**Full title:** STRIDER NZAus: A multicentre randomised controlled trial of sildenafil therapy in early-onset fetal growth restriction.

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**Short title:** STRIDER NZAus: an RCT of sildenafil for FGR.

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**Abstract**

**Objective:** To assess the effect of maternal sildenafil therapy on fetal growth in pregnancies with early-onset fetal growth restriction.

**Design:** A randomised placebo-controlled trial.

**Setting:** Thirteen maternal-fetal medicine units across New Zealand and Australia.

**Population:** Women with singleton pregnancies affected by fetal growth restriction at 22+0 to 29+6 weeks.

**Methods:** Women were randomised to oral 25mg sildenafil citrate or visually matching placebo three times daily until 32+0 weeks, birth or fetal death (whichever occurred first).

**Main Outcome Measures:** The primary outcome was the proportion of pregnancies with an increase in fetal growth velocity. Secondary outcomes included livebirth, survival to hospital discharge free of major neonatal morbidity and preeclampsia.

**Results:** Sildenafil did not affect the proportion of pregnancies with an increase in fetal growth velocity; 32/61 (52.5%) sildenafil-treated 39/57 (68.4%) placebo-treated, adjusted OR 0.49, 95% CI 0.23-1.05 and had no effect on abdominal circumference Z-scores (p=0.61). Sildenafil use was associated with a lower mean uterine pulsatility index after 48 hours treatment (1.56 vs 1.81 p=0.02). The livebirth rate was 56/63 (88.9%) sildenafil-treated 47/59 (79.7%) placebo-treated, adjusted OR 2.50 (95%CI 0.80-7.79); survival to hospital discharge free of major neonatal morbidity was 42/63 (66.7%) sildenafil-treated 33/59 (55.9%) placebo-treated, adjusted OR 1.93 (0.84-4.45); and new-onset preeclampsia was 9/51 (17.7%) sildenafil-treated and 14/55 (25.5%) placebo-treated, OR 0.67 (95%CI 0.26-1.75).

**Conclusions:** Maternal sildenafil use had no effect on fetal growth velocity. Prospectively planned meta-analyses will determine whether sildenafil exerts other effects on maternal and fetal/neonatal wellbeing.

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**Keywords:** fetal growth restriction, intrauterine growth restriction, small for gestational age, sildenafil, uterine artery Doppler, preeclampsia.

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**Tweetable abstract:** Maternal sildenafil use has no beneficial effect on growth in early-onset FGR, but also no evidence of harm.

**Introduction**

Fetal growth restriction, the failure to reach full growth potential before birth, imposes significant health risks for the affected individual as a fetus1, infant2 and child3, 4 with on-going risk through adult life.5 Utero-placental insufficiency is the most common cause of fetal growth restriction and the main contributor to severe early-onset disease when the risk of death and major disability is highest.2 In current practice planned early birth is the only therapeutic option available which imposes further life-long health risks. No current interventions alter fetal growth and wellbeing to allow safe prolongation of pregnancy, although a number of therapies are under investigation in a pipeline of preclinical and clinical studies aiming to modify the utero-placental circulation and in-utero environment.6 The most far advanced of these investigative therapies is the maternal administration of sildenafil citrate.

Sildenafil is a phosphodiesterase type-5 inhibitor which blocks the inactivation of the intracellular second messenger cyclic guanosine monophosphate within vascular smooth muscle cells and hence potentiates the action of nitric oxide leading to vasodilatation. Sildenafil is well tolerated in pregnancy.7 Animal models,8-10 *ex-vivo* and *in-vivo* human studies11, 12 and observational cohorts13 suggest it augments utero-placental circulation, enhances fetal growth and improves short term neonatal outcomes for infants affected by fetal growth restriction. High quality randomised placebo-controlled trials designed to assess both safety and efficacy are required before the introduction of antenatal sildenafil therapy into clinical practice should be considered.

The STRIDER NZ Aus trial was designed to assess the effect of sildenafil therapy compared with placebo therapy on fetal growth velocity in pregnancies affected by severe early-onset fetal growth restriction. The trial was designed in collaboration with investigators from other national STRIDER trials within the STRIDER Consortium.14 Each trial has been independently funded and executed and will be published as an individual trial. Prospectively planned individual participant data and trial level meta-analyses will allow assessment of outcomes up to 2-3 years corrected age.14, 15

**Methods**

We conducted a triple-blind, placebo-controlled, parallel, phase II-III trial randomised at the participant level (1:1 ratio) in 13 maternal fetal medicine units across New Zealand and Australia. National ethics approval was given by Northern A Region (CEN/12/06/028) in New Zealand and **Royal Brisbane & Women's Hospital Human Research Ethics Committee in** Australia (HREC/14/QRBW/178) and at sites; King Edward Memorial Hospital (2014071EW) and Mercy Health (R15/19). Governance approval was obtained at each site. The trial was prospectively registered with the Australian New Zealand Clinical Trials Registry ACTRN12612000584831, the trial protocol has been published,16 and the full trial protocol is publicly available.17 There was no formal patient involvement in trial development.

Women referred to participating units with a singleton pregnancy and fetal growth restriction between 22+0 to 29+6 weeks gestation were assessed by site investigators and maternal fetal medicine specialists. Gestational age was determined by last menstrual period date and first ultrasound. When first ultrasound was <16 weeks or ≥16 weeks gestation, estimated date of delivery was adjusted if difference was ≥ seven or ≥10 days respectively compared to last menstrual period date. Review by a maternal fetal medicine specialist aimed to exclude fetal causes of growth restriction. Women were eligible for the trial at 22+0 – 27+6 weeks gestation if the fetal abdominal circumference was ≤3rd percentile18 and at 28+0 – 29+6 weeks gestation if the estimated fetal weight19 was <700g. Women were ineligible if there was known fetal aneuploidy or other major fetal anomaly, syndrome or congenital infection deemed to be the likely cause for growth restriction; a plan for delivery had already been made; maternal disease (preeclampsia) where it was expected that delivery may be necessary within 48 hours; or any contraindication to maternal sildenafil therapy. All women participating in the trial provided written informed consent.

Baseline data regarding demographics, medical and obstetric history, medication use and pregnancy details were collected. Prior to and within 24 hours of randomisation all women underwent a baseline ultrasound scan including fetal growth parameters, amniotic fluid volume, and Doppler flow assessments (maternal uterine arteries and fetal umbilical artery and vein, middle cerebral artery and ductus venosus); maternal blood pressure; urinanalysis for proteinuria; and blood sample for assessment of renal and hepatic function and platelet count.

An independent perinatal trials unit prepared a computer generated randomisation sequence balanced in block sizes of two and four with stratification according to gestational age at recruitment (< or ≥ 24+0 weeks) and the presence or absence of end-diastolic velocity in the umbilical artery Doppler waveform. A central web-based randomisation service assigned participants to receive sildenafil or an identical in appearance placebo. Participants, care providers and investigators were blind to treatment allocation.

Participants received oral 25mg sildenafil citrate (SilvastaTM) or an identical in appearance placebo preparation three times daily from randomisation until 32+0 weeks gestation, delivery or fetal death (whichever occurred first). Both sildenafil and placebo tablets (containing no sildenafil citrate) were sourced from a single supplier (Actavis Limited, Malta). Trial drug packaging and long term stability analysis was performed by Anqual Laboratories, University of Auckland, New Zealand.

Each participant was supplied with a trial drug bottle containing 30 tablets and a subject medication diary. Repeat study drug bottles and diaries were issued as required. Compliance was assessed by investigators at each trial visit by pill counts and diary review; cross-checked centrally against drug accountability logs. Compliance was calculated as a percentage expected/actual tablets taken over duration of active trial period. Participants were encouraged to note adverse effects in the subject medication diary. Additional indications to stop trial drug were maternal request and investigator or clinician safety concern.

All participants undertook trial assessments at 48 hours, five days, 10 days, 14 days and then weekly whilst remaining on trial drug therapy; a final trial visit occurred >48 hours and within one week of completion of trial drug treatment. Each visit included ultrasound assessment of fetal growth, amniotic fluid volume and Doppler blood flow; blood pressure; urine analysis; renal and hepatic function and platelet count. Additional maternal and fetal wellbeing assessments were made at the discretion of local clinicians. Antenatal care and timing and mode of delivery were not mandated by the trial protocol but followed an expectant management approach until delivery was clearly indicated on fetal and/or maternal grounds determined by local clinicians. Data regarding antenatal, intrapartum and postnatal care were collected from maternal medical records.

Maternal outcome data were collected to the time of primary maternal hospital discharge. Fetal and neonatal outcome data were collected until primary discharge from hospital or estimated date of delivery (whichever occurred later) or death. For infants discharged prior to their estimated date of delivery, mothers were contacted by telephone to collect information for any new admissions or diagnoses since discharge. Postpartum questionnaires were sent to all participants 6-12 weeks after delivery including assessment of satisfaction with care. Data quality was systematically and manually reviewed at regular intervals throughout the trial.

As there were no established fetal growth core outcome datasets at the time of trial development we selected clinically relevant, reproducible and easily defined neonatal and maternal outcomes. The primary outcome was the proportion of pregnancies with any increase in fetal growth velocity after treatment commenced; determined by a comparison of pre- and post-treatment fetal growth velocity. Fetal growth velocity was measured as the difference in abdominal circumference Z-scores.20 Pre-treatment growth velocity was calculated from Z-score of the most recent measurement taken >12 days before recruitment and Z-score at recruitment. Where no measure >12 days before recruitment was available the mean abdominal circumference growth standard at 16 weeks gestation20 was used. Post-treatment growth velocity was calculated from Z-scores at the recruitment and day 14 assessments. Where delivery or fetal death occurred before the day 14 assessment, the longest interval available was used (day 10, day five or 48 hour). Secondary outcomes and their definitions are provided in Appendix S1. Pulmonary hypertension of the newbornwas not included as a secondary outcome but data regarding primary pulmonary hypertension was collected defined by our bi-national criteria22.

The statistical analysis plan was finalised and made publicly available prior to commencement of analysis.23 The proportion of women with an increase in post-randomisation fetal growth velocity was estimated using published data available at the time of trial design (41% placebo-treated vs 90% sildenafil-treated).13, 24 To demonstrate a change in the proportion of pregnancies with a more conservative increase in post-randomisation growth velocity from 50% (placebo-treated) to 80% (sildenafil-treated) we required 58 women in each group to yield 90% power (α 0.05, two sided). To allow for 5% drop-out we recruited 122 women.

Data were analysed on an intention-to-treat basis. Wilcoxon rank sum test for continuous variables and Chi-square test for categorical variables were used for unadjusted analyses. Statistical models of logistic regression for binary outcomes and multiple linear regression for continuous outcomes were used, adjusted for the randomisation variables and for the presence/absence of preeclampsia (neonatal outcomes only). Investigation of the potential effect of recruiting site was non-significant for randomisation to delivery interval, gestational age at delivery and incidence of major neonatal morbidity. Recruiting site was therefore not adjusted for in the statistical model as planned in our analysis plan.23 For repeatedly measured continuous outcomes, the mixed model for repeated measures analyses was used to test for treatment, time, and treatment by time interaction adjusting for randomisation variables and baseline value as fixed effects, and subject as a random effect. Kenward-Roger method was used to estimate the denominator degrees of freedom for fixed effects. Two-sided p-value <0.05 determined statistical significance. All confidence intervals are given at a two-sided 95% level. Analysis was performed using SAS software version 9.4.

A Safety Committee reviewed all adverse and serious adverse events. An independent Data Monitoring Committee monitored trial progress and all serious adverse events. The trial was funded by the Health Research Council of New Zealand (13/242) with additional support from Cure Kids (3565), both grants were awarded through external peer reviewed processes. The funders had no role in trial design; data collection, analysis, or interpretation; or writing of the report. The trial was sponsored by The University of Auckland.

**Results**

Between 7th February 2014 and 17th March 2017 we screened 241 women for eligibility. Of which, 122 eligible women were recruited and randomised; 63 women were assigned to the sildenafil group and 59 women were assigned to the placebo group (Figure 1). Most women were recruited <24+0 weeks (81/122, 66.4%) and had positive umbilical artery end-diastolic velocity at randomisation (94/122, 77.0%). Baseline maternal demographic parameters and medical, obstetric and pregnancy characteristics prior to and at randomisation are shown in Tables 1 and S1.

All women received at least one dose of their intended treatment. Trial drug compliance >90% was achieved by 114 women (93.4%) (Table S2). The mean duration of trial drug use was 34.1 (±19.9) days and similar between groups (Table S2). Participants attended a mean of 6.7 (range 0-12) subsequent trial visits. The number and type of reported side effects were similar between the treatment groups (Table S2). One woman who received sildenafil therapy developed large bilateral multicystic ovarian cysts; these resolved spontaneously after birth. Five women elected to proceed with termination of pregnancy after commencing treatment; three due to severity of fetal growth restriction of a pre-viable fetus and predicted poor prognosis, one following post-randomisation diagnosis of Silver Russell syndrome and one due to fulminating preeclampsia. Two women had liveborn babies but elected not to pursue active resuscitation (severe fetal growth restriction with delivery for fulminating preeclampsia at 25 weeks, and post-randomisation diagnosis of severe coarctation of the fetal aorta). The use of antenatal corticosteroids and magnesium sulphate to optimise neonatal outcomes was high in those women where active intervention was planned (Table S2). Indications for delivery are reported in Table S2.

The primary outcome was assessed in 118 participants; in the remaining four cases, delivery or fetal death occurred within 48 hours of randomisation and so post-treatment growth velocity could not be calculated. Sildenafil did not affect the proportion of pregnancies with an increase in fetal growth velocity; 32/61 (52.5%) sildenafil-treated and 39/57 (68.4%) placebo-treated, adjusted OR 0.49, 95% CI 0.23-1.05. This lack of effect persisted with subgroup analysis of those pregnancies with positive umbilical artery end-diastolic velocity at randomisation; 27/49 (55.1%) sildenafil-treated and 30/44 (68.2%) placebo-treated, adjusted OR 0.56, 95% CI 0.24-1.33. Sildenafil had no effect on abdominal circumference Z-scores throughout time on treatment, when all cases were considered (p=0.61) (Figure S1) and when only those with positive umbilical artery end-diastolic velocity at randomisation were analysed (p=0.58).

Sildenafil use was associated with a lower mean uterine pulsatility index 48 hours after treatment commenced, 1.56 vs 1.81 p=0.02 (Table 2), but this effect was not sustained with time on treatment (p=0.27) (Figure S2). Sildenafil use had no effect on umbilical artery, middle cerebral artery or ductus venosus pulsatility index 48 hours after treatment commenced (Table 2) or with more time on treatment (Figures S3-5). Sildenafil use had no effect on amniotic fluid volume over the duration of treatment (p=0.09) (Figure S6).

Sildenafil had no effect on maternal systolic or diastolic pressure 48 hours after commencing treatment (Table 2) or throughout duration of treatment (p=0.4, Figures S7 and S8). The number of cases of new onset preeclampsia after randomisation was 9/51 (17.7%) sildenafil-treated and 14/55 (25.5%) placebo-treated, OR 0.67 (95%CI 0.26-1.75 and there was no difference in the use of new antihypertensive therapy (Table 2). The rate of caesarean delivery for all livebirths was 82/103 (79.6%) (Table 2).

Pregnancy, neonatal and infant outcome data were available for all 122 participants (Tables 3 and S3 for all participants and table S4 for those with positive umbilical artery end-diastolic velocity at randomisation). Only two cases of neonatal pulmonary hypertension were recorded; one identified in routine reporting22, and the second in adverse event reporting in association with pulmonary haemorrhage (one case sildenafil-treated and one case placebo-treated).

Most women completed postpartum questionnaires (99/122, 81.0%) and reported high levels of satisfaction with antenatal care (mean score 8.7/10) and STRIDER NZAus trial care (mean score 9.2/10). Scores were similar for those in sildenafil- and placebo-treated groups and whether their infant survived or not (Tables S4 and S5).

**Discussion**

*Main findings*

Maternal sildenafil administration was not associated with a positive effect on growth velocity in pregnancies complicated by early-onset fetal growth restriction. It could even be interpreted that sildenafil was associated with a non-significant tendency towards fewer pregnancies with an increase in growth velocity. However, it is more likely that our binary primary outcome was too crude and that the secondary outcome of change in abdominal circumference Z-score over time more accurately reflects the lack of effect. Sildenafil was associated with a short but significant positive effect on uterine artery blood flow but this was not sustained with time on treatment. We did not see any significant differences in maternal, fetal or neonatal outcomes, including the incidence of pulmonary hypertension of the newborn. However, non-significant trends towards improved perinatal outcomes, fewer cases of new-onset preeclampsia and fewer cases requiring early delivery due to preeclampsia are worthy of consideration.

*Strengths and Limitations*

This was a high quality bi-national, triple-blind, placebo-controlled randomised trial recruiting cases of clearly defined early-onset fetal growth restriction from specialised centres. A limitation of the trial is the use of an ultrasound measure to assess the primary outcome, however, inclusion of accredited maternal fetal medicine units only aimed to ensure high quality ultrasound skills and randomisation ensured observer variation was similar across groups. A further limitation is the sample size and lack of sufficient power to assess meaningful clinical outcomes. A major strength of the trial is the international STRIDER Consortium which elected to prospectively design and conduct a series of independent STRIDER trials rather than a single world-wide trial. This removed some of the challenges of study design, funding and governance and enhances the validity of results. Data were designed to be compatible for subsequent individual participant data and trial level meta-analyses to allow assessment of these meaningful clinical outcomes.14, 15

*Interpretation*

The STRIDER NZAus trial was completed prior to the early stopping of the Dutch STRIDER trial which created global media interest.25 The Dutch trial was stopped following a planned interim analysis that suggested futility to demonstrate a beneficial effect and a potential signal of harm relating to an increased incidence of persistent pulmonary hypertension of the newborn and a non-significant trend towards more neonatal deaths. Currently we await fully validated and complete outcome data from the Dutch STRIDER trial. Our trial did not demonstrate evidence of harm to the neonate; findings that are consistent with the published STRIDER UK trial which also found no association of sildenafil with persistent pulmonary hypertension of the newborn or neonatal death.25

The STRIDER UK trial and our trial were also consistent in demonstrating a lack of effect on fetal growth, measured by our UK collaborators as absolute change in abdominal circumference,26 but inconsistent with a preclinical meta-analysis assessing the effect of sildenafil during pregnancy across several animal species that reported significant positive effects on *in-utero* growth.9 It has been suggested that STRIDER trials may have selected too low a dose of sildenafil to show beneficial effects on growth and birthweight27 but any consideration of dose increases should not be made until current safety issues have been fully explored.

The non-significant trends towards improved fetal and neonatal outcomes may be chance findings. However, if the same size of effect persisted once tested in a larger group of mothers and babies without evidence of harm these would be important clinically significant differences. To date, only two other randomised placebo-controlled trials of sildenafil therapy in fetal growth restriction have reported and published birth outcomes. El-Sayed and colleagues included 54 women with preterm fetal growth restriction with a once daily 50mg dose of sildenafil or placebo. Sildenafil was associated with significant pregnancy prolongation and later gestational age at birth. There were no neonatal deaths but further neonatal and longer-term outcomes were not reported.28 The STRIDER UK trial followed the same sildenafil dosing regimen as our trial but did not see any difference in perinatal outcomes.26 Women were recruited at similar gestational ages, however, all fetuses in the UK trial had umbilical artery Doppler absent or reversed end-diastolic flow velocities at randomisation, and required delivery earlier (median gestation at birth 28 weeks) with shorter randomisation to delivery interval (median 17 days). The STRIDER UK trial included participants with more advanced disease, possibly too late for an intervention to have an ameliorating effect. Conversely our trial included some participants whose fetuses were small but had normal umbilical artery Doppler waveform. This may have represented growth restriction before the onset of advanced disease but may also include some fetuses that were constitutionally small, not at risk and less likely to respond to treatment. Our finding of a short term effect on utero-placental resistance has been demonstrated in other randomised cohorts of fetal growth restricition.11, 28, 29 This may be sufficient to enhance fetal wellbeing and allow a short pregnancy prolongation and consequent improved perinatal outcomes.28

Sildenafil has also been proposed as a therapy for preeclampsia. The first reported placebo-controlled randomised trial of sildenafil in women with early-onset preeclampsia included 35 women and did not demonstrate any difference in pregnancy prolongation (median 4 days vs 4.5 days).30 Trapani and colleagues have further tested this hypothesis in a trial of 100 women with early-onset preeclampsia randomised to 50mg sildenafil or placebo three times daily and demonstrated lowered mean arterial pressure, improved utero-placental resistance and a short but significant pregnancy prolongation (14.4 vs 10.4 days, p=0.008) although no corresponding improvement in neonatal outcomes.31 Our trial was not designed to assess the effect of sildenafil on preeclampsia although, as expected, a proportion of women had preeclampsia at the time of randomisation and some went on to develop it during their course in the trial. A non-significant trend to fewer cases of new-onset preeclampsia and preeclampsia as the delivery indication in women treated with sildenafil warrants further investigation. It is also possible that sildenafil influences fetal and infant wellbeing more directly via mechanisms such as fetal pulmonary vasculature adaptation,32 resulting in potential for benefit or harm.

To date there are no systematic reviews of phosphodiesterase type-5 inhibitor use for the treatment of fetal growth restriction in humans. The STRIDER Consortium14 and our prospectively planned individual participant data meta-analyses15 provide an excellent opportunity to further explore the effects of sildenafil, particularly in subgroup analyses. Data are stored in individual but compatible centralised data management systems making data merging and analysis efficient and simple and interpretation of results well founded. STRIDER investigators are committed to high quality reporting of all trials and formal 2-3 year outcome studies of surviving children to fully assess the potential benefits and/or harm of sildenafil therapy.

**Conclusions**

The question of whether or not sildenafil is a safe and effective therapy for fetal growth restriction remains unanswered. This trial will contribute important data to prospectively planned meta-analyses providing significant opportunity to explore this question further. In the meantime, we strongly recommend that sildenafil should only be prescribed for fetal growth restriction in the setting of high quality controlled research studies.

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STRIDER NZAus was presented to and peer reviewed by the Perinatal Society of Australia and New Zealand (PSANZ) Interdisciplinary Maternal  Perinatal Australasian Collaborative Trials (IMPACT) Clinical Trials Network for Mothers’ and Babies’ Health.

**Conflicts of Interest/Disclosures**

We declare no competing interests.

**Contribution to Authorship**

All authors contributed to the conception and design of the trial; or the acquisition, analysis, or interpretation of trial data. All authors have contributed to revision of the manuscript for important intellectual content. KG was the Chief Investigator of the trial leading conception and design of the trial, the conduct of the trial and drafting and editing of the manuscript. PB, LMcC, LM and PS contributed to conception and design of the trial, conduct of the trial and drafting and editing of the manuscript. AL was the trial statistician responsible for data analysis and contributed to drafting and editing of the manuscript. GG, JU, RS, JD, PM, RR, DW, AW, JMa, SW, JH, JMo contributed to the conduct of the trial and editing of the manuscript.

**Details of ethics approval**

New Zealand: Northern A Region multi-centre approval (CEN/12/06/028) (date of approval 2nd October 2012)**. Australia: Royal Brisbane & Women's Hospital Human Research Ethics Committee** multi-centre approval (HREC/14/QRBW/178) (date of approval 12th May 2014); King Edward Memorial Hospital (2014071EW) (date of approval 17th September 2014); and Mercy Health (R15/19) (date of approval 14th August 2015).

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References

1. McCowan LM, George-Haddad M, Stacey T, Thompson JM. Fetal growth restriction and other risk factors for stillbirth in a New Zealand setting. Aust N Z J Obstet Gynaecol. 2007;47(6):450-6.

2. Engineer N, Kumar S. Perinatal variables and neonatal outcomes in severely growth restricted preterm fetuses. Acta Obstet Gynecol Scand. 2010;89(9):1174-81.

3. Kallankari H, Kaukola T, Olsen P, Ojaniemi M, Hallman M. Very preterm birth and foetal growth restriction are associated with specific cognitive deficits in children attending mainstream school. Acta Paediatr. 2015;104(1):84-90.

4. Tedner SG, Ortqvist AK, Almqvist C. Fetal growth and risk of childhood asthma and allergic disease. Clin Exp Allergy. 2012;42(10):1430-47.

5. Barker DJ, Larsen G, Osmond C, Thornburg KL, Kajantie E, Eriksson JG. The placental origins of sudden cardiac death. Int J Epidemiol. 2012;41(5):1394-9.

6. Groom KM, David AL. The role of aspirin, heparin, and other interventions in the prevention and treatment of fetal growth restriction. Am J Obstet Gynecol. 2018;218(2S):S829-S40.

7. Dunn L, Greer R, Flenady V, Kumar S. Sildenafil in Pregnancy: A Systematic Review of Maternal Tolerance and Obstetric and Perinatal Outcomes. Fetal Diagn Ther. 2017;41(2):81-8.

8. Oyston C, Stanley JL, Oliver MH, Bloomfield FH, Baker PN. Maternal Administration of Sildenafil Citrate Alters Fetal and Placental Growth and Fetal-Placental Vascular Resistance in the Growth-Restricted Ovine Fetus. Hypertension. 2016;68(3):760-7.

9. Paauw ND, Terstappen F, Ganzevoort W, Joles JA, Gremmels H, Lely AT. Sildenafil During Pregnancy: A Preclinical Meta-Analysis on Fetal Growth and Maternal Blood Pressure. Hypertension. 2017;70(5):998-1006.

10. Stanley JL, Andersson IJ, Poudel R, Rueda-Clausen CF, Sibley CP, Davidge ST, et al. Sildenafil citrate rescues fetal growth in the catechol-O-methyl transferase knockout mouse model. Hypertension. 2012;59(5):1021-8.

11. Dastjerdi MV, Hosseini S, Bayani L. Sildenafil citrate and uteroplacental perfusion in fetal growth restriction. J Res Med Sci. 2012;17(7):632-6.

12. Wareing M, Myers JE, O'Hara M, Baker PN. Sildenafil citrate (Viagra) enhances vasodilatation in fetal growth restriction. J Clin Endocrinol Metab. 2005;90(5):2550-5.

13. von Dadelszen P, Dwinnell S, Magee LA, Carleton BC, Gruslin A, Lee B, et al. Sildenafil citrate therapy for severe early-onset intrauterine growth restriction. BJOG. 2011;118(5):624-8.

14. Ganzevoort W, Alfirevic Z, von Dadelszen P, Kenny L, Papageorghiou A, van Wassenaer-Leemhuis A, et al. STRIDER: Sildenafil Therapy In Dismal prognosis Early-onset intrauterine growth Restriction--a protocol for a systematic review with individual participant data and aggregate data meta-analysis and trial sequential analysis. Syst Rev. 2014;3:23.

15. Groom KM, Pels A, Jakobsen J, Alfirevic Z, Baker PN, Von Dadelszen P, et al. Phosphodiesterase type 5 (PDE-5) inhibitors for the treatment of fetal growth restriction: individual patient data metaanalysis. 2017.

16. Pels A, Kenny LC, Alfirevic Z, Baker PN, von Dadelszen P, Gluud C, et al. STRIDER (Sildenafil TheRapy in dismal prognosis early onset fetal growth restriction): an international consortium of randomised placebo-controlled trials. BMC Pregnancy Childbirth. 2017;17(1):440.

17. Groom KM, Baker P, McCowan LM, Stone PR, Lee AC. STRIDER (NZAus): A Randomised Controlled Trial of Sildenafil Therapy In Dismal Prognosis Early-Onset Intrauterine Growth Restriction (New Zealand and Australia) 2016 [31/08/2017].

18. Westerway SC, Davison A, Cowell S. Ultrasonic fetal measurements: new Australian standards for the new millennium. Aust N Z J Obstet Gynaecol. 2000;40(3):297-302.

19. Hadlock FP, Harrist RB, Sharman RS, Deter RL, Park SK. Estimation of fetal weight with the use of head, body, and femur measurements--a prospective study. Am J Obstet Gynecol. 1985;151(3):333-7.

20. Papageorghiou AT, Ohuma EO, Altman DG, Todros T, Cheikh Ismail L, Lambert A, et al. International standards for fetal growth based on serial ultrasound measurements: the Fetal Growth Longitudinal Study of the INTERGROWTH-21st Project. Lancet. 2014;384(9946):869-79.

21. Anderson NH, Sadler LC, Stewart AW, McCowan LM. Maternal and pathological pregnancy characteristics in customised birthweight centiles and identification of at-risk small-for-gestational-age infants: a retrospective cohort study. BJOG. 2012;119(7):848-56.

22. ANZNN, editor. Sydney, Australia, 2015.2016. Australian and New Zealand Neonatal Network. ANZNN 2016 Data Dictionary.

23. Groom KM, Mackay LK, Lee AC. STRIDER (NZAus): A Randomised Controlled Trial of Sildenafil Therapy In Dismal Prognosis Early-Onset Intrauterine Growth Restriction (New Zealand and Australia) - Statistical Analysis Plan 2017 [22/04/2018]. Available from: <https://zenodo.org/record/843527#.WtvOmmcUG3E>

24. Von Dadelszen P, Lim KI, Magee LA, Lalji S. STRIDER Canada: A Randomized Controlled Trial of Sildenafil Therapy In Dismal Prognosis Early-Onset Intrauterine Growth Restriction 2016 [31/08/2017].

25. Groom KM, Ganzevoort W, Alfirevic Z, Lim K, Papageorghiou AT, Consortium S. Clinicians should stop prescribing sildenafil for fetal growth restriction (FGR): comment from the STRIDER Consortium. Ultrasound Obstet Gynecol. 2018;52(3):295-6.

26. Sharp A, Cornforth C, Jackson R, Harrold J, Turner MA, Kenny LC, et al. Maternal sildenafil for severe fetal growth restriction (STRIDER): a multicentre, randomised, placebo-controlled, double-blind trial. Lancet Child Adolesc Health. 2017;2(2):93-102.

27. Terstappen F, Paauw N D, Joles J A, Gremmels H, T LA. No improvement of pregnancy outcomes in first STRIDER trial: result of a low dose? The Lancet Child & Adolescent Health. 2018;2(6):e11.

28. El-Sayed MA, Saleh SA, Maher MA, Khidre AM. Utero-placental perfusion Doppler indices in growth restricted fetuses: effect of sildenafil citrate. J Matern Fetal Neonatal Med. 2018;31(8):1045-50.

29. Trapani A, Jr., Goncalves LF, Trapani TF, Franco MJ, Galluzzo RN, Pires MM. Comparison between transdermal nitroglycerin and sildenafil citrate in intrauterine growth restriction: effects on uterine, umbilical and fetal middle cerebral artery pulsatility indices. Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology. 2016;48(1):61-5.

30. Samangaya RA, Mires G, Shennan A, Skillern L, Howe D, McLeod A, et al. A randomised, double-blinded, placebo-controlled study of the phosphodiesterase type 5 inhibitor sildenafil for the treatment of preeclampsia. Hypertens Pregnancy. 2009;28(4):369-82.

31. Trapani A, Jr., Goncalves LF, Trapani TF, Vieira S, Pires M, Pires MM. Perinatal and Hemodynamic Evaluation of Sildenafil Citrate for Preeclampsia Treatment: A Randomized Controlled Trial. Obstet Gynecol. 2016;128(2):253-9.

32. Iacovidou N, Syggelou A, Fanos V, Xanthos T. The use of sildenafil in the treatment of persistent pulmonary hypertension of the newborn: a review of the literature. Curr Pharm Des. 2012;18(21):3034-45.

**Table 1.** Participant Baseline Characteristics

|  |  |  |
| --- | --- | --- |
|  | **Sildenafil group (n=63)** | **Placebo group (n=59)** |
| **Maternal characteristics** | | |
| Maternal age – years | 31.4 (5.6) | 31.4 (5.5) |
| BMI - kg/m2 | 27.1 (6.9) | 26.4 (5.02) |
| Ethnicity  European  Maori  Asian  Other/unclassified | 39 (61.9)  5 (7.9)  13 (20.6)  6 (9.5) | 36 (61.0)  1 (1.7)  14 (23.7)  8 (13.6) |
| Current smoker | 5 (7.9) | 7 (11.9) |
| Pre-existing hypertension requiring medication | 3 (4.8) | 5 (8.5) |
| Pre-existing diabetes – type I or II | 0 | 1 (1.7) |
| At least one previous pregnancy ≥20 weeks | 25 (39.7) | 29 (49.2) |
| **Pregnancy characteristics prior to randomisation** | | |
| Gestational hypertension | 12 (19.1) | 7 (11.9) |
| Preeclampsia | 12 (19.1) | 4 (6.8) |
| **Pregnancy characteristics at randomisation** | | |
| Gestational age  <24+0 weeks  ≥24+0 weeks | 41 (65.1)  22 (34.9) | 40 (67.8)  19 (32.2) |
| Gestational age - weeks | 24.5 (1.7) | 24.8 (1.7) |
| Abdominal circumference percentile | 0.5 (0.8) | 0.5 (0.7) |
| Estimated fetal weighta - grammes | 479.3 (148.1) | 495.7 (170.2) |
| Umbilical artery EDFb velocity absent or reversed | 14 (22.2) | 14 (23.7) |
| Umbilical artery EDFb velocity positive  EDFb present with normal PIc ≤95th percentiled  EDFb present with abnormal PIc >95th percentiled  Intermittent absent EDFb | 49 (77.8)  36 (73.5)  10 (20.4)  3 (6.1) | 45 (76.3)  34 (75.5)  8 (17.7)  3 (6.6) |
| Uterine artery PIc (mean left and right) | 1.7 (0.7) | 1.7 (0.8) |
| Diastolic blood pressure - mm Hg | 76.4 (14.8) | 73.3 (13.1) |
| Systolic blood pressure - mm Hg | 125.3 (21.0) | 119.7 (17.5) |

Data expressed as number (%) or mean (±SD)

aEstimated fetal weight calculated by Hadlock C formula19

bEDF - end diastolic flow

cPI – pulsatility index

dUmbilical artery PI percentile

**Table 2.** Utero-placental and Fetal Doppler Flow, Maternal and Birth outcomes

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Sildenafil group (n=63)** | **Placebo group (n=59)** | **Odds ratio or**  **least squares mean difference (95%CI)** | **p value** |
| **Doppler waveform mean pulsatility index 48 hours after commencing treatment** | | | | |
| Uterine artery (mean left and right) | 1.51  (0.60) | 1.77  (0.91) | -0.25  (-0.46, -0.05)a | 0.02 |
| Umbilical artery | 1.81  (1.05) | 1.61  (0.58) | 0.04  (-0.22, 0.29)a | 0.86 |
| Middle cerebral artery | 1.73  (0.53) | 1.66  (0.52) | 0.03  (-0.15, 0.20)a | 0.74 |
| Ductus venosus | 0.83  (0.42) | 0.87  (0.71) | 0.02  (-0.17, 0.21)a | 0.82 |
| **Maternal and birth outcomes** | | | | |
| Systolic blood pressure 48 hours after commencing treatment (mm Hg) | 121.48 (14.82) | 119.91 (16.16) | -0.98  (-4.97, 3.02)a | 0.63 |
| Diastolic blood pressure 48 hours after commencing treatment (mm Hg) | 72.95  (10.83) | 73.47  (11.14) | -1.63  (-4.38, 1.12)a | 0.24 |
| New onset preeclampsia | 9/51  (17.7) | 14/55  (25.5) | 0.67  (0.26, 1.75)b | 0.41 |
| New use of antihypertensive agent | 17/63  (27.0) | 13/59  (22.0) | 1.32  (0.56, 3.12)b | 0.52 |
| Birth by caesarean section, livebirths only | 44/56  (78.6) | 38/47  (80.9) | 0.90  (0.34, 2.39)b | 0.83 |
| Postpartum haemorrhage requiring transfusion | 2/63  (3.2) | 0/59  (0) | c | c |

Data expressed as number (%) or mean (±SD)

aMixed model for repeated measure with unstructured variance covariance matrix, including treatment, time, treatment by time interaction, randomisation variables and baseline value as fixed effects, and subject as random effect. Kenward-Roger method was used to estimate the denominator degrees of freedom for fixed effects. P-values reported are the p-values at 48 hours from the treatment by time interaction effects.

bLogistic regression adjusted for gestational age at recruitment and presence/absence of umbilical artery end diastolic velocity used for binary outcomes.

cEvent rate too low for formal testing.

**Table 3.** Neonatal Outcomes

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Sildenafil group (n=63)** | **Placebo group (n=59)** | **Odds ratio or**  **least squares mean difference (95%CI)** | **p value** |
| Randomisation to delivery (or stillbirth) interval – days | 50.5  (33.1) | 45.6  (32.2) | 5.8  (-3.5, 15.1)a | 0.22 |
| Livebirth | 56/63  (88.9) | 47/59  (79.7) | 2.5  (0.80, 7.79)b | 0.11 |
| Gestational age at delivery (or stillbirth) – days | 222.2  (31.7) | 219.2  (32.3) | 4.5  (-5.1, 14.0)a | 0.35 |
| Birthweight – grammes | 1233  (774) | 1184  (823) | 64.3  (-197.0, 325.7)a | 0.63 |
| Birthweight customised percentilec | 0.04  range 0-19.8 | 0.01  range 0-50.5 | 1.10  (-0.88 to 3.08)a | 0.27 |
| Birthweight <10th customised percentilec | 38/63  (60.3) | 36/59  (61.0) | 0.94  (0.44, 2.01)b | 0.87 |
| Birthweight <5th customised percentilec | 34/63  (54.0) | 34/59  (57.6) | 0.84  (0.40, 1.75)b | 0.63 |
| Birthweight <3rd customised percentilec | 29/63  (46.0) | 32/59  (54.2) | 0.68  (0.32, 1.42)b | 0.3 |
| Neonatal death or infant death prior to hospital discharge (livebirths only) | 5/56  (8.9) | 4/47  (8.5) | d | d |
| Major neonatal morbiditye (livebirths only) | 10/56  (17.9) | 11/47  (23.4) | 0.68  (0.24, 1.89)b | 0.46 |
| Survival to hospital discharge | 51/63  (81.0) | 43/59  (72.9) | 2.16  (0.75, 6.21)b | 0.15 |
| Survival to hospital discharge free of major neonatal morbidity|| | 42/63  (66.7) | 33/59  (55.9) | 1.93  (0.84, 4.45)b | 0.12 |
| Neonatal intensive care unit admissionf | 33/56  (58.9) | 24/47  (51.1) | 1.38  (0.63, 3.00)b | 0.42 |
| Duration of neonatal intensive care unit admission - daysg | 22.9 (31.1)  range 0-107 | 25.6 (34.6)  range 0-123 | - | 0.81 |
| Duration of hospital stay - daysg | 49.3 (44.8)  range 0-183 | 46.3 (39.4)  range 0-123 | - | 0.79 |

Data expressed as number (%) or mean (±SD)

aMultiple linear regression adjusted for gestational age at recruitment, presence/absence of umbilical artery end diastolic velocity and presence/absence of preeclampsia. Results expressed as observed mean (SD) and least squares mean difference (95% CI).

bLogistic regression adjusted for gestational age at recruitment, presence/absence of umbilical artery end diastolic velocity and presence/absence of preeclampsia. Results expressed as observed number n/N (%) and adjusted odds ratio (95% CI).

cCustomised birthweight percentiles adjusting for infant sex, gestation at delivery, and maternal variables (parity, ethnicity, height, and early pregnancy weight) were used to identify SGA infants.21

dEvent rate too low for formal testing.

eMajor neonatal morbidity defined as need for ambulatory oxygen >36 weeks corrected gestational age, intraventricular haemorrhage grade 3-4, periventricular leukomalacia, retinopathy of prematurity ≥grade 3 requiring treatment and/or necrotising enterocolitis requiring surgery. Individual components of composite neonatal outcome are shown in supplementary tables.

fUnadjusted Chi square test. Results expressed as observed number n/N (%) and unadjusted odds ratio (95% CI).

gWilcoxon two sample test. Results expressed as observed mean (SD) and range.