The Canadian STRIDER Randomised Controlled Trial of Sildenafil for Severe, Early-onset Fetal Growth Restriction

Peter von Dadelszen (pvd@kcl.ac.uk)
King's College London https://orcid.org/0000-0003-4136-3070
François Audibert
University of Montreal: Universite de Montreal
Emmanuel Bujold
Laval University Faculty of Medicine: Universite Laval Faculte de medecine
Jeffrey N Bone
The University of British Columbia
Ash Sandhu
The University of British Columbia
Jing Li
The University of British Columbia
Chirag Kariya
The University of British Columbia
Youkee Chung
The University of British Columbia
Tang Lee
The University of British Columbia
Kelvin Au
The University of British Columbia
M Amanda Skoll
The University of British Columbia
Marianne Vidler
The University of British Columbia
Laura A Magee
King's College London
Bruno Piedboeuf
Laval University: Universite Laval
Philip N Baker
University of Leicester
Sayrin Lalji

The University of British Columbia

Kenneth I Lim

The University of British Columbia

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Abstract

Objectives

To determine the efficacy and safety of sildenafil citrate to improve outcomes in pregnancies complicated by early-onset, dismal prognosis, fetal growth restriction (FGR). Eligibility: women ≥18 years, singleton, 18 +0–27 +6 weeks' gestation, estimated fetal weight <700g, and ≥1 of (i) abdominal circumference <10 th percentile for gestational age (GA); or (ii) reduced growth velocity and either abnormal uterine artery Doppler or prior early-onset FGR with adverse outcome. Ineligibility criteria included: planned termination or reversed umbilical artery end-diastolic flow. Eligibility confirmed by placental growth factor <5 th percentile for GA. Women randomly received (1:1) either sildenafil 25 mg three times daily or matched placebo until either delivery or 31 +6 weeks. Primary outcome: delivery GA. The trial stopped early when the Dutch STRIDER trial signalled potential harm. NCT02442492 [registered 13/05/2015].

Results

Between May 2017 and June 2018, 21 (90 planned) women were randomised (10 sildenafil; 11 placebo [1 withdrawal]). Baseline characteristics, PlGF levels, maternal and perinatal outcomes, and adverse events did not differ. Delivery GA: 30 +1 weeks (sildenafil) vs 28 +6 weeks (placebo); p=0.555. Early trial termination precluded statistical power; however, there were signals of neither benefit nor harm. Data will contribute to an individual participant data meta-analysis.

Introduction

Women with pregnancies complicated by severe, early-onset fetal growth restriction (FGR) have limited options. A 50% chance of intact perinatal survival (i.e., survival without major complications of prematurity or perinatal asphyxia) requires both birth at least at 28 +0 weeks' and birth weight of at least 700g (1). Therefore, in the absence of effective pharmacological interventions, intensive fetal surveillance is employed to prolong pregnancies for as long as possible until either fetal or maternal deterioration requires delivery (2).

Antenatally, the performance of combined ultrasound estimates of fetal biometry and Doppler waveform indices to discriminate early-onset FGR due to placental dysfunction from constitutionally-small fetuses (2) can be improved by determining maternal plasma placental growth factor (PlGF) <5 th percentile for gestational age (GA) (3).

As sildenafil citrate vasodilates the myometrial arteries isolated from women with FGR-complicated pregnancies (4), 10 women attending BC Women's Hospital were offered sildenafil (25 mg three times daily until delivery) if their pregnancy was complicated by early-onset FGR (abdominal circumference [AC] <5 th percentile) and either the gestational age (GA) was <25 +0 weeks or an estimate of fetal weight was <600 g (excluding known fetal anomaly/syndrome and/or planned termination) (5). Sildenafil treatment

was associated with increased fetal AC growth, compared with 17 institutional sildenafil-naive early-onset FGR controls]) (5).

Therefore, as part of an international consortium of STRIDER (Sildenafil TheRapy in dismal prognosis early onset fetal growth restriction) trials co-ordinated from the University of British Columbia's PRE-EMPT research group and in support of the Global Obstetric Network (GONet) (6), a Canadian STRIDER randomised controlled trial was undertaken.

Main Text

The STRIDER Canada trial was a national multisite individual participant double-blind, placebo-controlled randomised controlled trial (NCT02442492 [registered 13 May 2015]). (Figure 1. CONSORT diagram). An independent Data Safety Monitoring Board (DSMB) monitored the progress of the trial and all serious adverse events (SAEs). As the trial was halted early, only three sites became active, BC Women's Hospital and Health Centre (BC Women's, Vancouver), Ste Justine (Montréal), and Centre hospitalier universitaire de Québec (Québec).

Recruitment

Women were eligible to be approached to provide written informed consent if they were aged ≥18 years with a singleton pregnancy at 18 +0 – 27 +6 weeks' gestation, estimated fetal weight <700g, and at least one of (i) fetal AC <10 th percentile for GA (local criteria); or (ii) reduced fetal growth velocity (<50% of anticipated) and either abnormal uterine artery Doppler or prior early-onset FGR with adverse perinatal outcome (defined as either a perinatal or infant death related to FGR or a life-altering complication of either prematurity or FGR [e.g., hypoxic-ischaemic encephalopathy, cerebral palsy, or chronic lung disease]).

Exclusion criteria were (i) decision made to terminate the index pregnancy; (ii) reversed end-diastolic flow by umbilical artery Doppler; (iii) prior participation in a STRIDER trial; (iv) maternal factors (e.g., pre-eclampsia or gestational hypertension [index pregnancy]; known HIV positive status [drug-drug interaction between sildenafil and antiretrovirals]; known significant maternal heart disease; current cocaine or crystal meth drug use; receiving prazosin, other peripheral alpha-blockers, or nitrates; or allergy to sildenafil); or (v) fetal factors (e.g., known aneuploidy, anomaly, syndrome, or congenital infection confirmed at enrolment).

Once consent had been obtained, eligibility was confirmed in real-time by Alere (San Diego, CA) Triage™ plasma PlGF <5 th percentile for GA (7); for gestational ages 18 +0 – 20 +0 weeks, the 5 th percentile was determined from samples from women attending the BC Women's EMMA (Evaluating Maternal Markers of Adverse placental outcomes) Clinic at 16 +0 – 24 +0 weeks who delivered normally-grown infants (10th – 90th percentile for GA) at term without either hypertension or diabetes. The EMMA Clinic 5 th percentile PlGF values were contiguous with the NORMALS cohort 5% percentile line (7).

Randomisation

Randomisation was centrally controlled using a web-based computerised randomisation platform integrated System for Trial Allocation and Randomisation (iSTAR) developed by the PRE-EMPT (PREgnancy Evidence, Monitoring, Partnerships & Treatment) team, BC Children's Hospital Research Institute (BCCHR). Randomisation was stratified by centre with random blocks of 2 or 4. Women were randomised to receive either sildenafil (25mg three times daily) or matched placebo (three times daily). Each study drug bottle contained 30 over-encapsulated capsules (to mask arms), equivalent to a 10-day supply of either sildenafil or placebo. Sildenafil tablets were sourced from Pharmascience Inc (DIN 02317559). The Bay Area Health Trust (BARL), ON, made placebo capsules through the process of over-encapsulation.

Follow-up

STRIDER Canada was a pragmatic trial; in the absence of standardised care available at all participating centres, the Canadian STRIDER trial protocol allowed centres to provide their usual pattern of care. All women received enhanced fetal and maternal surveillance based on concurrent Society of Obstetricians and Gynaecologists of Canada guidance regarding the diagnosis management of FGR (8).

At enrolment, baseline data were collected regarding current and past medical history and demographics including ethnicity, past obstetric history, medication use, allergies, aneuploidy screening, invasive testing, and congenital infection results.

Fetal biometry (biparietal diameter, head circumference, AC, and femur length) and Doppler indices (uterine artery, umbilical artery, middle cerebral artery, and ductus venosus) were collected from the latest pre-randomisation ultrasound scan. Similarly, data for maternal assessment prior to randomisation were collected for PlGF, complete blood count, renal (creatinine, urea) and liver function (aspartate and alanine transaminase, albumin), urinalysis, and blood pressure measurements. Doppler indices, PlGF testing, and blood pressure measurements were repeated at 48 hours post-1st dose. All participants undertook weekly maternal and fetal assessments and PlGF testing. Other clinically-indicated care was undertaken as per local practice or at the discretion of a treating clinician. No special restrictions were required with regards to diet, activities, or other lifestyle items.

In addition, each participant was given a patient medication diary and were encouraged to note any missed doses, adverse events, and symptoms. The dairy and pill counts were reviewed by the study team during antenatal visits.

Decisions to deliver were made by the treating physicians according to local practice. If undelivered, all participants discontinued the study drug once they reached 31 +6 weeks GA.

Outcomes

Primary outcome: gestational age at delivery (d) (sildenafil vs placebo). The unit of analysis was ‘fetus’. Secondary outcomes: livebirth, survival to hospital discharge, intact discharge, and combined non-CNS severe morbidity.

Stopping rule

Stopping rule: STRIDER Canada would be halted if two other STRIDER trials determined any potential benefit or harm before the STRIDER Canada trial was completed.

Data management

All data were entered into a REDCap (Research Electronic Data Capture, Vanderbilt University) platform developed and co-ordinated on behalf of all the STRIDER trials by the PRE-EMPT team. This approach was to facilitate the *a priori* planned STRIDER consortium individual participant data (IPD) meta-analysis (9).

Statistical analyses

Continuous variables were reported as means [95% confidence interval (CI)] for the between-arm mean difference. Categorical variables were presented as counts (percentages) and compared using chi-squared tests. $P<0.05$ was considered statistically significant. Data were analysed in R statistical software (version 3.6.3; R Foundation for Statistical Computing, Vienna, Austria).

Halting the trial

The STRIDER Canada trial was halted when the highly-publicised interim analysis of the Dutch STRIDER signaled the potential for harm to the neonate (increased risk in persistent pulmonary hypertension of the newborn) and a non-significant trend towards increased neonatal mortality (10). Initially, the trial was halted to enable a full and considered review of the evidence at that time, without exposing more pregnancies to potential harm. At that time, the UK group had published their results (11) and the STRIDER NZAus group had completed their trial, but not yet published their results (12); neither trial had identified any signal of benefit from sildenafil. Consultations were held within the trial steering group, with the UBC Clinical Research Ethics Board, and the DSMB. While no party felt that it would unethical to continue with the trial as the STRIDER Canada was recruiting women earlier, requiring low PlGF as an entry criterion, and not recruiting women with persistent reversed umbilical artery end-diastolic flow, the consensus was that it would be futile to continue given both the publicity and lack of evidence of potential benefit from either the NZAus or UK STRIDER trials. Therefore, the trial was halted.

Results

Between May 1, 2017 and June 28, 2018, 21 women gave informed consent and were recruited to the STRIDER Canada trial (trial profile, Figure 1).

At the time of halting the trial, nine women were randomized to the placebo arm and 11 to the sildenafil arm, with one post-randomization withdrawal from the placebo arm prior to commencing placebo medication. No women were actively participating in the trial when it was halted early, as all had delivered.

Recruited women were generally in their early 30s, nulliparous, overweight, Caucasian, and normotensive; recruitment was at around 22 weeks' gestation (Table 1). Fetuses were generally very growth restricted with uniform evidence of feto-placental compromise in terms of either abnormal uterine or umbilical artery or ductus venosus Doppler waveforms or critically-low maternal plasma PlGF levels.

Table 1
Baseline Characteristics (number (percent); median [interquartile range])

Variable	Placebo (n=9)	Sildenafil (n=11)	P-value*
Maternal age at estimated date of delivery (years)	30.0 [29.0, 31.0]	33.5 [31.5, 37.3]	0.109
Nulliparity	5 (55.6%)	6 (54.5%)	0.964
Height (cm)	160.0 [160.0, 165.0]	159.0 [155.5, 165.8]	0.471
Weight (kg)	75.0 [68.7, 77.7]	69.4 [59.0, 83.7]	0.743
Body-mass index	27.1 [24.7, 29.3]	27.6 [22.4, 34.3]	0.543
Ethnicity			0.514
Caucasian	7 (77.8%)	6 (54.5%)	
Afro-Canadian	1 (11.1%)	2 (18.2%)	
South or East Asian	0 (0%)	2 (18.2%)	
Other	1 (11.1%)	1 (9.1%)	
Current smoker	0 (0%)	1 (9.1%)	1.000
Current antihypertensive treatment	0 (0%)	1 (9.1%)	1.000
Gestational diabetes	1 (11.1%)	0 (0%)	0.918
Preterm prelabour rupture of membrane	0 (0%)	0 (0%)	NA
Systolic blood pressure with the highest prerandomization sBP (mmHg)	124.0 [108.0, 132.0]	124.0 [106.5, 136.0]	0.760
Diastolic blood pressure with the highest prerandomization dBP (mmHg)	72.0 [67.0, 75.0]	76.0 [70.5, 84.0]	0.127
Creatinine (µmol/L)	55.5 [53.75, 58.25]	56.0 [49.0, 57.8]	0.831
Uric acid (µmol/L)	265 [253, 278]	220 [210, 250]	0.571
Abnormal uterine artery Doppler †	6 (66.7%)	6 (54.5%)	1.00
Fetal abdominal circumference <1st percentile for GA	6 (66.7%)	8 (72.7%)	0.659

* Fisher's exact (dichotomous) or Mann Whitney U (continuous) test

† elevated uterine artery pulsatility index for gestational age or persistent unilateral or bilateral notching

Variable	Placebo (n=9)	Sildenafil (n=11)	P-value*
Estimated fetal weight (g)	301.0 [240.0, 488.0]	246.0 [234.5, 389.5]	0.403
Estimated fetal weight <500g	6 (66.7%)	9 (82.0%)	0.432
Umbilical artery Doppler end-diastolic flow			0.537
Intermittently absent	2 (22.2%)	1 (9.1%)	
Persistently absent	3 (33.3%)	2 (18.2%)	
Intermittently reversed	0 (0%)	1 (9.1%)	
Reversed ductus venosus a-wave	0 (0%)	2 (18.2%)	0.600
Maternal PlGF (immediately prior to randomization)	12.0 [12.0, 12.0]	12.0 [12.0, 19.8]	0.447
GA at PlGF collection, eligibility & randomisation (weeks + days)	22^{+4} [21^{+5}, 25^{+5}]	21^{+5} [21^{+4}, 23^{+5}]	0.379
* Fisher's exact (dichotomous) or Mann Whitney U (continuous) test			
† elevated uterine artery pulsatility index for gestational age or persistent unilateral or bilateral notching			

There were no differences between arms in the primary outcome (gestational age birth) or markers of maternal or perinatal compromise (Table 2). Of note, the two cases of PPHN occurred in neonates exposed to sildenafil, consistent with the Dutch experience (10)..

Table 2
Primary, Maternal, and Perinatal Outcomes (number (percent); median [interquartile range])

Outcome	Placebo (n=9)	Sildenafil (n=11)	P-value*
Primary outcome			
Gestational age at delivery (weeks + days)	29^{+2} [28^{+1}, 34^{+1}]	26^{+4} [25^{+6}, 31^{+0}]	0.200
Maternal			
Symptomatic hypotension	0 (0%)	0 (0%)	NA
Pre-eclampsia	3 (33.3%)	0 (0%)	0.211
Mode of delivery			0.348
Termination of pregnancy	1	4	
Vaginal birth	0	1	
Classical Caesarean section	4	4	
Lower segment Caesarean section	4	2	
Haemorrhage requiring transfusion	1 (11.1%)	0 (0%)	0.918
Perinatal			
Fetal growth velocity			
Biparietal diameter (mm/d)	0.36 [0.32, 0.49]	0.37 [0.26, 0.39]	0.508
Head circumference (mm/d)	1.28 [1.03, 2.07]	1.21 [1.04, 1.52]	0.605
Abdominal circumference (mm/d)	1.05 [0.97, 1.21]	1.37 [1.10, 1.38]	0.310
Femur length (mm/d)	0.28 [0.20, 0.31]	0.24 [0.16, 0.30]	0.627
Estimated fetal weight (g/d)	10.80 [6.07, 11.82]	7.19 [5.62, 9.40]	0.667
Deepest vertical amniotic fluid pocket (mm/d)	0.007 [0.000, 0.009]	0.013 [0.007, 0.070]	0.181
Stillbirth	1 (11.1%)	4 (36%)	0.436
Neonatal death	1 (11.1%)	1 (9%)	1
Intact survival†	7 (77.8%)	6 (55%)	0.528

* Fisher's exact (dichotomous) or Mann Whitney U (continuous) test

† defined as survival to estimated due date without evidence of severe central nervous system injury (by ultrasound and/or magnetic resonance imaging)

Outcome	Placebo (n=9)	Sildenafil (n=11)	P-value*
Persistent pulmonary hypertension of the newborn	0 (0%)	2 (18%)	0.164
* Fisher's exact (dichotomous) or Mann Whitney U (continuous) test			
† defined as survival to estimated due date without evidence of severe central nervous system injury (by ultrasound and/or magnetic resonance imaging)			

Limitations

Halted early in response to safety concerns and no evidence of efficacy, the STRIDER Canada trial was underpowered to provide any meaningful data as an isolated trial. However, because of the *a priori* planned IPD meta-analysis (9), the data from the trial will inform analysis of the larger international experience of sildenafil for early-onset FGR.

Although ethical review of the trial at the time of the Dutch data being publicised determined that it would be ethical to continue with the STRIDER Canada trial, given that the Canadian trial recruited earlier in gestation than the other trials and was the sole trial that required PlGF <5th percentile for GA as an eligibility criterion, the publicity was such that it was felt to make the trial unfeasible, especially as there was no signal of benefit in either of the completed trials (NZAus and UK).

The major strength of this undertaking was the ability to engage with varied international funders (Health Research Council of New Zealand, UK National Institute of Health Research, ZonMw [Netherlands], Health Research Board [Ireland (trial halted prior to initiation)], and CIHR) to fund a group of individually-powered trials with primary outcomes that are surrogates of risk, in the knowledge that the GONet consortium had established an *a priori* plan for the ongoing IPD meta-analysis. All funders agreed to the data being managed by a central team (UBC PRE-EMPT) using a shared REDCap database on a shared server (9). We believe that this is a model that should be considered for future obstetric trials to enable adequate sample sizes to examine less common, but more important outcomes. In this instance, the IPD meta-analysis primary outcome for babies is being alive at term gestation without evidence of serious adverse neonatal outcome (severe central nervous system injury (severe intraventricular haemorrhage [grades 3 and 4] or cystic periventricular leukomalacia, demonstrated by ultrasound and/or magnetic resonance imaging), or other severe morbidity [bronchopulmonary dysplasia, retinopathy of prematurity requiring treatment, or necrotising enterocolitis requiring surgery]).

Despite leading the examination of a potential role for sildenafil for the indication of severe, early-onset FGR (5), in that original paper we had stated that we did not believe that sildenafil should be prescribed outside either a randomised controlled trial or the perinatal pharmacological surveillance then provided by the Hospital for Sick Children's Motherisk Program. We are aware that a number of women were prescribed sildenafil for this indication internationally. This should no longer be the case (13).

International consortia are important to develop, co-fund, and deliver RCTs designed *a priori* for IPD meta-analyses for important, but uncommon, pregnancy complications. Having been halted early, the STRIDER Canada trial is underpowered to provide any independent guidance about the advisability of sildenafil use in pregnancy. However, the GONet consortium of STRIDER trials IPD meta-analysis means that the STRIDER Canada trial data will contribute to a meaningful analysis.

List Of Abbreviations

AC, abdominal circumference; BC, British Columbia; CIHR, Canadian Institutes of Health Research; DSMB, data safety and monitoring board; EMMA, Evaluating Maternal Markers of Adverse placental outcomes; FGR, fetal growth restriction; GA, gestational age; GONet, Global Obstetric Network; IPD, individual participant data; iSTAR, integrated System for Trial Allocation and Randomisation; NZAus, NZ-Australia; PlGF, placental growth factor; PPHN, persistent pulmonary hypertension of the newborn; PRE-EMPT, PREgnancy - Evidence, Monitoring, Partnerships & Treatment); STRIDER, Sildenafil TheRapy in dismal prognosis early onset fetal growth restriction; UBC, University of British Columbia

Declarations

Ethics approval and consent to participate

The study protocol was approved by the UBC Children's and Women's Research Ethics Board (REB) (H15-00899) and received a No Objection Letter (NOL) from Health Canada (NOL number: HC6-24-C1864589). All participants read and signed an approved informed consent form prior to PlGF measurement and randomisation.

Consent for publication

N/A

Availability of data and materials

Data are being shared with the STRIDER IPD consortium and are available through direct contact with the STRIDER Canada Trial team at STRIDERCanada@cw.bc.ca.

Competing interests

PvD has received support from Alere International.

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Authors' contributions

Trail conceptualisation: PvD, LAM, PNB; protocol and trial funding application: PvD, FA, EB, MAS, MV, LAM, BP, PNB, SL, KIL; trial database, management, and statistical analyses: JNB, AS, JL, CK, YC, TL. KA, MV; manuscript writing and revisions: all authors

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Figures

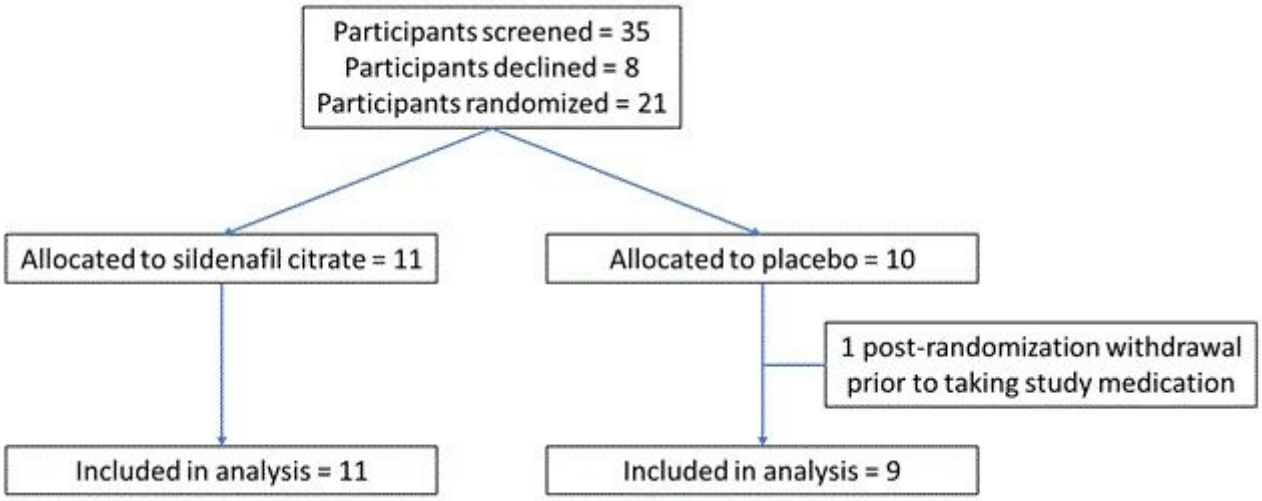

Figure 1

STRIDER Canada Trial Profile

Supplementary Files

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