**2-year Neurodevelopmental outcomes in children who received Sildenafil Therapy in utero: The STRIDER RCT**

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**Disclosure of Interests:**

Sharp, Khalil, Jackson, Johnstone, Harrold, Alfirevic, Cornforth, Turner, Vollmer

Disclosure of interest: None declared

Baker and Kenny are minority shareholders of Metabolomic Diagnostics, a spin-out company which seeks to develop screening tests for pregnancy complications

Papageorghiou is a co-founder of and shareholder of Intelligent Ultrasound, a University spin–out company

Khalil is a Vice-President, Royal College of Obstetricians and Gynaecologists and Trustee of the International Society of Ultrasound in Obstetrics and Gynecology

von Dadelszen is a shareholder in Nightingale Medical, a University spin–out company

Tweetable abstract:

Antenatal Sildenafil did not improve neurodevelopmental outcomes in children with fetal growth restriction when compared to placebo

**Short Title:**

Neurodevelopmental outcomes at 2 year after Sildenafil Therapy

**Abstract:**

**Objective:** Severe early-onset fetal growth restriction (FGR) causes stillbirth, neonatal death and neurodevelopmental impairment. Poor maternal spiral artery remodelling maintains a vasoactive responsiveness which is susceptible to treatment with sildenafil, a phosphodiesterase type 5 inhibitor, which may improve perinatal outcomes.

**Design:** Superiority, double-blind randomised controlled trial

**Setting:** 20 UK fetal medicine units

**Population:** FGR, defined as an abdominal circumference <10th centile with absent end diastolic flow in the umbilical artery between 22+0 and 29+6 weeks.

**Methods:** Treatment with sildenafil (25mg three times/day) or placebo until delivery or 32 weeks.

**Main Outcome Measures:** All infants alive at hospital discharge were assessed for cardiovascular function, neuromotor, cognitive, speech and language impairment at two years of age. Primary outcome was survival without cerebral palsy or neurosensory impairment, or Bayley III composite score of >85.

**Results:** 135 women were randomised between November 2014 and July 2016 (70 to sildenafil, 65 to placebo). We previously published that there was no improvement in time to delivery or perinatal outcomes with sildenafil. 75 babies (55.5%) were discharged alive with 61 infants eligible for follow up (32 sildenafil and 29 placebo). One infant died (placebo), three declined and 10 were uncontactable. There was no difference in neurodevelopment or blood pressure following treatment with sildenafil. Infants who received sildenafil had a larger head circumference at 2-years of age (median difference 49.2 cm, IQR 46.4-50.3 vs 47.2 cm, 95%CI 44.7-48.9).

**Conclusions:** Sildenafil therapy did not prolong pregnancy, or improve perinatal outcomes, and did not improve infant neurodevelopment in FGR survivors. Therefore, sildenafil should not be prescribed for this condition.

**Keywords:**

Sildenafil citrate, neurodevelopment, fetal growth retardation, infant, newborn, pregnancy, birth weight, placenta

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**BJOG at a glance**

Severe early-onset fetal growth restriction (FGR) is associated with stillbirth, neonatal death and neurodevelopmental impairment. Inadequate uterine vascular adaptation is a feature of FGR and therefore the vasodilator sildenafil may be beneficial at improving fetal growth and prolonging pregnancy.

This study assessed the role of antenatal treatment with 25mg oral sildenafil three times per day versus placebo in severe early-onset FGR. The primary outcome was a prolongation of pregnancy by 1 week and impact on neurodevelopmental function at 2 years of age.

This study found no benefit on time to delivery, perinatal mortality or morbidity or neurodevelopmental and behavioural outcomes at 2 years of age in survivors. We suggest that sildenafil has no role in severe-early onset FGR.

**Introduction**

Severe early-onset fetal growth restriction (FGR) is associated with stillbirth [1, 2], neonatal death and prolonged neonatal admission [3]. Currently, there is no effective treatment for FGR with elective preterm delivery the only management option. FGR poses the dilemma of early delivery with prematurity or the risk of intrauterine death secondary to critical fetal hypoxia [4].

Being born too small and too early can pose significant health risks throughout the child’s life. In particular, FGR has adverse effects on brain structure and function, which are independent of gestational age at birth [5] and often compounded by poor postnatal growth, ultimately leading to an increased risk of neurological impairment, cognitive impairment, inattention, and specific difficulties with executive functions and impulsivity [6].

Between 25-40% of surviving growth-restricted very preterm infants have developmental impairment [7, 8], in particular in the areas of fine and gross motor function, attentional abilities [5] and language [9], and with a mean difference in Full Scale IQ of almost 1 standard deviation by the time they reach school age compared with preterm and term appropriate for gestational age (AGA) controls [10, 11]. In addition, FGR is a well-recognised risk factor for later life diseases such as hypertension, diabetes, and ischaemic heart disease [12] due to increased arterial stiffness [13] and aortic wall thickening [14].

FGR often occurs secondary to abnormal placental development and failure to remodel the maternal vessels leading to retention of their muscular layer, and therefore their responsive to NO [15]. Therefore, sildenafil, an inhibitor of phosphodiesterase type 5 (PDE-5) potentiates the effect of nitric oxide (NO) and has the potential to increase uteroplacental circulation and perfusion.

Sildenafil has shown promise in animal models to improve placental function and infant growth [15-17], for the treatment of preeclampsia [18, 19] and as an agent for improving fetal growth [18, 20, 21]. We set out to investigate whether oral treatment with sildenafil was effective in reducing poor outcomes in early-onset FGR. This study compromised a randomised controlled trial with the primary outcome of a one week prolongation of pregnancy [22] and a 2 year follow-up phase to assess neurological impairment and behaviour. However, prolonging the time that the fetus remains within a hostile uterine environment could lead to worse long-term outcomes for the infant. Here we present the two-year infant outcome data from the UK STRIDER trial.

**Methods**

Study Design and Participants

Participants were recruited from 19 UK tertiary obstetric units with a high standard of fetal medicine and neonatal services.

Women with a singleton pregnancy between 22+0 weeks gestation and 29+6 weeks gestation, confirmed by first trimester ultrasound, with a diagnosis of severe early-onset FGR and a plan for expectant management were eligible for inclusion. FGR was defined as a fetus with an estimated fetal weight (EFW) or abdominal circumference (AC) below the 10th centile using local charts and absent or reversed end-diastolic flow (EDF) in the umbilical artery (UA) on Doppler velocimetry. We excluded women from the study if they were less than 16 years of age, had a known contraindication to sildenafil, were cocaine users, had a known or suspected significant chromosomal or structural anomaly, or were likely to need delivery within 72 hours (such as severe pre-eclampsia).

Ethical approval for this follow up study was given by the North East Research Ethics Committee (14/NE/0011) in the UK. Each participating site provided site-specific approval and all participants provided written informed consent. An Independent Safety Data Monitoring Committee (ISDMC) was established to review the safety and efficacy data. The trial protocol was first registered on 31st July 2014, 4 months prior to the first participant being recruited (ISRCTN 39133303).

Randomisation and masking

We used a web-based application to allocate treatment (1:1) with randomisation stratification by site and gestation (<26+0 and ≥26+0 weeks).

A full history was taken, measurements of maternal cardiovascular parameters (blood pressure and pulse rate), fetal biometry and Doppler velocimetry were performed and maternal venepuncture for angiogenic bloods undertaken.

Participants were reviewed 2 hours after receiving the first dose, at 3-4 days and at least weekly thereafter. The remainder of clinical care was at the discretion of the local fetal medicine experts and included regular ultrasound assessment of growth and Doppler and antenatal cardiotocography. Criteria for delivery were not dictated by the study protocol but were expected to follow the TRUFFLE study protocol [4].

Study medication was over encapsulated (Sharp Clinical Services, Crickhowell UK) to ensure that participants, clinicians and pharmacists were blinded to the study drug [22]. Medication was dispensed in 10-day supplies with a new supply being provided weekly to ensure there was no period where medication was missed. All participants received oral sildenafil at a dose of 25mg 3 times per day or placebo prescribed orally. This dosage regimen was determined by previous studies [18, 20]. Pharmacy logs were used to determine adherence. Treatment ended at 31+6 weeks gestation or delivery, whichever came first. All participants were advised of the potential side-effects of the medication.

Data regarding pregnancy outcomes 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 was monitored regularly by central and on-site monitoring methods.

Outcome measures

The primary outcome measure was time from randomisation to delivery, measured in days, which has previously been reported [22]. This pragmatic design relied upon an assumption that an increase in survival would be clinically significant if sildenafil were able to prolong pregnancy by one week.

The follow up component aimed to assess all babies alive at discharge for cardiovascular function, neuromotor impairment, cognitive, speech and language, and motor development at two years of age. The primary outcome was survival without cerebral palsy or neurosensory impairment, or a Bayley III composite score of greater than 85 but was not powered for this outcome based as it was on survivors.

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 two 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)[23, 24]; Hempel’s Neurological Examination for Toddler Age [25] to identify major neurological impairment (Cerebral Palsy; CP) and subtle deviations from typical neurological and neuromotor function [26]. 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 [27] (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 ‘quality of health 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) [28].

TheChild Behavior Checklist(CBCL) 1.5-5 [29] was used to assess emotional and behavioural difficulties. Raw scores are normalised into *T*-scores (mean: 50, SD: 10). Higher *T*-scores represent more problematic behavior. *T*-scores below 60 are in the normal range, *T*-scores of 60 to 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) [29].

The Behaviour Rating Inventory of Executive Function – Preschool version (Brief-P) [30] is a parent questionnaire for early assessment of executive function to assess severity of executive dysfunction in day to day situations [30]. Age-based T-scores are computed for each subscale and index, and a score of 65 or higher is considered a clinically significant problem.

Adverse events and adherence

We assessed and recorded adverse events at weekly clinical reviews from recruitment to delivery. Participants were encouraged to report side effects or adverse events. We assessed adherence during the weekly clinical reviews and considered adherence to treatment to be good if the reported intake of medication was 90% or more of the total expected to have been taken up to this point.

Statistical analysis

Participants’ groups for analysis were defined on an intention to treat (ITT) basis. As the primary outcome is a measure of time Kaplan Meier estimates are provided to summarise the data. As there are no censored observations, standard linear regression techniques are used to analyse the data. Analyses were stratified by gestation period but not site due to low numbers of patients in each site. 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 were compared across treatment groups using a chi-squared (X2) 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).

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. RJ, CC, AS and ZA had full access to the data in the study and the corresponding author had final responsibility for the decision to submit for publication.

**Results**

We recruited 135 participants between 21st November 2014 and 6th July 2016. 75 participants were recruited before 26+0 weeks gestation and 60 between 26+0 and 29+6 weeks gestation. 70 participants were randomly assigned to receive sildenafil and 65 to placebo. None of the participants either withdrew their consent or were lost to follow-up prior to delivery; therefore, additional ‘per protocol’ analysis was not performed. The follow-up phase was able to assess 81% of eligible participants at 2 years of age. Out of 75 babies who were discharged alive from the neonatal unit, 61 infants (81.3%) were included in the follow up phase. Of those not followed up, 1 infant died (placebo), 3 declined follow up and 10 were uncontactable. This left the infants of 32 mothers who had received sildenafil and 29 had received placebo for assessment in the follow-up phase (Figure 1).

Differences at baseline were not clinically important between the sildenafil group and the placebo group and are reported in our previous paper [22]. The median gestation at randomisation was 24.4 weeks (IQR 24.0-27.5). Two babies were postnatally diagnosed with Down’s syndrome (one sildenafil and one placebo) and 2 had confirmed cytomegalovirus infection (one sildenafil and one placebo); all four babies were included in the ITT analysis [22]. There was no beneficial effect on maternal cardiovascular function from treatment with sildenafil [31].

The follow-up phase was delayed due to the impact of the Covid-19 pandemic on research staff availability and access to patients. 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 between the two groups (Table 1).

The physical characteristics of the population are shown in Table 2. There was no difference in height or weight. Head circumference was slightly larger in those treated with sildenafil (49.25, 46.43-50.26) vs placebo (47.18, 44.71-48.95). There was no difference between systolic and diastolic blood pressure between those children treated with sildenafil or placebo. Median values were appropriate for children aged 2 years. The proportion of infants without Cerebral Palsy was 22/26 (85%) in those with mothers treated with sildenafil, and 19/24 (80%) when treated with placebo (Table 3).

The Bayley assessment showed no meaningful 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 (Table 3). 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 (Table 4) 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 (Table 5) also showed no difference between infants whose mothers were treated with sildenafil vs placebo for any of the assessed domains.

TheHSCS scores are shown as a total score by domain and as individual components (Table 6). 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, direct neurological assessments could not be made. However, we were able to obtain information on neurology from the medical notes and there was no difference in the incidence of CP between the sildenafil (n=4) and the placebo group (n=5).

Unfortunately, no infants were able to remain calm and relaxed during the NICOM cardiovascular test, leaving blood pressure as the sole assessment of infant cardiovascular status.

**Discussion**

**Principal findings:**

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 [22]. These results have subsequently been confirmed in a number of other studies [32-34].

Our study demonstrated a lack of benefit on any neurodevelopmental, emotional or behavioural assessment from treatment with sildenafil, although the study was only powered for short term perinatal outcomes and so caution should be exercised in interpreting this neurodevelopmental result.

**Results:**

This study defines the impact of antenatal treatment with sildenafil in women with severe early-onset FGR on their infants’ wellbeing at 2 years of age. Previously we showed no benefit on prolongation of pregnancy or perinatal outcome [22]. This study now confirms the ineffectiveness of this treatment to improve longer-term outcomes in infants with severe early-onset FGR and is supportive of the similar study recently published from Australia and New Zealand [35].

**Clinical implications**:

Further to this lack of benefit, concerns were raised during the Dutch STRIDER trial of increased perinatal mortality in the sildenafil group [32]. 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 [36]. 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 [37].

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 [38].

**Research implications:**

It is possible that future pharmacokinetic and pharmacodynamics experiments using PDE5 inhibitors may establish an efficacious therapeutic dose for FGR studies. However, on current evidence, we do not believe that there is any beneficial effect of sildenafil treatment on fetal growth, perinatal outcomes or neurodevelopment in this patient group and would advise that further use of this drug in this population should be stopped.

**Strengths and limitations:**

This study is the first of its kind to report the 2-year outcomes for infants treated with sildenafil for severe early-onset FGR. The cohort represents a unique and high-risk FGR cohort managed to the highest standards within tertiary fetal medicine units within the UK. This challenging patient group represents an important addition to the literature for both sildenafil therapy and severe early-onset FGR outcomes.

Unfortunately, due to practical limitations we were unable to assess neurology with the Hempel test and the cardiovascular effects on the infants. While this is a limitation in this very challenging patient group, the information obtained remains very important. The lack of cardiovascular assessment is unlikely to be critical due to the overall negative impact of sildenafil on all other parameters.

**Conclusions:**

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

Summary of key findings

* Sildenafil did not prolong pregnancy in severe early-onset IUGR compared with placebo
* Sildenafil did not improve perinatal outcomes in severe early-onset IUGR
* Sildenafil did not improve maternal cardiovascular parameters in severe- early-onset IUGR
* Sildenafil did not improve infant neurodevelopmental function at age 2 years
* Sildenafil did not improve infant emotional or behavioural status at age 2 years

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Ethical approval was obtained on 20th March 2014, Research Ethics Committee (REC; North East - Newcastle and North Tyneside 2, Chair Dr Alasdair MacSween (REC Ref: 14/NE/0011 (Phase 1) and REC Ref: 16/LO/2225 (Phase 2)).

Patient and Public Involvement (PPI) was through the antenatal results and choice (ARC) charity. ARC was involved with the STRIDER study from the first design stages and through to delivery of the study and results.

Contributions to Authorship

Prof Philip Baker (Obstetrician) conceived the idea for the study. Prof Louise Kenny (Obstetrician), Prof Zarko Alfirevic (Obstetrician), Prof Peter von Dadelszen (Obstetrician), Prof Aris Papageorghiou (Obstetrician) and Prof Philip Baker developed the STRIDER study consortium. Prof Zarko Alfirevic and Dr Andrew Sharp (Obstetrician) wrote the initial submission for funding.

Dr Christine Cornforth (Senior Trial Manager, Psychologist), Dr Andrew Sharp and Prof Zarko Alfirevic wrote the submission for Phase two funding for the study. Dr Andrew Sharp, Dr Christine Cornforth and Prof Zarko Alfirevic supervised the conduct of the RCT. Prof Asma Khalil (Obstetrician) assessed the cardiovascular results. Prof Mark Turner (Neonatologist) supervised neonatal outcomes. Dr Christine Cornforth performed neurodevelopmental assessments and assessed impact with Prof Brigitte Vollmer (Neurologist). Dr Jane Harrold (Trial Manager) collated trial data. Dr Richard Jackson (Statistician) performed statistical analysis. Prof Edward Johnstone (Obstetrician) reviewed trail data. Dr Andrew Sharp, Dr Christine Cornforth, Prof Brigitte Vollmer and Prof Zarko Alfirevic wrote the manuscript. All authors reviewed the final manuscript and prepared the results for publication.

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