Maternal Sildenafil vs Placebo in Pregnant Women With Severe Early-Onset Fetal Growth Restriction
A Randomized Clinical Trial

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Abstract

IMPORTANCE Severe early onset fetal growth restriction caused by placental dysfunction leads to high rates of perinatal mortality and neonatal morbidity. The phosphodiesterase 5 inhibitor, sildenafil, inhibits cyclic guanosine monophosphate hydrolysis, thereby activating the effects of nitric oxide, and might improve uteroplacental function and subsequent perinatal outcomes.

OBJECTIVE To determine whether sildenafil reduces perinatal mortality or major morbidity.

DESIGN, SETTING, AND PARTICIPANTS This placebo-controlled randomized clinical trial was conducted at 10 tertiary referral centers and 1 general hospital in the Netherlands from January 20, 2015, to July 16, 2018. Participants included pregnant women between 20 and 30 weeks of gestation with severe fetal growth restriction, defined as fetal abdominal circumference below the third percentile or estimated fetal weight below the fifth percentile combined with Dopplers measurements outside reference ranges or a maternal hypertensive disorder. The trial was stopped early owing to safety concerns on July 19, 2018, whereas benefit on the primary outcome was unlikely. Data were analyzed from January 20, 2015, to January 18, 2019. The prespecified primary analysis was an intention-to-treat analysis including all randomized participants.

INTERVENTIONS Participants were randomized to sildenafil, 25 mg, 3 times a day vs placebo.

MAIN OUTCOMES AND MEASURES The primary outcome was a composite of perinatal mortality or major neonatal morbidity until hospital discharge.

RESULTS Out of 360 planned participants, a total of 216 pregnant women were included, with 108 women randomized to sildenafil (median gestational age at randomization, 24 weeks 5 days [interquartile range, 23 weeks 3 days to 25 weeks 5 days]; mean [SD] estimated fetal weight, 458 [160] g) and 108 women randomized to placebo (median gestational age, 25 weeks 0 days [interquartile range, 22 weeks 5 days to 26 weeks 3 days]; mean [SD] estimated fetal weight, 464 [186] g). In July 2018, the trial was halted owing to concerns that sildenafil may cause neonatal pulmonary hypertension, whereas benefit on the primary outcome was unlikely. The primary outcome, perinatal mortality or major neonatal morbidity, occurred in the offspring of 65 participants (60.2%) allocated to sildenafil vs 58 participants (54.2%) allocated to placebo (relative risk, 1.11; 95% CI, 0.88-1.40; P = .38). Pulmonary hypertension, a predefined outcome important for monitoring safety, occurred in 16 neonates (18.8%) in the sildenafil group vs 4 neonates (5.1%) in the placebo group (relative risk, 3.67; 95% CI, 1.28-10.51; P = .008).

(continued)
CONCLUSIONS AND RELEVANCE  These findings suggest that antenatal maternal sildenafil administration for severe early onset fetal growth restriction did not reduce the risk of perinatal mortality or major neonatal morbidity. The results suggest that sildenafil may increase the risk of neonatal pulmonary hypertension.

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Introduction

Severe early onset fetal growth restriction is a rare condition, complicating approximately 0.4% of all pregnancies.\(^1,2\) It is associated with a high risk of fetal death, iatrogenic preterm birth, long-lasting stay at the neonatal intensive care unit, neonatal mortality, and long-term morbidity.\(^3,4\) Severe early-onset fetal growth restriction is also strongly associated with neurodevelopmental impairment later in childhood.\(^5,6\) To our knowledge, no effective treatment to promote fetal growth has been identified, and management consists of intensive monitoring to determine the best moment to deliver the fetus, balancing the consequences of prematurity vs undernutrition and hypoxia.\(^7\)

Recently, phosphodiesterase type 5 inhibitors, most often sildenafil, have been investigated as potential treatment for fetal growth restriction.\(^8-16\) The Sildenafil Therapy in Dismal Prognosis Early Onset Fetal Growth Restriction (STRIDER) consortium designed and conducted in synchrony 4 randomized clinical trials to study sildenafil's hypothesized improvement of placental circulation through its effects on the uteroplacental circulation.\(^8-16\) In the Dutch STRIDER trial, the hypothesis that sildenafil reduces the chance of perinatal mortality and morbidity was tested using a composite outcome of perinatal mortality and major neonatal morbidity.

Methods

We conducted this placebo-controlled randomized clinical trial in 10 tertiary care centers and 1 general hospital in the Netherlands. Ethical approval was granted by Amsterdam UMC. All participating women provided written informed consent. The protocol was registered on September 29, 2014 (Trial Protocol in Supplement 1), before the first participant was randomized. This study is reported following the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline.

Study Design

An independent data safety monitoring board (DSMB) monitored the safety of the participants after data were available for each 50 participants, as well as the efficacy after the outcomes were known for half of the participants.\(^17\) The DSMB charter included the provision to recommend stopping the trial in case the safety of current or future participants was considered to be compromised. Furthermore, a stopping rule was included, indicating that the trial would be stopped if a significant difference between the 2 treatment groups was observed at interim analysis (according to the O'Brien-Fleming spending function, \(P < .005\)).

Participants

Pregnant women were eligible if they were between 20 weeks 0 days and 27 weeks 6 days of gestation and if the fetal abdominal circumference was below the 3rd percentile or the estimated fetal weight (EFW) below the 5th percentile, combined with either unilateral or bilateral notching of the uterine artery, Pulsatility Index (PI) of the umbilical artery above the 95th percentile, PI of the middle cerebral artery below the 5th percentile, or a maternal hypertensive disorder. Participants
with gestation between 28 weeks 0 days and 29 weeks 6 days were eligible if the EFW was less than 700 g, combined with the aforementioned Doppler anomalies or a maternal hypertensive disorder, to select the patients with unfavorable prognosis. Gestational age estimation was based on a first trimester ultrasound. Exclusion criteria were anticipated imminent termination of pregnancy for maternal or fetal indications, multifetal pregnancy, identified congenital anomalies (affecting outcomes), identified congenital infection, maternal age younger than 18 years, cocaine use, current use of sildenafil, current use of cytochrome P450 3A5 isozyme inhibitors, and recent myocardial infarction or stroke.

Maternal race/ethnicity was collected because maternal race/ethnicity is associated with placental dysfunction and pregnancy outcomes. Whether the maternal race/ethnicity was European descent, African descent, or Asian descent was indicated by the investigator. In case of doubt, the patient was asked to report her race/ethnicity.

In participating centers, samples of maternal blood were collected at randomization by venipuncture and stored at −80 °C for batch testing of placental growth factor (PGF) level. Measurement of PGF level was performed on the Kryptor immunoassay (Thermo Fisher Scientific) and compared with the fifth percentile of a reference population (ie, 106.54 pg/mL).

Randomization and Masking
The web-based randomization had a 1:1 ratio, random block sizes of 2 to 6, and was stratified per participating center. Participants, clinicians, investigators, and outcome assessors were blinded for the treatment allocation.

Procedures
Trial medication was manufactured specifically for this trial by Tiofarma, and tablets contained either sildenafil 25 mg or placebo and were taken orally 3 times daily. Active and placebo medications were matching in color, size, weight, and taste. The dosage regimen was based on previous studies by the collaborators on this project.

Participants used the trial medication until fetal death, 32 weeks of gestation, or birth. Adherence was participant-reported at each antenatal outpatient clinic visit. Additionally, at the end of the exposure period, medication bottles were collected, and the remaining number of tablets was counted. Participants kept a record of adverse effects. Trial medication was ended at the discretion of the patient. The fetal monitoring (ultrasonography and cardiotocography) and interventions other than the trial medication were at the discretion of the attending gynecologist and in line with Dutch national guidelines and local protocols, depending on the gestational age and EFW. In most participating centers, active management was installed after extensive counseling of parents by a gynecologist and neonatologist and at a minimum gestational age of 26 weeks 0 days combined with an EFW of 500 g. Data were collected from the patient’s electronic health record and entered into a secure electronic database (REDCAP).

Outcomes
The primary outcome was a composite of either perinatal mortality or major neonatal morbidity before the neonate was discharged from the hospital. Major neonatal morbidity was defined as intraventricular hemorrhage grade 3 or more, periventricular leukomalacia grade 2 or more, moderate or severe bronchopulmonary dysplasia, necrotizing enterocolitis Bell stage 2 or more, or retinopathy of prematurity requiring laser therapy. We defined the neonatal period as the time until hospital discharge. Mortality after hospital discharge was considered not to be the mortality of interest in the primary outcome, since the chance of this mortality being associated with the intervention was considered small.

The secondary outcomes were (1) the proportion of mothers experiencing either pre-eclampsia or hemolysis, elevated liver enzymes, and low platelets syndrome; (2) PI of umbilical artery, the first PI measured at the ultrasound performed more than 24 hours after start trial medication; (3)
birth weight, with birth weight of live born neonates and birth weight of stillborn fetuses described separately; (4) gestational age at birth or fetal death; and (5) the proportion of neonates with neurodevelopmental impairment at age 2 years, assessed on the 2-year Bayley Scales of Infant Development, Third Edition (BSID-III) and its cognitive and motor subscales. The latter secondary outcome is not reported here because the 2-year follow-up is not yet complete. When possible, we reported outcomes according to the core outcome set for fetal growth restriction that was developed after the start of the trial.

**Statistical Analysis**

We aimed to find a decrease in the incidence of the primary outcome from 71% in the control group to 56% in the experimental group, which is equal to a relative risk reduction of 21%. Allowing for 10% loss to follow-up and interim analysis for efficacy according to the O'Brien-Fleming spending function ($P < .005$), and with an accepted type I error of 5% and type II error of 80%, we needed to randomize 180 women per group.

The statistical analysis plan, published elsewhere and available in Supplement 1, provides the details of the statistical analysis. In short, the prespecified primary analysis was an intention-to-treat analysis including all randomized participants. Additionally, several prespecified sensitivity analyses were conducted for the primary outcome: adjusting for gestational age and EFW at randomization; only including participants who had a fetus or neonate without any congenital anomaly that could either explain the small fetal size in hindsight or would have a likely effect on the primary outcome (originally defined as a subgroup analysis, since not all congenital anomalies can be known antenatally); and a per-protocol analysis for the primary outcome that included only participants who used at least 1 tablet of trial medication. Relative risks were calculated using generalized linear models (log link function), and continuous outcomes were analyzed using linear regression.

Predefined subgroup analyses were conducted for participants with a serum level of PGF (categorized as less than the fifth percentile and fifth percentile or higher), gestational age at randomization (categorized as <25 weeks of gestation and ≥25 weeks of gestation), and EFW at randomization (categorized as <300 g, 300 to 599 g, and ≥600 g).

All statistical analyses were conducted independently by 2 researchers (C.N. and R.G.D., supervised by J.C.J.) using R statistical software version 3.5.1 (R Project for Statistical Computing) and SAS statistical software version 9.4 (SAS Institute). $P$ values were 2-sided, and statistical significance was set at $P < .05$. Data were analyzed from January 20, 2015, to January 18, 2019.

**Results**

Between January 20, 2015 and July 16, 2018, 281 women were eligible, of whom 216 were randomized (Figure). Among these, 108 women were randomized to sildenafil (median gestational age at randomization, 24 weeks 5 days [interquartile range, 23 weeks 3 days to 25 weeks 5 days]; mean [SD] estimate fetal weight, 458 [160] g) and 108 women were randomized to placebo (median gestational age, 25 weeks 0 days [interquartile range, 22 weeks 5 days to 26 weeks 3 days]; mean [SD] estimate fetal weight 464 [186] g). On July 19, 2018, the DSMB recommended to discontinue the trial based on the findings at the interim analysis on the data from the first 183 participants (eAppendix 1 in Supplement 2). The main consideration for the DSMB to recommend stopping was an increased incidence of neonatal pulmonary hypertension (a predefined outcome important for monitoring safety), whereas it was considered unlikely that benefit would be shown on the primary outcome of perinatal mortality or major neonatal morbidity until hospital discharge if the trial were continued to its completion. Moreover, no positive effects on the primary, secondary, or exploratory outcomes, as defined in the statistical analysis plan, were seen. The results of the recently published STRIDER UK trial as well as the (at that time unpublished) data of the STRIDER New Zealand/Australia trial were included in the DSMB deliberations, as was foreseen in the DSMB.
The trial leadership stopped the trial immediately on July 19, 2018, at which point 7 remaining participants using trial medication were advised to stop using the trial medication, and drug allocation of all participants was unblinded for the participants and the researchers. Owing to the unforeseen stopping of the trial, we were not able to carry out all analyses as planned (eAppendix 2 in Supplement 2).

Of 216 participants randomized at the time of halting the trial, 1 participant was lost to follow-up for all outcomes after having moved abroad, and 12 participants did not start trial medication and were therefore excluded from the per-protocol analysis. The mean (SD) adherence in the per-protocol group was 91% (23%) of the tablets taken.

Baseline characteristics are shown in Table 1. There were no clinically relevant differences between the sildenafil and placebo groups in the maternal or fetal baseline characteristics, other than a slight imbalance in fetal sex (sildenafil: 51 [47.2%] boys; placebo: 59 [54.6%] boys).

No difference was observed in the composite primary outcome of perinatal mortality or major neonatal morbidity until hospital discharge: 65 participants (60.2%) in the sildenafil-group and 58 participants (54.2%) in the placebo-group experienced perinatal death or major neonatal morbidity (relative risk [RR], 1.11; 95% CI, 0.88-1.40; P = .38) (Table 2). Bayes factor analysis indicated that the results on the primary outcome were 3.7-fold more likely compatible with no effect than with the risk reduction hypothesized in the sample size calculation. No differences were observed in the subcomponents of the primary outcome. Perinatal mortality was comparable (sildenafil: 44 deaths [40.7%]; placebo: 40 deaths [37.4%]; RR, 1.09; 95% CI, 0.78-1.52; P = .61). Two more children in the sildenafil group died after hospital discharge: 1 died 1 day after hospital discharge owing to sepsis resulting from necrotizing enterocolitis; another died at age 18 months owing to cardiogenic shock resulting from sepsis. Trial sequential analysis on the data from this trial showed that the boundary for futility was crossed for the primary outcome (eAppendix 3 in Supplement 2).

The proportion of mothers experiencing either pre-eclampsia or hemolysis, elevated liver enzymes, and low platelets syndrome was 46 mothers (42.6%) in the sildenafil group vs 48 mothers (44.9%) in the group allocated to placebo (RR, 0.95; 95% CI, 0.70-1.29) (Table 3). The mean PI of the maternal uterine artery or the fetal umbilical and middle cerebral artery arteries after treatment with study medication did not differ between groups (eTable 1 in Supplement 2).

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**Figure. CONSORT Flow Diagram**

1. **Assessed for eligibility**: 281
2. **Excluded**: 65
   - Declined to participate: 65
3. **Randomized**: 216
4. **Allocated to sildenafil**: 108
   - Received allocated intervention: 103
     - Did not receive allocated intervention: 5
     - Birth before start of intervention: 3
     - Intrauterine death before start of intervention: 1
     - Did not start intervention on participant request: 1
5. **Lost to follow-up**: 0
6. **Analyzable**: 108
   - Excluded from per-protocol analysis; did not start intervention: 5
   - Excluded from intention-to-treat analysis: 0
7. **Allocated to placebo**: 108
   - Received allocated intervention: 101
     - Did not receive allocated intervention: 7
     - Birth before start of intervention: 6
     - Intrauterine death before start of intervention: 1
9. **Lost to follow-up (moved out of the country during pregnancy)**: 1
10. **Analyzable**: 107
    - Excluded from per-protocol analysis; did not start intervention: 7
    - Excluded from intention-to-treat analysis: 1
No difference in birth weight was observed between the treatment groups. Mean (SD) birth weight of the neonates who were stillborn was 414 (143) g in the sildenafil group vs 362 (115) g in the placebo group (P = .15). Mean (SD) gestational age of birth or fetal death was 29 weeks 3 days (4 weeks 0 days) in the sildenafil group vs 29 weeks 3 days (4 weeks 3 days) in the placebo group (P > .99).

The results of all exploratory outcomes are reported in Table 2 and Table 3. Because the DSMB based their advice to stop the trial on the increased occurrence of neonatal pulmonary hypertension in the sildenafil group, we composed an expert adjudication committee of 4 neonatologists (W.O., A.F.J.v.H., I.K.M.R., and E.L.) experienced in treating neonates who are preterm and growth restricted and a pediatric cardiologist (R.M.F.B.) knowledgeable on the subject of neonatal and pediatric pulmonary hypertension to carefully review this outcome. The committee, blinded for treatment allocation, reviewed all neonatal records with the purpose of consensus validation of this diagnosis after discontinuation of the trial. Persistent pulmonary hypertension was defined as either confirmed by cardiac ultrasonagraphic examination or as a difference in oxygen saturation between the right upper extremity and either lower extremity (ie, postductal) of more than 10%. There was an increase of neonates in the sildenafil group who experienced pulmonary hypertension vs the placebo group (16 of 85 neonates [18.8%] vs 4 of 78 neonates [5.1%]; RR, 3.67; 95% CI, 1.28-10.51; P = .008). The adjudication committee observed that 2 different forms of pulmonary hypertension had occurred (eTable 2 in Supplement 2), including persistent pulmonary hypertension in the neonate.

### Table 1. Baseline Characteristics

| Characteristic                                | No. (%)          |
|-----------------------------------------------|------------------|
|                                              | Sildenafil (n = 108) | Placebo (n = 108) |
| Age, mean (SD), y                            | 31 (5.1)         | 31 (5.0)         |
| BMI, mean (SD)                                | 26 (4.7)         | 26 (5.8)         |
| Race/ethnicity, descent                       |                  |
| European                                      | 84 (77.8)        | 86 (79.6)        |
| African                                       | 7 (6.5)          | 11 (10.2)        |
| Asian                                         | 2 (1.9)          | 5 (4.6)          |
| Other                                         | 13 (12.0)        | 6 (5.6)          |
| Maternal smoking                              | 13 (12.0)        | 10 (9.3)         |
| Gestational age at randomization, median (IQR), wk | 24 5/7 (23 3/7 to 25 5/7) | 25 0/7 (22 5/7 to 26 3/7) |
| Ultrasonagraphic examination results, mean (SD) |                  |
| Estimated fetal weight, g                    | 458 (160)        | 464 (186)        |
| Fetal abdominal circumference, mm             | 165 (2)          | 164 (26)         |
| Sex                                           |                  |
| Boys                                          | 51 (47.2)        | 59 (54.6)        |
| Girls                                         | 57 (52.8)        | 48 (44.4)        |
| Notching uterine artery (1- or 2-sided)       | 61 (56.5)        | 64 (59.3)        |
| PI                                            |                  |
| Umbilical artery >95th percentile             | 51 (47.2)        | 53 (49.1)        |
| Middle cerebral artery <5th percentile        | 47 (43.5)        | 43 (39.8)        |
| End-diastolic flow                            |                  |
| Positive                                      | 73 (67.6)        | 65 (60.2)        |
| Absent                                        | 27 (25.0)        | 33 (30.6)        |
| Reversed                                      | 7 (6.5)          | 7 (6.5)          |
| Pregnancy hypertension                        | 22 (20.4)        | 24 (22.2)        |
| Pre-eclampsia                                 | 23 (21.3)        | 26 (24.1)        |
| HELLP syndrome                                | 1 (0.9)          | 2 (1.9)          |
| Blood pressure, mean (SD), mm Hg              |                  |
| Systolic                                      | 132 (22)         | 132 (20)         |
| Diastolic                                     | 83 (15)          | 83 (15)          |
| PGF <5th percentile of reference value, No./total No. (%) | 56/61 (91.8)  | 53/59 (89.8) |

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); HELLP, hemolysis, elevated liver enzymes, and low platelets; IQR, interquartile range; PI, Pulsatility Index; PGF, placental growth factor.

* Reference value was 106.54 pg/L; 5th percentile of reference population.
and later-onset pulmonary hypertension associated with either sepsis or bronchopulmonary dysplasia. Neonatal death was attributable to pulmonary hypertension in 4 infants, 2 in each group (eTable 2 and eTable 3 in Supplement 2). We plan to publish a separate article on the diagnosis of pulmonary hypertension and the validation process within the trial.

No subgroup differences were detected when assessed by adding interaction terms to the models, and the sensitivity analyses did not lead to statistically significant results on the primary outcome (Table 4). However, the RR slightly increased when analyses were adjusted for gestational age and EFW at inclusion (RR, 1.23; 95% CI, 0.69-2.23; \( P = .48 \)) and in a post hoc analysis that explored the potential effect of the imbalance of sex at inclusion (RR, 1.33; 95% CI, 0.77-2.30; \( P = .31 \)).

We observed 10 maternal and 2 fetal or neonatal serious adverse events in the sildenafil group vs 8 maternal and 2 fetal or neonatal serious adverse events in the placebo group that could be directly attributed to the high-risk nature of the study population (eg, hospitalization of the neonate) (eTable 4 in Supplement 2). Other than pulmonary hypertension, there were no differences in the

| Outcome | Sildenafil | Placebo | RR (95% CI) | Mean difference (95% CI) | P value |
|---------|------------|---------|-------------|--------------------------|---------|
| Primary outcome | 65/108 (60.2) | 58/107 (54.2) | 1.11 (0.88 to 1.40) | NA | .38 |
| Birth weight, mean (SD), g | 829 (537) | 884 (627) | NA | −55 (−211 to 101) | .49 |
| Stillbirth | 23/108 (21.3) | 29/107 (27.1) | 0.79 (0.49 to 1.27) | NA | .32 |
| Birth weight, mean (SD), g | 414 (143) | 362 (115) | NA | 53 (−17 to 123) | .15 |
| Percentile | | | | | |
| <Tenth | 10/13 (76.9) | 11/11 (100) | 0.77 (0.57 to 1.04) | NA | .08 |
| <Third | 8/13 (61.5) | 10/11 (90.9) | 0.68 (0.42 to 1.08) | NA | .10 |
| Live birth | 85/108 (78.7) | 78/107 (72.9) | 1.08 (0.93 to 1.26) | NA | .32 |
| Birth weight, mean (SD), g | 942 (549) | 1078 (628) | NA | −136 (−318 to 44) | .14 |
| Percentile | | | | | |
| <Tenth | 33/73 (45.2) | 30/68 (44.1) | 1.02 (0.71 to 1.48) | NA | .90 |
| <Third | 20/73 (27.4) | 19/68 (27.9) | 0.98 (0.57 to 1.67) | NA | .94 |
| Apgar score 5 min <7 | 32/108 (37.6) | 25/107 (31.2) | 1.17 (0.77 to 1.79) | NA | .46 |
| Cord blood gas pH <7.10 | 2/48 (4.2) | 0/31 (0) | NA | | |
| Neonatal death | 21/85 (24.7) | 11/78 (14.1) | 1.75 (0.9 to 3.39) | NA | .10 |
| Survival | | | | | |
| At hospital discharge | 64/85 (75.3) | 67/78 (85.9) | 0.88 (0.75 to 1.02) | NA | .09 |
| With major morbidity at hospital discharge | 21/85 (24.7) | 18/78 (23.1) | 1.07 (0.62 to 1.85) | NA | .81 |
| Without major morbidity at hospital discharge | 43/85 (50.6) | 49/78 (62.8) | 0.81 (0.61 to 1.06) | NA | .12 |
| Postmenstrual age at first discharge home, mean (SD), wk | 42 (7.9) | 40 (2.3) | NA | 2.04 (0.04 to 4.03) | .047 |
| IVH grade III or IV | 3/85 (3.5) | 2/78 (2.6) | 1.38 (0.24 to 8.02) | NA | .72 |
| PVL grade II or more | 0/85 (0) | 0/78 (0) | NA | >.99 |
| BPD | | | | | |
| Moderate or severe | 23/85 (27.1) | 16/78 (20.5) | 1.32 (0.75 to 2.31) | NA | .33 |
| None | 41/85 (48.2) | 47/78 (60.3) | 0.80 (0.61 to 1.06) | NA | .13 |
| ROP treated by laser or surgery | 8/85 (9.5) | 3/78 (3.8) | 2.45 (0.67 to 8.9) | NA | .17 |
| 1 or more culture-proven episode of infection or clinical episode of infection with antibiotic treatment necessary \( \leq 14 \) d | 44/85 (51.8) | 35/78 (44.9) | 1.15 (0.84 to 1.59) | NA | .38 |
| NEC grade II or more | 7/85 (8.3) | 8/78 (10.3) | 0.80 (0.31 to 2.11) | NA | .66 |
| Abdominal circumference, initial growth rate between randomization and 14 d, mean (SD), mm/wk | 7.4 (6.2) | 8.8 (7.3) | NA | −1.4 (−3.43 to 0.69) | .19 |

Abbreviations: BPD, bronchopulmonary dysplasia; EFW, estimated fetal weight; IVH, intraventricular hemorrhage; NA, not applicable; NEC, necrotizing enterocolitis; PVL, periventricular leukomalacia; ROP, retinopathy of prematurity; RR, relative risk.

a Intention-to-treat analysis corrected for gestational age and EFW at randomization, and per-protocol analysis had similar results.

b The primary outcome was perinatal death or major neonatal morbidity before discharge.

c Birth weight percentiles were only calculated for infants born after 23 weeks gestational age.
other serious adverse events. Several adverse effects of the trial medication with different frequencies were reported by the participants and are presented in eTable 5 in Supplement 2. The primary causes of neonatal death and the congenital anomalies observed are described in eTable 6 and eTable 7 in Supplement 2.

Discussion

This randomized clinical trial found that sildenafil compared with placebo did not reduce the risk of perinatal mortality or major neonatal morbidity. This finding is in line with 2 other published STRIDER trials from the UK and from New Zealand and Australia, and is confirmed by trial sequential analysis of this outcome that includes all 3 trials.

Our present finding of an increased incidence of pulmonary hypertension after antenatal sildenafil administration was not observed in the 2 other STRIDER trials. This difference may be explained by definition differences, diagnostic strategies, or thresholds of suspicion. Our finding may indicate an important safety signal, and causality is a possibility because sildenafil targets the pulmonary vasculature. We hypothesize that the causal mechanisms might be rebound vasoconstriction (or lack of dilatation) of the pulmonary arteries to structural changes within the pulmonary vasculature.

Table 3. Maternal Outcomes (Intention-to-Treat Analysis)*

| Outcome                                                                 | No./total No. (%) | RR (95% CI) Mean difference (95% CI) | P value |
|------------------------------------------------------------------------|-------------------|--------------------------------------|---------|
| Treatment duration, mean (SD), d                                       | Sildenafil 24/108 (18) Placebo 20/107 (43) NA | 3.73 (−5.44 to 12.91) | .43     |
| Gestational age at birth, mean (SD), wk                                | 29 3/7 (4 0/7)     29 3/7 (4 1/7) NA | −0.01 (−1.12 to 1.11) | .99     |
| Preterm birth, wk                                                       | <28 46/108 (42.6) 48/107 (44.9) 0.95 (0.70 to 1.29) | NA | .74     |
|                                                                       | <37 97/108 (89.8)  90/107 (84.1) 1.07 (0.96 to 1.18) | NA | .22     |
| Pregnancy prolongation after randomization, mean (SD), d               | 34 (28)           33 (32) NA | 0.64 (−7.4 to 8.67) | .88     |
| Mode of delivery                                                       |                   |                                     |         |
| Cesarean                                                               |                   |                                     |         |
| On fetal indication                                                    | 57/108 (52.8)     51/107 (47.7) NA | NA |         |
| On maternal indication                                                 | 14/108 (13.0)     14/107 (13.1) NA | NA |         |
| Induced vaginal birth                                                  |                   |                                     |         |
| On fetal indication                                                    | 7/108 (6.5)       12/107 (11.2) NA | NA |         |
| On maternal indication                                                 | 8/108 (7.4)       3/107 (2.8) NA | NA |         |
| Spontaneous vaginal birth                                              | 9/108 (8.3)       11/107 (10.3) NA | NA |         |
| Induction of labor after intrauterine death                            | 12/108 (11.1)     16/107 (15.0) NA | NA |         |
| Pregnancy hypertension                                                 | 74/108 (68.5)     72/107 (67.3) 1.02 (0.85 to 1.22) | NA | .85     |
| Pre-eclampsia                                                          | 42/108 (38.9)     44/107 (41.1) 0.95 (0.68 to 1.31) | NA | .74     |
| HELLP syndrome                                                         | 12/108 (11.1)     10/107 (9.3) 1.19 (0.54 to 2.63) | NA | .67     |
| Maternal use of antihypertensive treatment antenatal or postnatal, No. used |                   |                                     |         |
| None                                                                   | 50/108 (46.3)     53/107 (49.5) NA | NA | .61     |
| 1                                                                      | 32/108 (29.6)     34/107 (31.8) NA | NA |         |
| 2                                                                      | 16/108 (14.8)     15/107 (14.0) NA | NA |         |
| ≥3                                                                     | 10/108 (9.3)      5/107 (4.7) NA | NA |         |
| Maternal magnesium sulphate for hypertension                            | 14/108 (13.0)     15/107 (14.0) 0.92 (0.47 to 1.82) | NA | .82     |
| Antenatal corticosteroids for fetal lung maturation before birth       |                   |                                     |         |
| 48 h to 14 d (complete course)                                         | 52/85 (61.2)      56/78 (71.8) 0.85 (0.68 to 1.06) | NA | .15     |
| <48 h (incomplete course)                                              | 4/85 (4.8)        7/78 (9.0) 0.52 (0.16 to 1.72) | NA | .29     |

Abbreviation: NA, not applicable; HELLP, hemolysis, elevated liver enzymes, and low platelets; RR, relative risk.

* Intention-to-treat analysis corrected for gestational age and estimated fetal weight at randomization. Per-protocol analysis had similar results.
The Canadian STRIDER trial (NCT02442492) was terminated based on the results of this STRIDER trial. The planned individual patient data analysis that combines our data with all other STRIDER trials will have more power to draw conclusions based on all available data and hopefully to allow meaningful subgroup analysis to identify if there are specific participant groups that experience harm or benefit from the intervention.41

**Limitations**

Our trial has limitations. First, the trial was stopped before the planned sample size was reached because of an increased incidence of pulmonary hypertension in the sildenafil group, as well as indications of futility in our primary outcome. Pulmonary hypertension was predefined as an important safety outcome to monitor, but it was neither defined as a primary or secondary outcome, and pulmonary hypertension is a nonvalidated surrogate outcome regarding more patient-centered outcomes. Although each adverse event should be seriously regarded,42 it might be argued that the pulmonary hypertension result should only be regarded as hypothesis-generating and should be tested in the planned individual patient data analysis.41 Second, when assessing the primary outcome of perinatal mortality or major neonatal morbidity, the trial sequential analysis showed that the boundary for futility was crossed, indicating that we could reject that sildenafil reduces the risk of the primary outcome by 20%. However, we cannot reject that sildenafil reduces the risk of the primary outcome by smaller and perhaps clinically important margins, or that sildenafil reduces the risk of any of the secondary outcomes.

It could be argued that the trial was stopped too soon owing to the lack of robustness on the findings of harm. However, the advice of the independent DSMB was not only based on potential harms but also on lack of benefits. In addition to the increase in pulmonary hypertension observed at the interim analysis, it became evident that it was unlikely that benefit of sildenafil treatment would be shown on the primary outcome if the trial were continued to its completion. This was also demonstrated in the trial sequential analysis on the primary outcome that showed that the boundary for futility was crossed when taking the results of the UK39 and Australian/New Zealand40 STRIDER trials into account.

### Table 4. Prespecified Sensitivity and Subgroup Analyses on the Primary Outcome According to Treatment

| Analysis                                      | No./total No. (%) | RR (95% CI)     | P value<sup>a</sup> |
|-----------------------------------------------|-------------------|-----------------|---------------------|
| Sildenafil Placebo                            |                   |                 |                     |
| Per protocol                                  | 60/103 (58.3)     | 54/100 (54.0)   | 1.08 (0.85-1.38)    | .54                 |
| Adjusted for EFW and GA at randomization      | 65/108 (60.2)     | 58/107 (54.2)   | 1.23 (0.69-2.23)    | .48                 |
| Post hoc adjustment for sex                   | 65/108 (60.2)     | 58/107 (54.2)   | 1.33 (0.77-2.30)    | .31                 |
| Excluding                                     |                   |                 |                     |
| Neonates who appeared to have a congenital anomaly | 60/102 (58.8) | 54/101 (53.5)   | 1.10 (0.86-1.40)    | .44                 |
| Participants who were pregnant or for whom the neonate was admitted at NICU when trial was stopped (post hoc) | 60/97 (61.9) | 55/98 (56.1)   | 1.10 (0.87-1.39)    | .42                 |
| Placental growth factor, percentile of the reference value |                   |                 |                     |
| <Fifth                                        | 36/56 (64.3)      | 25/53 (47.2)    | 1.36 (0.96-1.93)    | .99                 |
| ≥Fifth                                        | 4/5 (80.0)        | 3/6 (50.0)      | 1.60 (0.64-3.98)    |                     |
| GA at randomization, wk                       |                   |                 |                     |
| <25                                           | 42/60 (70.0)      | 36/54 (66.7)    | 1.05 (0.82-1.35)    | .85                 |
| ≥25                                           | 23/48 (47.9)      | 22/53 (41.5)    | 1.15 (0.75-1.78)    |                     |
| EFW at randomization, g                       |                   |                 |                     |
| <300                                          | 15/19 (78.9)      | 21/26 (80.8)    | 0.98 (0.73-1.32)    |                     |
| 300-599                                       | 44/67 (65.7)      | 23/48 (47.9)    | 1.37 (0.97-1.93)    | .70                 |
| ≥600                                          | 3/18 (16.7)       | 10/26 (38.5)    | 0.43 (0.14-1.36)    |                     |

Abbreviations: EFW, estimated fetal weight; GA, gestational age; NICU, neonatal intensive care unit; RR, relative risk.<sup>a</sup> The P value is from the interaction term for subgroup analyses and from the treatment effect for the sensitivity analyses.
It could also be argued that the STRIDER trials were premature. However, there was extensive evidence in appropriate animal models of fetal growth restriction and increasing human evidence suggesting potential for a positive effect on fetal growth. The dosage used in this study (ie, 25 mg 3 times daily) was based on a previous trial and is slightly higher than the dosage used for the treatment of pulmonary hypertension in adults. A meta-analysis of animal studies suggested that a higher dosage than the current study used might be necessary to reach adequate serum levels of sildenafil. Sildenafil is approved to improve exercise ability and delay clinical worsening of pulmonary arterial hypertension in adult patients (World Health Organization Group I). In 2012, the US Food and Drug Administration recommended that sildenafil should not be prescribed to children ages 1 through 17 years for pulmonary arterial hypertension. However, there were no reported safety concerns for the use of sildenafil in fetal growth restriction. In contrast, there was an ongoing inclusion of this drug into clinical practice in this at-risk patient category. Adequately powered randomized clinical trials are necessary to assess the validity of an intervention before it is implemented. The concerted approach of the STRIDER trials aimed to prevent premature implementation of sildenafil based on a few underpowered trials and sought to thoroughly test the beneficial claims before implementation.

Conclusions

This randomized clinical trial found that antenatal maternal sildenafil administration for severe early onset fetal growth restriction did not reduce the risk of perinatal death or major neonatal morbidity. Our results suggest that sildenafil may increase the risk of neonatal pulmonary hypertension.
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Data Sharing Statement: See Supplement 3.
REFERENCES

1. Perined. Yearbooks Healthcare in the Netherlands [in Dutch]. Accessed April 22, 2020. https://www.perined.nl/producten/jaarboeken

2. Spencer R, Rossi C, Lees M, et al; EVEREST Consortium. Achieving orphan designation for placental insufficiency: annual incidence estimations in Europe. BJOG. 2019;126(9):1157-1167. doi:10.1111/1471-0528.15590

3. Severi FM, Rizzo G, Brocchi C, D’Antona D, Verzuri MS, Aurdiini D. Intrauterine growth retardation and fetal cardiac function. Fetal Diagn Ther. 2000;15(1):8-19. doi:10.1159/000020969

4. Pels A, Beune IM, van Wassenaer-Leenhuys AG, Limpens J, Ganzevoort W. Early-onset fetal growth restriction: a systematic review on mortality and morbidity. Acta Obstet Gynecol Scand. 2020;99(2):153-166. doi:10.1111/aogs.13702

5. Levine TA, Grunau RE, McAuliffe FM, Pinnamaneni R, Foran A, Alderdice FA. Early childhood neurodevelopment after intrauterine growth restriction: a systematic review. Pediatrics. 2015;135(1):126-141. doi:10.1542/peds. 2014-1143

6. Murray E, Fernandes M, Fazel M, Kennedy SH, Villar J, Stein A. Differential effect of intrauterine growth restriction on childhood neurodevelopment: a systematic review. BJOG. 2015;122(8):1062-1072. doi:10.1111/1471-0528.13435

7. Nardozza LM, Caetano AC, Zamarian AC, et al. Fetal growth restriction: current knowledge. Arch Gynecol Obstet. 2017;295(5):1061-1077. doi:10.1007/s00404-017-4341-9

8. Pauw 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. doi:10.1161/HYPERTENSIONAHA.117.09690

9. Sharp A, Cornforth C, Jackson R, et al; STRIDER group. Maternal sildenafil for severe fetal growth restriction (STRIDER): a multicentre, randomised, placebo-controlled, double-blind trial. Lancet Child Adolesc Health. 2018;2(2):93-102. doi:10.1016/S2352-4642(17)30173-6

10. Choudhary R, Desai K, Parekh H, Ganla K. Sildenafil citrate for the management of fetal growth restriction and oligohydramnios. Int J Womens Health. 2016;8:367-372. doi:10.2147/IJWH.S108370

11. Dastjerdi MV, Hosseini S, Bayani L. Sildenafil citrate and uteroplacental perfusion in fetal growth restriction. J Res Med Sci. 2012;17(7):632-636.

12. Samangaya RA, Mires G, Shennan 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):369-382. doi:10.3109/10641950802601278

13. Trapani A Jr, Gonçalves 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 Obstet Gynecol. 2016;48(1):61-65. doi:10.1002/uog.15673

14. Trapani A Jr, Gonçalves 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):253-259. doi:10.1097/AOG.0000000000001518

15. von Dadelszen P, Dwinnell S, Magee LA, et al; Research into Advanced Fetal Diagnosis and Therapy (RAFT) Group. Sildenafil citrate therapy for severe early-onset intrauterine growth restriction. BJOG. 2011;118(5):624-628. doi:10.1111/j.1471-0528.2010.02879.x

16. Russo FM, Conings S, Allegaert K, et al. Sildenafil crosses the placenta at therapeutic levels in a dually perfused human cotyledon model. Am J Obstet Gynecol. 2018;219(6):619.e1-619.e10. doi:10.1016/j.ajog.2018.08.041

17. Ganzevoort W, Bloemenkamp K, von Dadelszen P, et al. Dutch STRIDER: Data Monitoring Committee Charter. Zenodo. June 21, 2016. doi:10.5281/zenodo.56147

18. Webster LM, Gill C, Seed PT, et al. Chronic hypertension in pregnancy: impact of ethnicity and superimposed preeclampsia on placental, endothelial, and renal biomarkers. Am J Physiol Regul Integr Comp Physiol. 2018;315(1):R36-R47. doi:10.1152/ajpregu.00139.2017

19. Escuto DC, Green A, Kurlak L, et al. Postpartum evaluation of cardiovascular disease risk for women with pregnancies complicated by hypertension. Pregnancy Hypertens. 2018;13:218-224. doi:10.1016/j.preghy.2018.06.019

20. Dröge LA, Höller A, Ehrlich L, Verloren S, Henrich W, Perschel FH. Diagnosis of preeclampsia and fetal growth restriction with the sFlt-1/PlGF ratio: diagnostic accuracy of the automated immunoassay Kryptor. Pregnancy Hypertens. 2017;8:31-36. doi:10.1016/j.preghy.2017.02.005

21. Hinojoa-Rodriguez M, Harmony T, Carrillo-Prado C, et al. Clinical neuroimaging in the preterm infant: diagnosis and prognosis. Neuroimage Clin. 2017;16:355-368. doi:10.1016/j.nicl.2017.08.015
22. Papile LA, Burstein J, Burstein R, Koffler H. Incidence and evolution of subependymal and intraventricular hemorrhage: a study of infants with birth weights less than 1,500 gm. J Pediatr. 1978;92(4):529-534. doi:10.1016/S0022-3476(78)80282-0

23. Towbin A. Cerebral intraventricular hemorrhage and subependymal matrix infarction in the fetus and premature newborn. Am J Pathol. 1968;52(1):121-140.

24. Chen CC, Huang CB, Chung MY, Huang LT, Yang CY. Periventricular echogenicity is related to delayed neurodevelopment of preterm infants. Am J Perinatol. 2004;21(8):483-489. doi:10.1055/s-2004-835966

25. Grunnet ML. Periventricular leukomalacia complex. Arch Pathol Lab Med. 1979;103(1):6-10.

26. Bancalari E, Clause N. Definitions and diagnostic criteria for bronchopulmonary dysplasia. Semin Perinatol. 2006;30(4):164-170. doi:10.1053/j.semperi.2006.05.002

27. Finer NN, Bates R, Tomat P. Low flow oxygen delivery via nasal cannula to neonates. Pediatr Pulmonol. 1996;21(1):48-51. doi:10.1002/(SICI)1099-0496(19960121)21:1<48::AID-PPUL8>3.0.CO;2-M

28. Jobe AH, Bancalari E. Bronchopulmonary dysplasia. Am J Respir Crit Care Med. 2001;163(7):1723-1729. doi:10.1164/rccm.163.7.110160

29. Walsh MC, Wilson-Costello D, Zadell A, Newman N, Fanaroff A. Safety, reliability, and validity of a physiologic definition of bronchopulmonary dysplasia. J Perinatol. 2003;23(6):451-456. doi:10.1038/sj.jp.7210963

30. Walsh MC, Yao Q, Gettner P, et al; National Institute of Child Health and Human Development Neonatal Research Network. Impact of a physiologic definition on bronchopulmonary dysplasia rates. Pediatrics. 2004;114(5):1305-1311. doi:10.1542/peds.2004-0204

31. Bell MJ, Ternberg JL, Feigin RD, et al. Neonatal necrotizing enterocolitis: therapeutic decisions based upon clinical staging. Ann Surg. 1978;187(1):1-7. doi:10.1097/00000658-197801000-00001

32. Hintz SR, Kendrick DE, Stoll BJ, et al; NICHD Neonatal Research Network. Neurodevelopmental and growth outcomes of extremely low birth weight infants after necrotizing enterocolitis. Pediatrics. 2003;112(6):1305-1311. doi:10.1542/peds.2003-0963

33. Heath P. Pathology of the retinopathy of prematurity: retrolental fibroplasia. Am J Ophthalmol. 1951;34(9):1249-1259. doi:10.1016/0002-9394(51)91859-4

34. Hellström A, Smith LE, Dammann O. Retinopathy of prematurity. Lancet. 2013;382(9902):1445-1457. doi:10.1016/S0140-6736(13)60178-6

35. Tranquilli AL, Brown MA, Zeeman GG, Dekker G, Sibai BM; Statements from the International Society for the Study of Hypertension in Pregnancy (ISSHP). The definition of severe and early-onset preeclampsia. Pregnancy Hypertens. 2013;3(1):44-47. doi:10.1016/j.preghy.2012.11.001

36. Bayley N. Bayley Scales of Infant and Toddler Development. 3rd ed. Pearson Assessments; 2006.

37. Healy P, Gordijn SJ, Ganzevoort W, et al. A core outcome set for the prevention and treatment of fetal growth restriction: developing endpoints: the COSGROVE study. Am J Obstet Gynecol. 2019;221(4):339.e1-339.e10. doi:10.1016/j.ajog.2019.05.039

38. Pels A, Jakobsen JC, Ganzevoort W, et al. Detailed statistical analysis plan for the Dutch STRIDER (Sildenafil Therapy in Dismal Prognosis Early-Onset Fetal Growth Restriction) randomised clinical trial on sildenafil versus placebo for pregnant women with severe early onset fetal growth restriction. Trials. 2019;20(1):42. doi:10.1186/s13063-018-3136-z

39. Sharp A, Cornforth C, Jackson R, et al. STRIDER group. Maternal sildenafil for severe fetal growth restriction (STRIDER): a multicentre, randomised, placebo-controlled, double-blind trial. Lancet Child Adolesc Health. 2018;2(2):93-102. doi:10.1016/S2352-4642(17)30173-6

40. Groom KM, McCowan LM, Mackay LK, et al. STRIDER NZAus: a multicentre randomised controlled trial of sildenafil therapy in early-onset fetal growth restriction. BJOG. 2019;126(8):997-1006. doi:10.1111/1471-0528.15658

41. Ganzevoort W, Alfirevic Z, von Dadelszen P, 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. doi:10.1186/2046-4053-3-23

42. European Medicines Agency. Guideline on multiplicity issues in clinical trials. Accessed April 22, 2020. https://www.ema.europa.eu/en/documents/scientific-guideline/draft-guideline-multiplicity-issues-clinical-trials_en.pdf

43. US Food and Drug Administration. FDA Drug Safety Communication: FDA clarifies warning about pediatric use of Revatio (sildenafil) for pulmonary arterial hypertension. Updated January 2016. Accessed April 22, 2020. https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-clarifies-warning-about-pediatric-use-revatio-sildenafil-pulmonary
44. Martin A, Lines A. "Viagra saved my baby's life": Mum's 11-week premature child still alive thanks to anti-impotence drug. Mirror. October 9, 2015. Accessed April 22, 2020. https://www.mirror.co.uk/news/uk-news/viagra-saved-babys-life-mums-6606806

SUPPLEMENT 1.
Trial Protocol and Statistical Analysis Plan

SUPPLEMENT 2.
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SUPPLEMENT 3.
Data Sharing Statement