenic biomarkers was also performed.

All participants had further blood pressure and pulse rate measurements and blood sampling 2 hours after receiving the first dose of the study drug. Subsequently, participants were followed-up within 3-4 days and at weekly intervals thereafter, or earlier if clinically indicated. The remainder of clinical care was at the discretion of the local fetal medicine experts and included regular ultrasound assessment of growth and Doppler blood flow and antenatal cardiotocography.

Study medication was over encapsulated (Sharp Clinical Services, Crickhowell UK) to ensure that participants, clinicians and pharmacists were masked to the study drug.

Medication was dispensed in 10 day supplies with a new supply being provided weekly to ensure there was no period where medication was missed. Treatment ended at 31+6 weeks gestation or delivery, whichever came first. All participants were advised of the potential side-effects.

Data on pregnancy outcome was collected prospectively from clinical maternity notes and entered onto a secure electronic Case Report Form (eCRF) platform at research sites. Data quality and protocol compliance was monitored regularly by central and on-site monitoring methods.

3.2 Start of Study

Prior to the start of recruitment on 11th November 2014, the following approvals were obtained on the respective dates: Sponsorship - 9th October 2013, Research Ethics Committee (REC; North East - Newcastle and North Tyneside 2, Chair Dr Alasdair MacSween) - 20th March 2014, Clinical Trial Authority (CTA) - 18th July 2014, and Trial Greenlight Approval - 6th November 2014. All approvals for participating research sites were in place within 12 months of opening. The trial protocol was first registered on 31st July 2014, 4 months prior to the first participant being recruited (Appendix 1 – STRIDER Protocol Version 4.1, 24-NOV-2016). The first participant was recruited and randomised on 21st November 2014.

3.3 End of Study Definition

As defined in the protocol, the end of study was 'when the last recruited woman/baby is discharged from hospital, or the baby has reached expected date of birth, whichever is later'. The last participant to be recruited to the study was on 6th July 2016 and the last infant to be discharged from hospital was on 13th February 2017. Therefore, the end of study for the STRIDER trial was reported as 13th February 2017.

3.4 Study Objectives

The **primary objective** of the study was to determine whether sildenafil compared to placebo therapy delays the need to deliver a severely growth restricted fetus by a minimum of one week.

The **secondary objectives** were as follows:

I. To investigate impact on fetal growth and fetal well-being by comparing differential effect on vascular resistance in the uterine arteries, umbilical, fetal middle cerebral artery and fetal ductus venosus and differences in birth weight centiles in infants treated in-utero with sildenafil and placebo.

II. To examine, through collaboration with an international consortium, the hypothesis that sildenafil therapy compared to placebo therapy increases the rate of infant survival free of major handicap.

III. To report frequency of adverse and serious adverse events associated with sildenafil use.

IV. To investigate the impact on maternal cardiovascular parameters by measurements of maternal heart rate and peripheral blood pressure before and after administration of study medication.

V. To elucidate the precise mechanism and location of action of Sildenafil in pregnancy by investigating the effects of sildenafil therapy on omental (representative of the wider maternal systemic vasculature), myometrial (uterine vasculature) and chorionic plate artery (placental vasculature) reactivity.

3.5 Inclusion and Exclusion Criteria

The study **inclusion criteria** were as follows:

- Singleton pregnancy with severe, early-onset IUGR between 22^{+0} and 29^{+6} weeks gestation **AND** a clinical decision to manage expectantly,
- IUGR defined as an Estimated Fetal Weight <10^{th} centile **OR** Abdominal Circumference <10^{th} centile **AND** absent or reversed end diastolic flow in the umbilical artery,
- 16 years of age or older, and
- Consent to take part in the trial.

The **exclusion criteria** for the study were as follows:

- Multiple pregnancy,
- Known or suspected structural or chromosomal fetal abnormality,
- Maternal illness (such as pre-eclampsia) expected to require delivery for maternal reasons within 72 hours,

- Maternal wish not to have active management of the pregnancy, such as a decision to have a termination of pregnancy,
- Inability to give informed consent,
- Cocaine use in the current pregnancy, and
- Contraindication to sildenafil therapy,
    - Known maternal cardiac disease,
    - Left ventricular outflow tract obstruction,
    - Concomitant treatment with nitrates, nitrate drugs for chest pains / heart problems including nitroglycerin (glyceryl trinitrate, GTN), isosorbide dinitrate, isosorbide mononitrate,
    - Nitrates - some recreational drugs contain amyl nitrate("poppers"),
    - Previous allergy to sildenafil, including hives, difficulty breathing, swelling of the face, lips or tongue.

3.6 Sample Size Estimation

Internal audits of early-onset IUGR cohorts revealed an average diagnosis to delivery interval of around 20 days with a standard deviation of 11 days. In order to confirm that sildenafil could prolong pregnancy by one week (7 days), a total recruitment of 104 women (alpha 5%, power 90%) was required. Although loss to follow-up was not anticipated, recruitment of 135 women was planned in order to account for any possible post-randomisation withdrawal of consent or missing data.

The secondary hypothesis was that sildenafil will improve utero-placental circulation and therefore delay the development of fetal cardiovascular changes (reduced short term heart rate variability, deterioration of fetal Doppler indices) that lead to the indication for iatrogenic delivery. With a complete data set for approximately 100 participants, it was predicted that a clinically meaningful 20% difference in mean Doppler Pulsatility Index (PI) values of uterine arteries (0.86, SD 0.20), middle cerebral artery (2.21, SD 0.39) and ductus venosus (0.62, SD 0.22) would be detectable (alpha 5%, power >80%).

3.7 Randomisation

Randomisation was performed using a web-based randomisation service operating at the Clinical Trials Unit (CTU), British Columbia Women's Hospital (Vancouver,

Canada). Passwords and login details were provided to each STRIDER research site at the point of site 'green light' authorisation by the LCTU.

Treatments were allocated with equal probability by means of computer generated random permuted blocks of size two and four in equal proportions. The randomisation was stratified by two factors, the participating research sites and the gestational age at diagnosis: < 26+0 and ≥26+0 weeks of gestation.

As STRIDER was a double blind placebo controlled trial, both the participant and any clinical staff were blinded to the treatment allocation. It was a requirement that any unbinding that occurred during the running of the study was reported as a major protocol deviation. Unblinded participants would then be retained in the intention to treat (ITT) population, but removed from any per protocol analyses.

3.8 Study Endpoints

The **primary endpoint** for the study was – the difference in length of gestation (days), defined as the time from estimated gestation until birth.

The **secondary endpoints** were divided into sub-groups for fetal, infant and maternal safety and were as follows:

Fetal Endpoints

I. Estimated fetal weight – measures in lb,
II. Abdominal circumference growth velocity between randomisation and discharge,
III. Measurements of gestational age adjusted Doppler pulsatility index in the umbilical artery, middle cerebral artery and ductus venosus and uterine arteries; and
IV. Measurements of short term variability of the fetal heart rate recorded by transabdominal cardiotocography.

Infant Endpoints

I. Gestational age at birth,
II. Survival to discharge,
III. Birth weight centile (adjusted for gestational age and gender),
IV. Length of admission on the Neonatal Intensive Care Unit,
V. Oxygen dependency at day 28 and 36 weeks corrected age,
VI. Necrotising enterocolitis,
VII. Retinopathy of prematurity,
VIII. Significant (grade III/IV) cerebral haemorrhage detected by cerebral ultrasound,
IX. Number of doses of surfactant,
X. Ventilator days,
XI. Supplemental oxygen days, and
XII. Number of days to full feeds.

Maternal Safety

I. Mode of delivery,
II. Standardised blood pressure and pulse monitoring during treatment,
III. Postpartum haemorrhage,
IV. Recording of the side effects e.g. headache, facial flushing, and
V. In-patient postnatal stay.

3.9 Statistical Analysis

Participants' groups for analysis were defined on an ITT basis. Unadjusted estimates with Kaplan Meier estimates were presented and analysed with linear regression techniques, including the stratification factor as a main effect. The treatment effect was reported as the mean difference between groups. Statistical significance was determined as p=0.05 or less and participants randomised before 26+0 weeks and at 26+0 weeks or later were included in the subgroup analyses.

For continuous data, the analysis of secondary endpoints matched the analysis for the primary endpoint. Binary data was compared across treatment groups using a chi-squared (X^2) test or Fisher's exact test as appropriate and reported using RR with 95% confidence intervals (95% CI). All analyses were performed using the statistical software package, *R* (version 3.3.3).

3.10 Quality Control and Data Validation

The STRIDER study was subject to regular data checks and reviews as set out in the trial specific Data Management Plan. The study was also subject to both central and on-site monitoring as set out in the trial specific Monitoring Plan. Regular Central Monitoring Reports were produced and reviewed by the Trial Management Team. In addition, on-site monitoring visits were carried out for each research site following the hospital discharge of the first participant and surviving infant. All visits were completed and any outstanding issues identified were actioned and closed accordingly.

An Independent Trial Steering Committee (TSC - Chair Professor Alan Cameron) and Safety and Data Monitoring Committee (ISDMC - Chair Professor Ed Juszczak) were established to provide oversight for the study. These committees met prior to the study opening, twice yearly while it was running and then one final time at the end of the study to review and approve the results. No significant issues relating to the management of the study or the safety of the participants were escalated.

The STRIDER randomisation list was reviewed to ensure provision of the correct number of strata, adequate randomisation numbers per stratum, appropriate block sizes and treatment allocations, and balanced allocation of treatments for various cumulative totals. This was found to be accurate. In line with the regular safety and efficacy review of the data by the ISDMC, checks were carried out for omitted, or, out of sequence allocations and balanced in treatment allocations.

At the end of the trial a multiple logistic regression model with treatment arm as response and baseline variables as explanatory variables was used to confirm whether the best fitting (minimum AIC) model was the one with no explanatory variables - that is, the baseline variable was uninformative as to treatment allocation.

All statistical coding relating to the analysis of the STRIDER data deriving the primary outcome variable was reviewed by an independent statistician who performed checks to ensure that the number of participants from the database matched the number in the analyses. A random check of at least 10% of participants was also performed to ensure that the derived gestational time and birth date was correct,

3.11 Adverse Events and Compliance

Adverse events and treatment adherence were assessed and recorded at weekly clinical visits from recruitment to delivery. Participants were encouraged to record any side-effects or adverse events, which were then reviewed and documented during each clinical visit. Adherence was assessed weekly during clinical review, with any temporary discontinuation in treatment being recorded. Treatment adherence was considered to be good if the reported intake of tablets was 90% or more of the total expected to have been taken between randomisation and the visit date.

4. Study Results

4.1 Trial Population

One hundred and thirty five participants were recruited to the STRIDER trial between 21st November 2014 and 6th July 2016 from 19 fetal medicine units within the UK. Seventy five participants were recruited before 26+0 weeks gestation and 60 between 26+0 and 29+6 weeks gestation. Seventy participants were randomly assigned to receive sildenafil and 65 to placebo. None of the participants withdrew their consent nor were lost to follow-up, therefore, additional 'per protocol' analysis was not performed.

There were no clinically important differences found between the sildenafil arm and the placebo arm for ethnicity, age, body-mass index (BMI), parity and pre-existing pre-eclampsia, but more participants self-reported smoking in pregnancy in the sildenafil arm (17% compared 3%; Appendix 2, Table 1).

The median gestation at randomisation was 24.4 weeks (IQR 24.0-27.5; Appendix 2, Table 1). At randomisation, a reversed Doppler umbilical artery end-diastolic flow was detected in 44 (33%) participants (Appendix 2, Table 1). An absent umbilical artery end-diastolic flow was detected in all of the remaining participants. The fetal ductus

venosus a-wave was found to be absent or reversed in 8 (6%) participants (Appendix 2, Table 1). The Estimated Fetal Weight at randomisation was 445g (IQR 344-608; Appendix 2, Table 1). Sixty nine (51%) fetuses had an Estimated Fetal Weight below 500g (Appendix 2, Table 1). Two babies were postnatally diagnosed with Down syndrome (one allocated to the sildenafil arm and the other to the placebo arm) and 2 had confirmed cytomegalovirus infection (one allocated to the sildenafil arm and the other to placebo arm); all four babies were included in the ITT analysis.

4.2 Primary Endpoint

The median time between randomisation and delivery was 18 days (IQR 8-27); 17 days (7-24) in the sildenafil arm and 18 days (8-28) in the placebo arm (p=0.23; Appendix 2, Table 2 and Figure 2). Linear regression showed that time to delivery did not differ between the two treatment arms for all participants (2.7 days, 95% CI -1.3 to 6.8; p=0.19; Appendix 2, Figure 2).

4.3 Secondary Endpoints

Of the 135 participants recruited to the STRIDER trial, 98 (73%) had at least 2 separate umbilical artery Doppler measurements a minimum 48 hours apart, 93 (69%) for ductus venosus, 90 (67%) for middle cerebral artery, and 87 (64%) for uterine arteries (Appendix 2, Table 3). Ductus venosus a-wave deteriorated over time in more participants treated with sildenafil than with placebo (Appendix 2, Table 3). Eighteen (95%) of the 19 babies in whom the ductus venosus deteriorated were randomly assigned before 26+0 weeks gestation (Appendix 2, Table 3). Between-group differences were not observed in the pattern of Doppler changes for any of the other fetal vessels examined (middle cerebral artery, umbilical artery and uterine arteries; Appendix 2, Table 3).

The exposure to antenatal corticosteroids and magnesium sulphate given for neuroprotection was similar in both treatment arms (Appendix 2, Table 3). There was also no difference in the caesarean section rate between the arms (Appendix 2, Table 3), with 98% (90 of 92) of all livebirths being delivered by caesarean section (Appendix 2, Table 4).

Livebirth rates and neonatal deaths did not differ between the treatment arms (Appendix 2, Table 4). Forty three (72%) of the 60 deaths reported occurred in utero and 48 (80%)

deaths occurred in the subgroup randomly assigned before 26+0 weeks gestation (Appendix 2, Table 4). No clinically significant differences were observed between the two treatment arms for any of the other pre-specified secondary endpoints (Appendix 2, Table 4).

4.4 Serious Adverse Events and Adherence

A total of 8 Serious Adverse Events (SAEs) were reported during the course of the study; none of these were attributed to sildenafil. Three (38%) were maternal hospital admissions in the placebo arm; one antepartum haemorrhage, one general malaise (unwell, dizzy and light-headed), and one hospital admission following a stillbirth with drowsiness. There were 2 reported neonatal SAEs in the sildenafil arm; a Down syndrome baby with an atrio-ventricular septal defect and a fetal intracranial haemorrhage grade 1, which was detected on an antenatal MRI performed in the context of a separate research study. In the placebo arm, 3 neonatal SAEs were reported; a Down syndrome baby, a fetal intracranial haemorrhage grade 1 and a baby with bone fractures that were postnatally attributed to osteopenia/metabolic bone disease.

Overall, 42 women reported 94 side effects; 24 (34%) in the sildenafil arm and 18 (28%) in the placebo arm (RR 1.24, 95% CI 0.74-2.06; p=0.41). The majority of the side effects reported were for facial flushing (45 of 94 (48%)). Other reported side effects included nasal congestion, a dry mouth and headaches.

Good treatment adherence was reported; of the 265 recorded cycles of therapy, 257 (97%) reported that drug adherence was at least 90%. At a participant level, 130 (96%) of the 135 participants had study drug compliance of at least 90% for all cycles of therapy.

5. Discussion

The results of the STRIDER study demonstrated that sildenafil did not result in prolongation of pregnancy when administered to pregnant women with a severely growth restricted fetus. In fact, the interval between randomisation and delivery was on average 2.7 days shorter in the sildenafil arm, although this difference did not reach conventional statistical significance in the gestational age adjusted logistic regression

analysis (p=0.19). The study also showed that were no clinically important differences in mortality or short-term neonatal morbidity, although the trial was not adequately powered for these secondary endpoints.

It was anticipated that, if sildenafil was effective, there may be a beneficial effect on placental function, as assessed by uteroplacental and fetal Doppler studies, even in the absence of a clear benefit on substantive clinical outcomes. The observed higher proportion of babies in whom Doppler findings in ductus venosus deteriorated with sildenafil treatment may have been a chance finding, but is also potentially worrying, particularly if linked to the somewhat shorter randomisation to delivery interval in this treatment arm. Interestingly, no such adverse effect from sildenafil on the blood flow in uterine arteries, umbilical artery or middle cerebral artery was found. It was not possible to obtain two separate measurements for all babies, but in this placebo controlled study, it is very unlikely that Doppler measurements were somehow systematically biased. At present, a plausible pathophysiological explanation cannot be offered for the possible adverse effect of sildenafil on the fetal blood flow in the STRIDER cohort.

The findings of the study are in contrast with animal and several previously reported clinical studies.[1,3-12] The sildenafil dose used was based on the consensus from researchers with most experience in clinical evaluation of sildenafil in pregnancy at the time[2,12] and a higher dose could possibly have been more effective. A recent systematic review identified 16 studies of sildenafil in human pregnancies, of which only four exceeded our daily dose of 75mg in 3 divided doses. Three reports of improved uteroplacental perfusion in IUGR pregnancies used a 50mg dose once daily and recruited participants at later gestations with umbilical end-diastolic flow present in most cases.[3-5] As pharmacokinetic studies of sildenafil in pregnancy are currently not available, it would be difficult to determine an ideal dosing schedule for future studies. More importantly, a possibility that the currently used dose of 25mg three times daily may have a deleterious effect on blood flow in the ductus venosus would require extreme caution in any future studies with a higher dose, particularly in fetuses with absent or reversed end-diastolic flow in the umbilical artery.

Another possibility is that the study's definition of growth restriction included fetuses with such advanced disease that it was not possible to improve or reverse the process. The STRIDER study recruited more than half of the IUGR babies before 26 weeks

gestation and all fetuses had severely compromised umbilical circulation with absent or reversed end-diastolic flow; overall mortality was around 45%. In comparison, the average gestational age at randomisation in the study by Dastjerdi et al was 35 weeks. The authors did not report the proportion of babies with absent or reversed umbilical artery blood flow, but given the reported gestation, it is likely that these babies would have been delivered rather than recruited.[3] El-Sayed et al[4] reported that only 11 (20%) of 54 babies developed absent or reversed end-diastolic umbilical artery blood flow at some point after randomisation, whereas in the study by Trapani et al [5], reversed umbilical artery blood flow was, in fact, an exclusion criterion. None of the studies reported any perinatal deaths or long term follow-up data and it is, therefore, far too early to speculate that the reported improvements in uteroplacental perfusion in less severe IUGR at later gestation would lead to improved survival and better long-term outcomes.

Although there was no firmly agreed fetal monitoring protocol, or uniform triggers for the delivery of compromised babies in this study, all participating units had access to fetal medicine experts, detailed Doppler assessment of fetal and uteroplacental circulation and antenatal cardiotocography. It is therefore not surprising that the overall survival observed is broadly in agreement with other recent studies that included severe early-onset IUGR with abnormal umbilical artery Doppler.[13,14] Long-term follow-up of the surviving infants of the STRIDER study has already started and it is planned to combine the study data in a prospective individual participant data (IPD) meta-analysis to look for any possible long-term effect of sildenafil, particularly on neurodevelopmental and cardiovascular outcome.[15]

In conclusion, when sildenafil was administered to pregnant women carrying a severely growth-restricted fetus, it did not prolong pregnancy, improve survival or reduce short-term neonatal morbidity.

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End of Study Clinical Trial Report Approval

This confirms approval of the End of Study Clinical Trial Report for the STRIDER trial.

Trial co-ordinator

Signature: ..... J.L. Hamdd .....

Date 26/FEB/2018

Trial statistician

Signature: .....

Date 26/FEB/2018

Chief Investigator

Signature: .....

Date 26/FEB/2018

Appendix 1: STRIDER Protocol Version 4.1 24-NOV-2016

STRIDER: A Randomized Controlled Trial of **S**ildenafil **T**herapy **I**n **D**ismal Prognosis **E**arly-Onset Intrauterine Growth **R**estriction

Version: 4.1
Date: 24/11/2016

Appendix 2: Results Tables and Figures

Table 1. Baseline characteristics

	Sildenafil N= 70	Placebo N=65
Age (years)	29 (26,34)	33 (28,36)
Height, (cm)	164 (158-167)	163 (158-166)
Weight, (kg)	68 (59-82)	70 (60, 82)
Body-mass index	25 (23-32)	26 (23-31)
Ethnicity		
White	48 (69%)	43 (66%)
Asian	6 (9%)	8 (12%)
African	6 (9%)	7 (11%)
Other	10 (14%)	7 (11%)
Current smoker	12 (17%)	2 (3%)
Non-smoker	58 (83%)	63 (97%)
Nulliparous	35 (50%)	25 (38%)
Pre-eclampsia	13 (19%)	11(17%)
Gestational hypertension	12 (17%)	23 (35%)
Current antihypertensive treatment	25 (36%)	27 (42%)
Gestational diabetes	2 (3%)	3 (5%)
Antepartum Haemorrhage	1 (1%)	0
Preterm prelabour rupture of membrane	0	1 (2%)
Gestation (weeks)	25.1 (24.0-27.5)	25.6 (24.1-27.4)
Gestation <26+0 weeks	40 (57%)	35 (54%)
Umbilical artery Doppler		
End-diastolic flow absent	46 (66%)	45 (69%)
End-diastolic flow reversed	24 (34%)	20 (31%)
Absent ductus venosus a-wave	4 (6%)	4 (6%)
Uterine artery Doppler abnormal*	50/63 (79%)	45/63 (78%)
Estimated Fetal Weight (g)	451 (352-613)	436 (326-594)
Estimated Fetal Weight <500g	33 (47%)	36 (55%)
Systolic blood pressure (mm Hg)	135.5 (125.5-147.5)	134.0 (120.5-144.5)
Diastolic blood pressure (mm Hg)	88.5 (80.5-95.5)	86.5 (78.0-94.5)
Mean arterial pressure (mm Hg)	103 (12)	109 (38)
Creatinine (mol/L)	57.4 (1.9)	62.4 (2.7)
Urea (mmol/L)	4.0 (0.2)	4.4 (0.5)
Uric acid (mmol/L)	300.6 (13.4)	288.6 (14.7)
Aspartate transaminase (U/L)	26.0 (3.3)	32.4 (5.7)
Albumin (g/L)	31.8 (0.7)	32.4 (0.7)
Platelets ($x10^9$/L)	277.1 (10.2)	233.5 (9.5)

Data are median (IQR), n (%), n/N (%), or mean (SD). *Pulsatility index of more than 1.45 or bilateral notching.

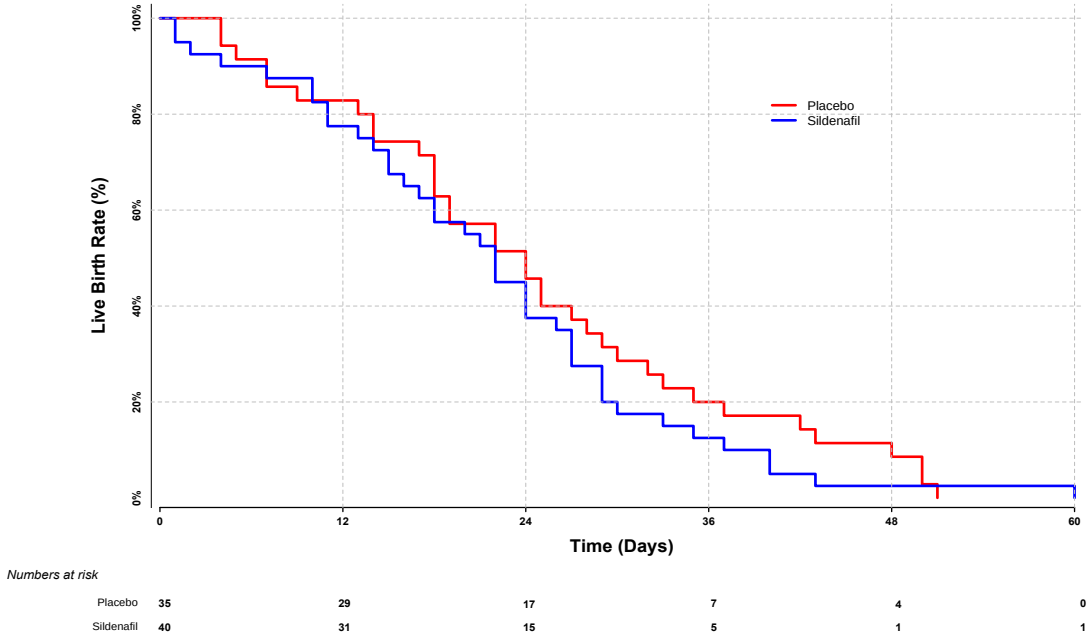
Table 2. Primary outcome according to treatment

	Sildenafil N=70	Placebo N=65	p value
Randomisation to delivery interval (days)	17 (7-24)	18 (8-28)	0.23
<26^{+0} weeks gestation	22 (14-29)	24 (16-33)	0.36
≥26+0 weeks gestation	10 (5-8)	14 (6-20)	0.34
Gestation (weeks)	28.1 (26.7-29.7)	28.4 (27.3-30.1)	0.28
<26^{+0} weeks gestation	26.9 (26.1-28.3)	27.6 (26.3-28.5)	0.55
≥26^{+0} weeks gestation	29.7 (28.3-30.7)	29.6 (28.4-30.9)	0.41

Data are median (IQR).

Figure 2. Kaplan-Meier plot of interval from randomization to birth

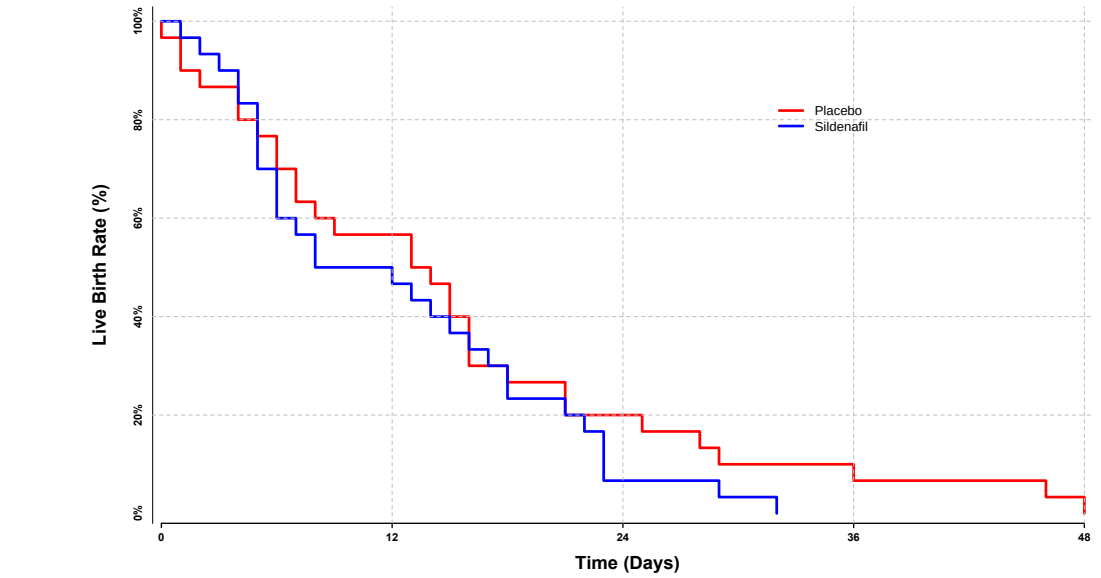
< 26 Weeks Gestational Age



Numbers at risk

Placebo	35	29	17	7	4	0
Sildenafil	40	31	15	5	1	1

≥ 26 Weeks Gestational Age



Numbers at risk

Placebo	30	17	6	2	0
Sildenafil	30	14	2	0	0

Table 3. Antenatal course and management

	Sildenafil	Placebo	RR (95%CI)
Umbilical artery Doppler (all)	N=51	N=47	
Improvement	5 (10%)	5 (11%)	0.92 (0.28-2.98)
No Change	25 (49%)	25 (53%)	0.92 (0.63-1.36)
Deterioration	21 (41%)	17 (36%)	1.14 (0.69-1.88)
Umbilical artery Doppler (<26^{+0} weeks)	N=35	N=28	
Improvement	4 (11%)	3 (11%)	1.07 (0.26-4.38)
No Change	16 (46%)	14 (50%)	0.91 (0.55-1.53)
Deterioration	15 (43%)	11 (39%)	1.09 (0.60-1.99)
Ductus venosus a-wave (all)	N=51	N=42	
Improvement	0	0	-
No Change	36 (71%)	38 (90%)	0.78 (0.64-0.96)
Deterioration	15 (29%)	4 (10%)	3.09 (1.11-8.60)
Ductus venosus a-wave (<26^{+0} weeks)	N=35	N=24	
Improvement	0	0	
No Change	21 (60%)	20 (83%)	0.72 (0.52-1.00)
Deterioration	14 (40%)	4 (17%)	2.40 (0.90-6.41)
Middle cerebral artery (all)	N=50	N=40	
Improvement	4 (8%)	2 (5%)	1.60 (0.31-8.30)
No Change	33 (66%)	24 (60%)	1.10 (0.80-1.52)
Deterioration	13 (26%)	14 (35%)	0.74 (0.40-1.39)
Middle cerebral artery (<26^{+0} weeks)	N=34	N=25	
No change	1 (3%)	1 (4%)	0.74 (0.05-11.2)
Improvement	23 (68%)	16 (64%)	1.06 (0.73-1.54)
Deterioration	10 (29%)	8 (32%)	0.92 (0.42-1.99)
Uterine artery Doppler (all)	N=45	N=42	
No change	41 (91%)	36 (86%)	1.06 (0.91-1.24)
Improvement	1 (2%)	3 (7%)	0.31 (0.03-2.88)
Deterioration	3 (7%)	3 (7%)	0.93 (0.19-4.38)
Abdominal circumference change (mm)	N=46	N=41	
All participants	14 (6-20)	18 (8-25)	-4.5 (-9.5-4.5)
<26^{+0} weeks	14 (8-21)	15 (7-29)	1.0 (-10.1-6.5)
≥26^{+0} weeks	12 (4-17)	19 (14-21)	-7.0 (-17.6-8.5)
Pre-eclampsia			
All participants	15/70 (21%)	12/65 (18%)	1.16 (0.59-2.29)
<26^{+0} weeks	8/40 (20%)	6/35 (17%)	1.17 (0.45-3.04)
Antenatal corticosteroids			
All participants	41/70 (59%)	37/65 (57%)	1.03 (0.77-1.37)
<26^{+0}weeks	21/40 (53%)	17/35 (49%)	1.08 (0.69-1.70)
$MgSO_4$ for neuroprotection			
All participants	40/70 (57%)	25/65 (38%)	1.49 (1.03-2.14)
<26^{+0} weeks	20/40 (50%)	12/35 (34%)	1.46 (0.84-2.54)
Caesarean section			
All participants	47/70 (67%)	43/65 (66%)	1.01 (0.80-1.29)
<26^{+0} weeks	20/40 (50%)	15/35 (43%)	1.17 (0.71-1.91)

Data are n/N (%), or median (IQR). $MgSO_4$ = magnesium sulphate.

Table 4. Neonatal outcome according to treatment

	Sildenafil (N=70)	**Placebo** (N=65)	**Relative risk** (95% CI)	**P-value**
Live births	49 (70%)	43 (66%)	1.06 (0.84-1.33)	0.62
<26^{+0} weeks gestation	22 (31%)	15 (23%)	1.28 (0.8-2.06)	0.31
≥26^{+0} weeks gestation	27 (39%)	28 (43%)	0.96 (0.83-1.12)	0.59
Fetal death	21 (30%)	22 (34%)	0.89 (0.54-1.45)	0.64
<26^{+0} weeks gestation	18 (26%)	20 (31%)	0.79 (0.5-1.23)	0.31
≥26^{+0} weeks gestation	3 (4%)	2 (3%)	1.50 (0.27-8.34)	0.64
Neonatal death	10 (14%)	7 (11%)	1.33 (0.54-3.28)	0.53
<26^{+0} weeks gestation	6 (9%)	4 (6%)	1.31 (0.40-4.28)	0.65
≥26^{+0} weeks gestation	4 (6%)	3 (5%)	1.33 (0.33-5.45)	0.69
Neonatal morbidity	37/49 (76%)	28/43 (65%)	1.23 (0.86-1.75)	0.25
<26^{+0} weeks gestation	20/22 (91%)	13/15 (87%)	1.35 (0.79-2.29)	0.27
≥26^{+0} weeks gestation	17/27 (63%)	15/28 (54%)	1.13 (0.70-1.82)	0.62
Infants with composite perinatal adverse outcome (perinatal death or neonatal morbidity)	58 (83%)	50 (77%)	1.08 (0.91-1.28)	0.38
<26^{+0} weeks gestation	37/40 (93%)	33/35 (94%)	0.98 (0.87-1.11)	0.74
≥26^{+0} weeks gestation	21/30 (70%)	17/30 (57%)	1.24 (0.84-1.83)	0.28
Birthweight (g)	604 (496-766)	590 (430-842)	-14 (-100-126)	0.81
<26^{+0} weeks gestation	520 (355-602)	450 (356-579)	-70 (-123-40)	0.32
≥26^{+0} weeks gestation	750 (663-1073)	856 (611-1015)	106 (-129-236)	0.25
Infants admitted to NICU	47/49 (96%)	38/43 (88%)	1.09 (0.96-1.23)	0.17
<26^{+0} weeks gestation	21/22 (95%)	14/15 (93%)	1.02 (0.87-1.20)	0.81
≥26^{+0} weeks gestation	26/27 (96%)	24/28 (86%)	1.12 (0.95-1.33)	0.19
Days on NICU	25 (10-50)	16 (8-55)	-9 (-18-2)	0.24
<26^{+0} weeks gestation	25 (11-58)	39 (12-57)	15 (-17-31)	0.24
≥26^{+0} weeks gestation	25 (10-46)	15 (7-35)	-11 (-28-11)	0.29
Age at NICU discharge (days)	79 (50-106)	73 (51-100)	-6 (-24-11)	0.50
<26^{+0} weeks gestation	97 (73-109)	87 (74-112)	10 (-32-27)	0.48
≥26^{+0} weeks gestation	59 (46-84)	63 (46-94)	4 (-24-16)	0.73
Oxygen dependency at 28 days	23/49 (47%)	14/43 (33%)	1.44 (0.85-2.43)	0.17
<26^{+0} weeks gestation	12/22 (55%)	6/15 (40%)	1.36 (0.66-2.82)	0.41
≥26^{+0} weeks gestation	11/27 (41%)	8/28 (29%)	1.43 (0.68-2.99)	0.34
Oxygen dependency at 36 weeks	10/49 (20%)	7/43 (16%)	1.25 (0.52-3.01)	0.62
<26^{+0} weeks gestation	6/22 (27%)	2/15 (13%)	2.05 (0.48-8.80)	0.33
≥26^{+0} weeks gestation	4/27 (15%)	5/28 (18%)	0.83 (0.25-2.77)	0.76
Necrotising enterocolitis	8/49 (16%)	12/43 (28%)	0.59 (0.26-1.30)	0.20
<26^{+0} weeks gestation	5/22 (23%)	5/15 (33%)	0.68 (0.24-1.95)	0.47
≥26^{+0} weeks gestation	3/27 (11%)	7/28 (25%)	0.44 (0.13-1.54)	0.19
Retinopathy of prematurity	6/49 (12%)	10/43 (23%)	0.54 (0.21-1.36)	0.20
<26^{+0} weeks gestation	3/22 (14%)	4/15 (27%)	0.54 (0.14-2.05)	0.37
≥26^{+0} weeks gestation	3/27 (11%)	6/28 (21%)	0.52 (0.14-1.87)	0.32

	Sildenafil (N=70)	**Placebo** (N=65)	**Relative risk** (95% CI)	**P-value**
Any intracranial haemorrhage	13/39 (33%)	8/33 (24%)	1.37 (0.65-2.91)	0.41
<26^{+0} weeks gestation	6/19 (32%)	4/12 (33%)	0.95 (0.34-2.68)	0.92
≥26^{+0} weeks gestation	7/20 (35%)	4/21 (19%)	1.84 (0.63-5.33)	0.26
Surfactant used	37/49 (76%)	25/43 (58%)	1.30 (0.96-1.75)	0.078
<26^{+0} weeks gestation	19/22 (86%)	9/15 (60%)	1.44 (0.92-2.25)	0.11
≥26^{+0} weeks gestation	18/27 (67%)	16/28 (57%)	1.17 (0.77-1.77)	0.46
Ventilator dependency	40/49 (82%)	28/43 (65%)	1.25 (0.97-1.62)	0.073
<26^{+0} weeks gestation	19/22 (86%)	12/15 (80%)	1.08 (0.80-1.46)	0.62
≥26^{+0} weeks gestation	21/27 (78%)	16/28 (57%)	1.36 (0.93-1.99)	0.11
Ventilator days	7 (2-21)	10 (3-27)	-3 (-12-7)	0.60
<26^{+0} weeks gestation	12 (5-23)	12 (7-24)	0 (-17-11)	1.00
≥26^{+0} weeks gestation	3 (1-17)	6 (3-29)	-3 (-16-11)	0.66

Data are n (%), mean weighted difference (95% CI), or as indicated. NICU = neonatal intensive care unit.

Appendix 3: Published Study Manuscript

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Articles
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Maternal sildenafil for severe fetal growth restriction (STRIDER): a multicentre, randomised, placebo-controlled, double-blind trial

Andrew Sharp, Christine Cornforth, Richard Jackson, Jane Harrold, Mark A Turner, Louise C Kenny, Philip N Baker, Edward D Johnstone, Asma Khalil, Peter von Dadelszen, Aris T Papageorghiou, Zarko Alfirevic, on behalf of the STRIDER group

Summary

Background Severe early-onset fetal growth restriction can lead to a range of adverse outcomes including fetal or neonatal death, neurodisability, and lifelong risks to the health of the affected child. Sildenafil, a phosphodiesterase type 5 inhibitor, potentiates the actions of nitric oxide, which leads to vasodilatation of the uterine vessels and might improve fetal growth in utero.

Methods We did this superiority, placebo-controlled randomised trial in 19 fetal medicine units in the UK. We used random computer allocation (1:1) to assign women with singleton pregnancies between 22 weeks and 0 days' gestation and 29 weeks and 6 days' gestation and severe early-onset fetal growth restriction to receive either sildenafil 25 mg three times daily or placebo until 32 weeks and 0 days' gestation or delivery. We stratified women by site and by their gestational age at randomisation (before week 26 and 0 days or at week 26 and 0 days or later). We defined fetal growth restriction as a combination of estimated fetal weight or abdominal circumference below tenth percentile and absent or reversed end-diastolic blood flow in the umbilical artery on Doppler velocimetry. The primary outcome was the time from randomisation to delivery, measured in days. This study is registered with BioMed Central, number ISRCTN 39133303.

Findings Between Nov 21, 2014, and July 6, 2016, we recruited 135 women and randomly assigned 70 women to sildenafil and 65 women to placebo. We found no difference in the median randomisation to delivery interval between women assigned to sildenafil (17 days [IQR 7–24]) and women assigned to placebo (18 days [8–28]; p=0·23). Livebirths (relative risk [RR] 1·06, 95% CI 0·84 to 1·33; p=0·62), fetal deaths (0·89, 0·54 to 1·45; p=0·64), neonatal deaths (1·33, 0·54 to 3·28; p=0·53), and birthweight (−14 g, −100 to 126; p=0·81) did not differ between groups. No differences were found for any other secondary outcomes. Eight serious adverse events were reported during the course of the study (six in the placebo group and two in the sildenafil group); none of these were attributed to sildenafil.

Interpretation Sildenafil did not prolong pregnancy or improve pregnancy outcomes in severe early-onset fetal growth restriction and therefore it should not be prescribed for this indication outside of research studies with explicit participants' consent.

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Department of Women's and Children's Health (A Sharp PhD, M A Turner PhD, Prof Z Alfirevic MD) and Liverpool Clinical Trials Unit, University of Liverpool, Liverpool, UK (C Cornforth PhD, R Jackson PhD, J Harrold PhD); The Irish Centre for Fetal and Neonatal Translational Research (INFANT), University College Cork, Cork, Ireland (Prof L C Kenny PhD); College of Life Sciences, University of Leicester, Leicester, UK (Prof P N Baker DM); Maternal and Fetal Health Research Centre, University of Manchester, Manchester, UK (E D Johnstone MBChB); Fetal Medicine Unit, St George's Hospital, University of London, London, UK (A Khalil PhD, A T Papageorghiou PhD); and Department of Women's and Children's Health, School of Life Course Sciences, King's College London, London, UK (Prof Peter von Dadelszen MBChB)

Correspondence to: Prof Zarko Alfirevic, Department of Women's and Children's Health, University of Liverpool, Liverpool Women's Hospital, Liverpool L8 7SS, UK
zarko@liverpool.ac.uk

Introduction

Severe early-onset fetal growth restriction and subsequent preterm birth are associated with a range of adverse pregnancy outcomes including fetal and neonatal death,[1–3] necrotising enterocolitis,[3] respiratory complications,[3] neurodisability,[4–7] and lifelong risks to the health of the affected child, such as obesity and hypertensive disease.[8–10] No effective treatment for fetal growth restriction is available and the mainstay of management is intensive surveillance to optimise the timing of delivery.[11] In a similar patient group at the threshold of viability, it has been suggested that the overall survival increases by 2% for each extra day in utero.[2] Delaying delivery, however, might increase the risk of long-term adverse outcomes because of prolonged exposure to a hostile uterine environment.

In normal pregnancy, trophoblasts invade and remodel maternal spiral arteries resulting in a low-resistance, high-flow placental bed circulation.[12] Failure of this remodelling process is a predominant feature of fetal growth restriction.[13,14] Retention of vasoactive smooth muscle cells within spiral arteries promotes placental under-perfusion and hypoxia-reperfusion injury.[15]

Placental perfusion is enhanced by nitric oxide (NO), which promotes vasodilatation of maternal vessels. The NO second messenger cGMP is degraded by the phosphodiesterase enzyme class. Sildenafil citrate is an inhibitor of phosphodiesterase type 5 (PDE-5), the predominant PDE type found in the reproductive tract.[16] Sildenafil has shown promise in cohort studies and randomised studies of fetal growth restriction,[17–20]