

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

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65 **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 child^{3, 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 studies^{11, 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

137 severe early-onset fetal growth restriction. The trial was designed in collaboration with
138 investigators from other national STRIDER trials within the STRIDER Consortium.¹⁴
139 Each trial has been independently funded and executed and will be published as an
140 individual trial. Prospectively planned individual participant data and trial level meta-
141 analyses will allow assessment of outcomes up to 2-3 years corrected age.^{14, 15}
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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

168 48 hours; or any contraindication to maternal sildenafil therapy. All women
169 participating in the trial provided written informed consent.

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

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

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

190 Each participant was supplied with a trial drug bottle containing 30 tablets and a
191 subject medication diary. Repeat study drug bottles and diaries were issued as
192 required. Compliance was assessed by investigators at each trial visit by pill counts

193 and diary review; cross-checked centrally against drug accountability logs.
194 Compliance was calculated as a percentage expected/actual tablets taken over
195 duration of active trial period. Participants were encouraged to note adverse effects in
196 the subject medication diary. Additional indications to stop trial drug were maternal
197 request and investigator or clinician safety concern.

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

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

291 The primary outcome was assessed in 118 participants; in the remaining four cases,
 292 delivery or fetal death occurred within 48 hours of randomisation and so post-treatment
 293 growth velocity could not be calculated. Sildenafil did not affect the proportion of
 294 pregnancies with an increase in fetal growth velocity; 32/61 (52.5%) sildenafil-treated
 295 and 39/57 (68.4%) placebo-treated, adjusted OR 0.49, 95% CI 0.23-1.05. This lack of
 296 effect persisted with subgroup analysis of those pregnancies with positive umbilical
 297 artery end-diastolic velocity at randomisation; 27/49 (55.1%) sildenafil-treated and
 298 30/44 (68.2%) placebo-treated, adjusted OR 0.56, 95% CI 0.24-1.33. Sildenafil had
 299 no effect on abdominal circumference Z-scores throughout time on treatment, when
 300 all cases were considered ($p=0.61$) (Figure S1) and when only those with positive
 301 umbilical artery end-diastolic velocity at randomisation were analysed ($p=0.58$).
 302 Sildenafil use was associated with a lower mean uterine pulsatility index 48 hours after
 303 treatment commenced, 1.56 vs 1.81 $p=0.02$ (Table 2), but this effect was not sustained
 304 with time on treatment ($p=0.27$) (Figure S2). Sildenafil use had no effect on umbilical
 305 artery, middle cerebral artery or ductus venosus pulsatility index 48 hours after
 306 treatment commenced (Table 2) or with more time on treatment (Figures S3-5).
 307 Sildenafil use had no effect on amniotic fluid volume over the duration of treatment
 308 ($p=0.09$) (Figure S6).
 309 Sildenafil had no effect on maternal systolic or diastolic pressure 48 hours after
 310 commencing treatment (Table 2) or throughout duration of treatment ($p=0.4$, Figures
 311 S7 and S8). The number of cases of new onset preeclampsia after randomisation was
 312 9/51 (17.7%) sildenafil-treated and 14/55 (25.5%) placebo-treated, OR 0.67 (95%CI
 313 0.26-1.75 and there was no difference in the use of new antihypertensive therapy
 314 (Table 2). The rate of caesarean delivery for all livebirths was 82/103 (79.6%) (Table
 315 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 restriction.^{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.

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429 **Conclusions**

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

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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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592 **Table 1.** Participant Baseline Characteristics
593

	Sildenafil group (n=63)	Placebo group (n=59)
Maternal characteristics		
Maternal age – years	31.4 (5.6)	31.4 (5.5)
BMI - kg/m ²	27.1 (6.9)	26.4 (5.02)
Ethnicity		
European	39 (61.9)	36 (61.0)
Maori	5 (7.9)	1 (1.7)
Asian	13 (20.6)	14 (23.7)
Other/unclassified	6 (9.5)	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	41 (65.1)	40 (67.8)
≥24+0 weeks	22 (34.9)	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 weight ^a - grammes	479.3 (148.1)	495.7 (170.2)
Umbilical artery EDF ^b velocity absent or reversed	14 (22.2)	14 (23.7)
Umbilical artery EDF ^b velocity positive	49 (77.8)	45 (76.3)
EDF ^b present with normal PI ^c ≤95 th percentile ^d	36 (73.5)	34 (75.5)
EDF ^b present with abnormal PI ^c >95 th percentile ^d	10 (20.4)	8 (17.7)
Intermittent absent EDF ^b	3 (6.1)	3 (6.6)
Uterine artery PI ^c (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)

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

595 ^aEstimated fetal weight calculated by Hadlock C formula¹⁹

596 ^bEDF - end diastolic flow

597 ^cPI – pulsatility index

598 ^dUmbilical artery PI percentile

599

600 **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

601 Data expressed as number (%) or mean (\pm SD)

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

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

609 ^cEvent rate too low for formal testing.

610

611 **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 percentile ^c	0.04 range 0- 19.8	0.01 range 0- 50.5	1.10 (-0.88 to 3.08) ^a	0.27
Birthweight <10 th customised percentile ^c	38/63 (60.3)	36/59 (61.0)	0.94 (0.44, 2.01) ^b	0.87
Birthweight <5 th customised percentile ^c	34/63 (54.0)	34/59 (57.6)	0.84 (0.40, 1.75) ^b	0.63
Birthweight <3 rd customised percentile ^c	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 morbidity ^e (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 ^{ll}	42/63 (66.7)	33/59 (55.9)	1.93 (0.84, 4.45) ^b	0.12
Neonatal intensive care unit admission ^f	33/56 (58.9)	24/47 (51.1)	1.38 (0.63, 3.00) ^b	0.42
Duration of neonatal intensive care unit admission - days ^g	22.9 (31.1) range 0-107	25.6 (34.6) range 0-123	-	0.81
Duration of hospital stay - days ^g	49.3 (44.8) range 0-183	46.3 (39.4) range 0-123	-	0.79

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

613 ^aMultiple linear regression adjusted for gestational age at recruitment,
614 presence/absence of umbilical artery end diastolic velocity and presence/absence of
615 preeclampsia. Results expressed as observed mean (SD) and least squares mean
616 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 \geq 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.