The efficacy of sildenafil therapy in dismal prognosis early-onset intrauterine growth restriction: the STRIDER RCT

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Scientific summary

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Scientific summary

Background

Severe early-onset intrauterine growth restriction (IUGR) is associated with stillbirth, neonatal death and neurodevelopmental impairment. There is currently no treatment for IUGR with timely delivery being the only management option available. The researchers know from human placentas from IUGR pregnancies that there is often a failure to remodel the maternal spiral arteries within the uterus and myometrium. This inadequate remodelling leads to the persistence of a vasoactive responsiveness within these vessels.

Sildenafil, a phosphodiesterase type 5 inhibitor, potentiates naturally occurring nitrous oxide (NO), encouraging vasodilation of vasoactive vessels. Previous studies in animal models and human ex vivo samples have shown recovery of placental function and improvement in fetal growth. Small numbers of clinical trials have also shown an increase in fetal growth or vascular flow (Doppler studies) from maternal use of sildenafil. The STRIDER trial aims to address whether maternal treatment with sildenafil is beneficial to fetal growth and perinatal and toddler outcomes.

Objectives

The STRIDER United Kingdom (UK) study was designed to answer the following objectives in two phases; phase 1 – recruitment to a randomised controlled trial of sildenafil versus placebo for the treatment of early-onset intrauterine fetal growth restriction, and phase 2 – follow-up at 2 years of age to assess cardiovascular and neurodevelopmental outcomes effect the surviving infants.

The primary objective of the phase 1 study was to determine whether sildenafil, compared to placebo therapy, delays the need to deliver a severely growth-restricted fetus by a minimum of 1 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 birthweight 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 neurodisability.
III. To report frequency of adverse and serious adverse events (SAEs) associated with sildenafil use.
IV. To investigate the impact on maternal cardiovascular parameters by measurements of maternal heart rate and peripheral blood pressure (BP) 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.

The objective of the phase 2 follow-up study was to examine neurodevelopmental and cardiovascular outcomes at 2 years of age in children born to mothers who received sildenafil compared with placebo during pregnancy.

It was hypothesised that:

- STRIDER UK children whose mothers received sildenafil will have improved neurodevelopmental outcomes at age 2–3 years (corrected) compared with controls exposed to placebo.
- There will be no difference in BP at 2–3 years (corrected) between STRIDER UK children whose mothers received sildenafil compared with controls exposed to placebo.

Methods

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.

The study was designed as a randomised double-blind, placebo-controlled trial with sildenafil or placebo prescribed orally at a dose of 25 mg three times per day. 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 10th centile using local charts and absent or reversed end-diastolic flow in the umbilical artery on Doppler velocimetry.

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 with a high level of fetal medicine and neonatal services provided.

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 (BP and pulse rate), fetal biometry and Doppler velocimetry were taken. Maternal venepuncture for angiogenic biomarkers was also performed.

All participants had further BP 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 were 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 were monitored regularly by central and on-site monitoring methods.

All surviving infants of mothers recruited to the STRIDER study were eligible and invited for follow-up. A study invitation pack was sent to all parents/carers of surviving children. This included an invitation letter, participant information sheet and informed consent form. Participants who did not contact the research team within 2 weeks were contacted by a member of the research team.

Assessments took place in a clinical research setting or in the child's home. Informed written consent was obtained before the assessment began. All assessments were performed by a single senior research

psychologist with expertise in developmental assessment techniques. This researcher was blinded to treatment allocation.

Assessments included the Cognitive, Language and Motor Subscales of the Bayley Scales of Infant and Toddler Development – III (BSID-III); Hempel's Neurological Examination for Toddler Age to identify major neurological impairment (cerebral palsy; CP) and subtle deviations from typical neurological and neuromotor function. In addition, a cardiovascular assessment was undertaken, which included brachial systolic BP and diastolic BP and arterial stiffness, assessed as aortic (central) augmentation index (AIx).

Where potential participants cancelled or failed to attend follow-up appointments on more than three occasions, they were invited to participate remotely. All such participants received a Follow-up questionnaire pack, which included participant information sheet, consent form and all questionnaires detailed as part of the main study in addition to the Ages and Stages Questionnaire-3 (in place of the BSID-III, neurodevelopmental assessment).

The health status classification system – preschool version (HSCS-PS) is a parental (or clinician) proxy measurement of the health status of a child. The overall health status is described as a 10-element vector consisting of one level for each domain. In this study, to facilitate comparisons between groups, a total 'disability score' for the overall health state of a child was calculated as the sum of the level codes for the original domains. Therefore, the range of the disability score varied from 10 (no disability on any domain) to 41 (maximum disability on all 10 domains).

The child behaviour checklist (CBCL) 1.5–5 was used to assess emotional and behavioural difficulties. Raw scores are normalised into T-scores [mean: 50, standard deviation (SD): 10]. Higher T-scores represent more problematic behaviour. T-scores below 60 are in the normal range, T-scores of 60–63 (84th to 90th percentile) are in the borderline range, and T-scores above 63 (above 90th percentile) are in the clinical range. The T-scores are dichotomised into typical (scores in the normal range) and atypical (scores in the borderline and clinical range). The behaviour rating inventory of executive function – preschool version (BRIEF-P) is a parent questionnaire for early assessment of executive function to assess severity of executive dysfunction in day-to-day situations. Age-based T-scores are computed for each subscale and index, and a score of 65 or higher is considered a clinically significant problem.

Results

The study recruited 135 participants between 21 November 2014 and 6 July 2016. A number of 75 participants were recruited before 26^{+0} weeks' gestation and 60 between 26^{+0} and 29^{+6} weeks' gestation. A total of 70 participants were randomly assigned to receive sildenafil and 65 to placebo. None of the participants withdrew their consent nor were lost to follow-up prior to delivery, therefore, additional 'per-protocol' analysis was not performed.

Differences at baseline were not clinically important between the sildenafil group and the placebo group. The median gestation at randomisation was 24.4 weeks [interquartile range (IQR) 24.0–27.5]. Two babies were postnatally diagnosed with Down syndrome (one sildenafil and one placebo) and two had confirmed cytomegalovirus infection (one sildenafil and one placebo); all four babies were included in the intention to treat (ITT) analysis. There was no beneficial effect on maternal cardiovascular function from treatment with sildenafil.

The follow-up phase was delayed due to the impact of the COVID-19 pandemic on research staff's availability and access to patients. Out of the 75 babies who were discharged alive from the neonatal unit, 61 babies (81.3%) were included in the follow-up phase. Of those not followed up, 1 baby died (placebo), 3 declined follow-up and 10 were uncontactable.

By the nature of follow-up participants were not randomised by treatment leaving 32 mothers who had received sildenafil and 29 had received placebo. There was no difference in the sex, birthweight, gestation at delivery (median 29.2 weeks vs. 29.9 weeks), mode of delivery, or oxygen usage.

The physical characteristics of the population available for follow-up showed no difference in height or weight. Head circumference was slightly larger in those treated with sildenafil (49.25, 46.43–50.26) versus placebo (47.18, 44.71–48.95). There was no difference between systolic and diastolic BP between those children treated with sildenafil or placebo. Median values were appropriate for children aged 2 years.

The Bayley assessment showed no significant differences in cognitive, language (including receptive and expressive language), or motor (including fine and gross motor) subscales between children of sildenafil- and placebo-treated mothers. Total scores were somewhat lower than expected across all three domains compared with standard population norms (i.e. 100, SD = 15); however, the difference was neither clinically nor statistically significant. There was no difference between the sildenafil and placebo groups for the presence of CP reported by parents.

Functional assessment with the BRIEF-P demonstrated no difference in adjusted T-scores between sildenafil and placebo for any of the assessed domains. Likewise, the median total CBCL scores and adjusted T-scores also showed no difference between babies whose mothers were treated with sildenafil versus placebo for any of the assessed domains.

The HSCS scores are shown as a total score by domain and as individual components. There was no difference between infants who had received sildenafil to those who had received placebo for any of the domains assessed.

It was not possible to record the HEMPEL assessments and as such neurology could not be assessed.

Unfortunately, no children were able to tolerate the NICOM (Non-invasive Cardiac Output Monitor) cardiovascular test, leaving BP as the sole assessment of infant cardiovascular status.

Conclusions

The results of the STRIDER study demonstrated that sildenafil did not result in prolongation of pregnancy, improvements in fetal growth, or perinatal outcome when administered to pregnant women with a severely-growth restricted fetus. These results have subsequently been confirmed in a number of other studies.

Our study demonstrated a lack of benefit on any neurodevelopmental, emotional or behavioural assessment from treatment with sildenafil. This study represents the first study to report to the impact of antenatal treatment of women with severe early-onset FGR on their infants' well-being at 2 years of age. Along with the findings of no benefit on prolongation of pregnancy or perinatal outcome this study it confirms the ineffectiveness of this treatment to improve outcomes in babies with severe early-onset FGR.

Further to this lack of benefit there were concerns raised during the Dutch STRIDER trial of increased perinatal mortality in the sildenafil group. Further assessment deemed this excess mortality to be predominantly due to persistent pulmonary hypertension of the neonates (PPHN), which has been proposed to be a pathophysiological mechanism of 'rebound' vasoconstriction after cessation of sildenafil. Both the UK and the New Zealand/Australia STRIDER Trials reviewed their data using the same criteria for PPHN as the Dutch STRIDER trial and did not find an increased mortality.

The international STRIDER studies are committed 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.

On current evidence, the researchers do not believe that there is likely to be any beneficial effect on fetal growth, perinatal outcomes or neurodevelopment in this patient group and would advise that further use of sildenafil in this population should be stopped. Prior to any further studies using PDE5 inhibitors to treat FGR being performed, pharmacokinetic and pharmacodynamic experiments specific to pregnancy should be performed to establish an efficacious therapeutic dose.

Therefore, the STRIDER study showed no beneficial effect for any perinatal outcome for mother or baby from treatment with 25 mg sildenafil TDS for severe early-onset FGR. The follow-up study confirmed that there was no beneficial effect from maternal treatment with sildenafil on behavioural assessment performed at 2 years of age in the surviving infants. There was also no effect on infant BP from treatment with sildenafil.

Trial registration

This trial is registered as ISRCTN39133303.

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