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RESEARCH ARTICLE
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OUTCOMES OF SILDENAFIL CITRATE IN EARLY ONSET OF FETAL GROWTH RESTRICTIONS– A SYSTEMATIC REVIEW

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Abstract

Background: Early-onset fetal growth restriction (FGR) is a critical obstetric challenge associated with placental insufficiency, resulting in increased perinatal morbidity and mortality. Sildenafil citrate, a phosphodiesterase-5 (PDE-5) inhibitor, has been explored as a therapeutic option to improve uteroplacental blood flow and fetal outcomes. However, its efficacy and safety remain subjects of debate.

Methods: A systematic review was conducted to evaluate the effects of sildenafil citrate in early-onset FGR. Comprehensive literature searches were performed in PubMed, Scopus, Web of Science, and Cochrane Library, including studies published from 2013 to 2023. Studies assessing sildenafil citrate in pregnancies complicated by early-onset FGR (diagnosed before 32 weeks) were included. Outcomes such as fetal growth parameters, uteroplacental blood flow, and neonatal morbidity were analyzed.

Results: The review included 10 studies after screening 2330 articles. Sildenafil citrate showed improvements in uteroplacental blood flow and maternal hemodynamics in some studies, with reductions in uterine artery pulsatility index and arterial stiffness. However, neonatal outcomes, including fetal growth velocity and survival, demonstrated inconsistent improvements. Safety concerns, such as neonatal pulmonary hypertension reported in the Dutch STRIDER trial, raised caution about its routine use. Variations in trial designs and population characteristics contributed to heterogeneity in results.

Conclusion: Sildenafil citrate shows potential to enhance uteroplacental blood flow in early-onset FGR, but its clinical benefits for fetal growth and neonatal outcomes remain inconclusive. Safety concerns warrant careful patient selection and further research to refine its use in this high-risk group.

Collaborative efforts through international consortia are essential for advancing evidence-based management of early-onset FGR.

Keywords: Sildenafil citrate, early-onset fetal growth restriction, uteroplacental blood flow, perinatal outcomes, placental insufficiency, STRIDER trials.

INTRODUCTION

Fetal growth restriction (FGR) is a significant obstetric challenge associated with increased perinatal morbidity and mortality.[1] Early-onset FGR, typically diagnosed before 32 weeks of gestation, poses greater risks due to the associated placental insufficiency and the limited capacity of the fetus to adapt to suboptimal intrauterine conditions.[2] Despite advancements in obstetric care, managing early-onset FGR remains a critical concern, necessitating innovative therapeutic approaches to improve maternal and fetal outcomes.

Sildenafil citrate, a phosphodiesterase-5 (PDE-5) inhibitor, has emerged as a potential therapeutic option for managing early-onset FGR.[3] By enhancing nitric oxide-mediated vasodilation, sildenafil citrate improves uteroplacental blood flow, thereby addressing the underlying issue of placental insufficiency.[4] Preclinical studies and early clinical trials have shown promise in using sildenafil to improve fetal growth parameters and prolong pregnancy duration, reducing complications associated with preterm delivery.[4] However, the efficacy and safety of sildenafil citrate in this context remain a topic of ongoing debate.

This systematic review aims to consolidate current evidence on the outcomes of sildenafil citrate in early-onset FGR. By critically analyzing data from recent clinical trials and observational studies, this review seeks to provide insights into the efficacy, safety profile, and implications of sildenafil citrate in optimizing perinatal outcomes in pregnancies complicated by early-onset FGR. The findings will contribute to evidence-based recommendations for the use of sildenafil citrate in obstetric practice.

METHODS

Literature search

A comprehensive literature search was conducted across multiple electronic databases, including PubMed, Scopus, Web of Science, and Cochrane Library, to identify relevant studies on the use of sildenafil citrate in early-onset fetal growth restriction (FGR). The search included articles published from 2013 up to 2023. Keywords and MeSH terms such as ***"sildenafil citrate," "early-onset fetal growth restriction," "placental insufficiency," "uteroplacental blood flow,"*** and *"**perinatal outcomes"*** were combined using Boolean operators (*AND, OR*). Additional searches were conducted by screening reference lists of included studies and consulting gray literature sources to ensure comprehensive coverage.

Eligibility criteria

Studies were considered eligible for inclusion based on the following criteria:

Inclusion criteria

1. Studies evaluating the use of sildenafil citrate in pregnancies diagnosed with early-onset FGR (before 32 weeks of gestation).
2. Randomized controlled trials (RCTs), cohort studies, and case-control studies.
3. Studies reporting on maternal or fetal outcomes, such as fetal growth parameters, uteroplacental blood flow, gestational age at delivery, and neonatal morbidity or mortality.
4. Articles with clearly defined intervention protocols for sildenafil citrate and control groups.

Exclusion criteria

1. Studies involving late-onset FGR or other pregnancy complications without specific focus on early-onset FGR.
2. Review articles, editorials, and commentaries

3. Studies with insufficient or incomplete outcome data.
4. Duplicate studies or those with overlapping data from the same population.

Statistical analysis

RESULTS

Study selection

The systematic literature search yielded a total of 2330 studies after an initial screening of titles and abstracts. After removing duplicates and further screening based on eligibility criteria, 106 full-text articles were assessed for final inclusion. Following a detailed evaluation, 10 studies were ultimately included in the systematic review.

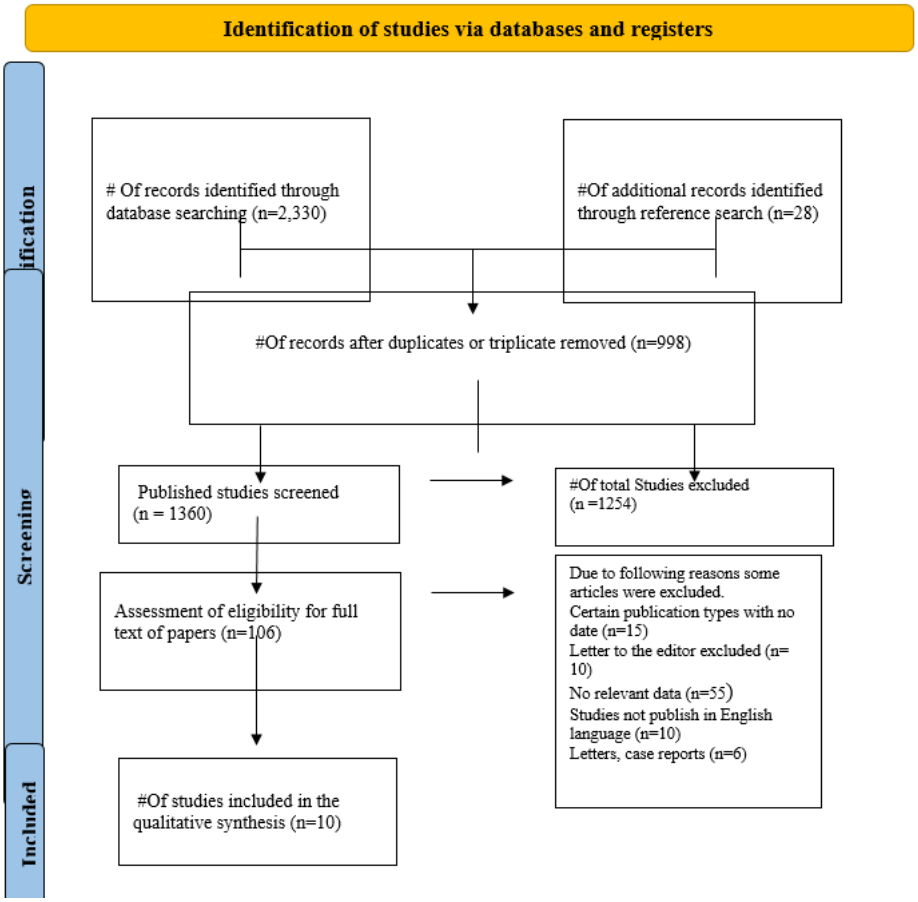

Fig 1 -PRISMA flow diagram for new systematic reviews which included searches of databases and registers only

Study characteristics

The characteristics of the included studies are summarized in Table 1. Studies investigating sildenafil citrate in fetal growth restriction (FGR) are primarily randomized controlled trials (RCTs), many of which are multicenter and double-blinded. These studies typically involve pregnant women diagnosed with severe early-onset FGR between 18 and 34 weeks of gestation. Diagnostic criteria often include fetal weight below the 10th percentile and abnormal Doppler velocimetry, such as absent or reversed end-diastolic flow in the umbilical artery. Sildenafil citrate is administered in doses of 25 mg three times daily, with treatment continuing until 32 weeks of gestation, delivery, or fetal demise. Control groups are provided with a placebo or no treatment. Data collection focuses on a range of maternal, fetal, and neonatal outcomes to assess efficacy and safety.

Sr. No.	Author(s) Year	Study Design	Sample Size (N)	Gestational Age at Enrollment	Intervention Details	Control Details	Primary Outcomes	Key Findings
1.	Rakhanova, Y. et al.,[5] 2023	Systematic Review & Meta-analysis	9 trials included	Not specified	Sildenafil citrate (PDE-5 inhibitor) vs. placebo/no intervention	Placebo/ no intervention	Increase in birth weight, Prolonged pregnancies	Sildenafil increased birth weight (SMD 0.69), prolonged pregnancies, but had no impact on stillbirth rate, neonatal death, or NICU admissions.
2.	Rashmi Yadav et al.,[6] 2022	Prospective RCT	Not specified	22–32 weeks gestation	Sildenafil citrate 25 mg orally three times daily until delivery	No treatment group (Group B)	Increase in abdominal circumference (AC), fetal weight, pregnancy duration	Sildenafil therapy significantly increased fetal AC, birth weight (2040.92 g vs. 1665.60 g), and pregnancy duration (64.85 ± 13.86 days vs. 55.35 ± 16.18 days).
3.	Anouk Pels, MD,[7] 2020	RCT (Placebo-controlled)	216	20–30 weeks gestation	Sildenafil citrate 25 mg orally three times daily vs. placebo	Placebo group	Composite of perinatal mortality or major neonatal morbidity	Sildenafil did not reduce perinatal mortality or morbidity and increased the risk of neonatal pulmonary hypertension. (Relative Risk 3.67)
4.	Khalil et al.[8] 2020	Multicenter randomized	134	22–29+6 weeks gestation	Sildenafil citrate 25 mg orally three	Placebo group	Maternal hemodynamics (HR, BP,	Changes were modest and short term, with

		controlled trial			times daily vs. placebo		arterial stiffness)	no clinical impact on maternal outcomes.
5.	Ahmed Abdelshafy,[9] 2019	Double-blind RCT	90	24–37 weeks gestation	Sildenafil citrate 25 mg orally every 8 hours vs. placebo	Placebo group	Improvement in Doppler indices, neonatal birth weight, gestational age at delivery	Sildenafil improved umbilical artery and middle cerebral artery indices ($p<0.001$), increased birth weight (1783±241 g vs. 1570±455 g, $p<0.001$), and gestational age at delivery (35.3±1.67 weeks vs. 33.5±1.7 weeks). Side effects (headache, palpitation, facial flushing) were higher in the sildenafil group.
6.	Katie M. Groom et al.[10] 2019	Multicentre, Double-blind RCT	120	22–29+6 weeks gestation	Sildenafil citrate 25 mg orally three times daily vs. placebo	Placebo group	Fetal growth velocity	Sildenafil had no effect on fetal growth velocity or AC Z-scores.
7.	Mohammed Maged,[11] 2018	Prospective Non-randomized	50	Not specified	Sildenafil citrate (dosage not specified) vs. no treatment	No treatment group	Umbilical artery Doppler indices, birth weight, neonatal nursery admission	Sildenafil significantly decreased umbilical artery Doppler indices, increased birth weight,

								and reduced neonatal nursery admissions.
8.	Andrew Sharp et al.[12] 2018	Multicentre, Double-blind RCT	135	22–29+6 weeks gestation	Sildenafil citrate 25 mg three times daily vs. placebo	Placebo group	Time from randomization to delivery (days)	Sildenafil did not prolong pregnancy or improve pregnancy outcomes in severe early-onset FGR.
9.	H.L. Premalatha[13] 2016	Observational Study	100	22–34 weeks gestation	Sildenafil citrate 25 mg orally three times daily until delivery	None	Doppler studies (Uterine artery, umbilical artery, MCA, ductus venosus), amniotic fluid volume, gestational age	Sildenafil improved Doppler indices, increased amniotic fluid volume, and reduced IUGR from 70% to 0% after intervention. Oligohydramnios improved from 30% to 10% ($p < 0.05$). Stillbirth rate was 2%, with 98% of women retained until delivery.
10.	Subrat Panda, Ananya Das, Hossain Md[14] 2014	Case Study	1	Not specified	Sildenafil citrate (PDE-5 inhibitor)	None	Improvement in uterine blood flow, favorable fetal outcome	Sildenafil improved uterine blood flow and resulted in favorable fetal outcomes at delivery

Outcomes of Sildenafil Citrate in Fetal Growth Restriction (FGR)

The outcomes of sildenafil citrate in FGR are mixed, with varying effects on fetal growth, maternal hemodynamics, and neonatal outcomes. Groom et al. reported that sildenafil did not significantly

increase fetal growth velocity, with growth improvements noted in 52.5% of the sildenafil group compared to 68.4% in the placebo group (OR 0.49, 95% CI 0.23–1.05). However, a significant reduction in uterine artery pulsatility index (PI) after 48 hours of treatment indicated improved uteroplacental blood flow. Khalil et al. observed that sildenafil led to reduced arterial stiffness (mean difference in aortic PWV, −0.90 m/s; P = 0.001) and systolic blood pressure (mean difference, −4.13 mmHg; P = 0.048) shortly after administration, consistent with its vasodilatory effects. These hemodynamic changes were transient and did not significantly impact maternal clinical outcomes.
Neonatal outcomes have also been inconsistent. Ganzevoort et al., in the Dutch STRIDER trial, reported a concerning increase in the risk of neonatal pulmonary hypertension (RR 3.67, 95% CI 1.24–10.87) associated with sildenafil, leading to the trial's premature termination. Conversely, in the STRIDER NZAus trial, Groom et al. observed no such adverse effects but noted no significant improvement in survival without severe neonatal morbidity. The findings of Pels et al. from the STRIDER consortium reinforce these results, showing no consistent benefit of sildenafil on neonatal morbidity or survival across multiple trials.

Risk of bias in individual studies

The domains of selection bias (random sequence generation and allocation concealment), performance bias (blinding), detection bias (assessor blinding), attrition bias (incomplete outcome data), and reporting bias (selective reporting) were the fundamentals for judging and rating the cumulative bias as high, uncertain, or low risk. Based on the domains and criteria, individual studies were classified as low, unclear, or high risk. Figure 2 displays the probability of bias among the 10 literatures analyzed for the present study. In this review, randomization was at high risk in 5% of the trials, and the risk was unclear and low in 31.67% and 63.33% of the trials [Figure 3].

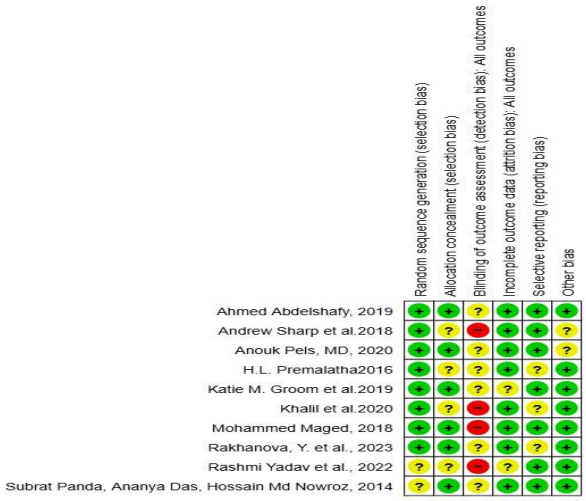

figure 2: The authors' conclusions for each item of risk of bias for each incorporated study are summarized in the risk of bias review

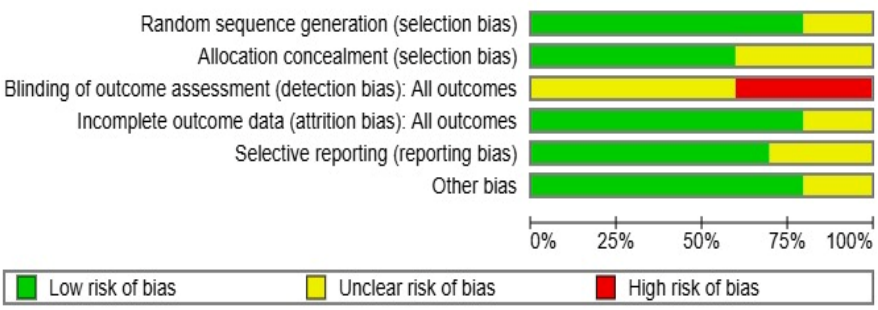

figure 3: Authors' assessments of each item of bias risk are expressed as percentages for all involved papers in the risk of bias graph review

DISCUSSION

The evaluation of sildenafil citrate in fetal growth restriction (FGR) has yielded mixed outcomes, reflecting its complex and context-specific effects. While some studies, such as **Khalil et al.**[8] and **Groom et al.,**[10] highlight its potential to enhance uteroplacental blood flow through reductions in uterine artery pulsatility index and maternal arterial stiffness, this did not consistently translate into improved fetal growth or neonatal outcomes. **Pels et al.**[7] reported an increased risk of neonatal pulmonary hypertension associated with sildenafil, prompting early termination of the Dutch STRIDER trial, and raising concerns about its safety profile in this context. Conversely, **Groom et al.,**[10] in the STRIDER NZAus trial, did not observe such adverse effects but found no significant improvement in growth velocity or neonatal survival rates.

Pels et al.[7] emphasized the value of international collaboration through the STRIDER consortium in standardizing outcome measures across trials. This enabled robust analyses through meta-analyses and systematic reviews. The hemodynamic findings by **Khalil et al.**[8] also align with the pharmacological action of sildenafil as a vasodilator, which may explain the modest reductions in maternal blood pressure and improvements in uteroplacental blood flow. However, the lack of consistent benefits in neonatal survival or morbidity underscores the complexity of FGR management, where placental pathology may not always respond adequately to vasodilatory interventions.

These findings collectively suggest that while sildenafil shows some promise in modifying maternal hemodynamics, its role in improving meaningful clinical outcomes in FGR remains uncertain. Variations in trial designs, study populations, and outcome measures may contribute to the observed heterogeneity in results.

Limitations

1. The trials varied in sample size and gestational age range, potentially affecting the generalizability of findings.
2. The STRIDER trials showed differences in primary outcomes, which could limit the comparability of results across studies.

CONCLUSION

Sildenafil citrate demonstrates the potential to improve uteroplacental blood flow and reduce arterial stiffness in pregnancies complicated by severe early-onset FGR. However, evidence regarding its efficacy in improving fetal growth velocity and neonatal outcomes remains inconsistent. Safety concerns, such as those raised by Ganzevoort et al., further complicate its use in this high-risk population. Future research should focus on refining patient selection criteria and addressing safety concerns to identify specific contexts where sildenafil may offer a favorable risk-benefit profile. Collaboration through international consortia, such as the STRIDER network, will remain pivotal in advancing evidence-based management of FGR.

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