P-ISSN : 2527-4627
Warmadewa Medical Journal
Available online http://ejournal.warmadewa.ac.id/index.php/warmadewa_medical_journal

WMJ (Warmadewa Medical Journal), Vol. 11, No.1, May 2026, Page. 39-53

Antenatal Sildenafil Citrate for Fetal Growth Restriction: Updated Evidence on Fetoplacental Pulsatility Indices and Perinatal Outcomes — Systematic Review and Meta-analysis

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Abstract

The aim of this study is to evaluate the impact of antenatal sildenafil citrate on fetoplacental pulsatility indices and perinatal outcomes in pregnancies complicated by FGR. A systematic review and meta-analysis were conducted in accordance with PRISMA guidelines. PubMed, Scopus, and Web of Science were searched up to October 2025. Randomized controlled trials (RCTs) comparing sildenafil citrate with placebo in FGR pregnancies were included. Primary outcomes included umbilical artery (UA) and middle cerebral artery (MCA) pulsatility indices, birth weight, gestational age at delivery, and stillbirth rate. Secondary outcomes included neonatal mortality, major morbidity, and NICU admission. Random-effects models were used to calculate pooled mean differences (MDs) or risk ratios (RRs) with 95% confidence intervals (CIs). Twelve RCTs involving a total of 1,083 pregnant women with FGR were analyzed. Sildenafil citrate significantly reduced UA-PI (MD = −0.22; 95% CI −0.33 to −0.11; $p < 0.0001$) and increased mean birth weight (MD = 178.39 g; 95% CI 61.48–295.30; $p = 0.003$). However, it showed no significant effects on MCA-PI, gestational age, stillbirth, neonatal mortality, severe intraventricular hemorrhage, or NICU admission. Conversely, an increased risk of persistent pulmonary hypertension of the newborn (PPHN) was observed (OR = 4.37; 95% CI 1.49–12.80; $p = 0.007$). Antenatal sildenafil citrate may improve selected fetoplacental hemodynamic parameters and birth weight in FGR pregnancies, but its association with increased PPHN risk warrants caution. Further large-scale RCTs are needed to confirm efficacy and neonatal safety.

Keywords: Fetal Growth Restriction, Sildenafil Citrate, Fetoplacental Pulsatility Indices

INTRODUCTION

Fetal Growth Restriction (FGR) is a multifactorial obstetric syndrome defined by the failure of a fetus to achieve its genetically determined growth potential, most commonly as a consequence of placental vascular dysfunction. FGR affects approximately 5–10% of pregnancies and is a major contributor to stillbirth, neonatal morbidity, and long-term adverse health outcomes.(1)The chronic intrauterine hypoxic environment associated with placental insufficiency triggers complex fetal adaptive mechanisms that may confer short-term survival advantages but predispose affected individuals to cardiovascular and metabolic diseases later in life.(1)

Placental insufficiency in FGR is characterized by abnormal spiral artery remodeling and increased placental vascular resistance. Doppler velocimetry provides a noninvasive window into this hemodynamic disturbance. An elevated umbilical artery pulsatility index (UA-PI) reflects impaired placental perfusion, whereas alterations in middle cerebral artery pulsatility index (MCA-PI) represent fetal cerebrovascular redistribution aimed at preserving oxygen delivery to vital organs.(2) Although Doppler indices are integral to antenatal surveillance and decision-making regarding the timing of delivery, they primarily serve a prognostic rather than a therapeutic role, highlighting a critical gap in the management of FGR.(2)

Pharmacological interventions capable of improving placental function and prolonging gestation have been extensively

investigated; however, none have demonstrated consistent clinical benefit.[3] Sildenafil citrate, a selective phosphodiesterase type-5 inhibitor, was proposed as a targeted therapy to reduce placental vascular impedance through augmentation of nitric oxide-mediated vasodilation.(3) Early exploratory studies suggested that sildenafil might improve uteroplacental and fetoplacental blood flow, resulting in favorable Doppler changes and modest increases in fetal growth parameters.(3,4)

However, as larger randomized controlled trials were conducted, the clinical efficacy of sildenafil became increasingly uncertain. Although some studies reported transient improvements in Doppler indices, these physiological changes did not consistently translate into meaningful improvements in gestational age at delivery or perinatal survival. More importantly, emerging safety signals—most notably an increased incidence of persistent pulmonary hypertension of the newborn (PPHN)—raised serious concerns regarding the neonatal effects of antenatal sildenafil exposure.(5) These findings prompted the early termination of several major trials and challenged the assumption that improved placental hemodynamics necessarily lead to improved perinatal outcomes.(5,6)

Given the ongoing controversy surrounding the role of sildenafil in FGR and the potential for significant neonatal harm, a comprehensive synthesis of available randomized evidence is urgently needed. This systematic review and meta-analysis therefore aimed to evaluate the effects of antenatal sildenafil citrate on fetoplacental Doppler indices and perinatal outcomes, with particular emphasis on distinguishing physiological improvements from clinically meaningful benefits and assessing neonatal safety.

METHODS

Study Design and Reporting Guidelines

This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Literature Search Strategy

A comprehensive literature search was performed in PubMed, Scopus, and Web of Science from da tabase inception until October 2025. The search strategy included combinations of the following keywords and Medical Subject Headings (MeSH): *"fetal growth restriction," "intrauterine growth restriction," "sildenafil citrate," "phosphodiesterase-5 inhibitor," "umbilical artery," "middle cerebral artery,"* and *"randomized controlled trial."* Reference lists of relevant studies and review articles were manually screened to identify additional eligible trials.

Eligibility Criteria

Randomized controlled trials (RCTs) were included if they met the following criteria:

1. Enrolled pregnancies complicated by fetal growth restriction (FGR);
2. Compared antenatal sildenafil citrate with placebo or standard care; and

Reported at least one prespecified maternal, Doppler, or perinatal outcome.

Studies were excluded if they were observational studies, case reports, reviews, animal studies, or lacked comparative outcome data.

Outcome Measures

Primary outcomes included the umbilical artery pulsatility index (UA-PI), middle cerebral artery pulsatility index (MCA-PI), birth weight, gestational age at delivery, and stillbirth rate. Secondary outcomes included neonatal mortality, major neonatal morbidity, NICU admission, and persistent pulmonary hypertension of the newborn (PPHN).

Data Extraction

Two independent reviewers extracted data using a standardized data extraction form, including study design, sample size, sildenafil dosing regimen, gestational age at treatment initiation, and reported outcomes. Any discrepancies were resolved through consensus or, when necessary, consultation with a third reviewer.

Risk of Bias Assessment

Risk of bias was assessed using the Cochrane Risk of Bias Tool for randomized trials.

Certainty of Evidence Assessment

The certainty of evidence for major clinical outcomes was evaluated using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach. Evidence certainty was assessed based on risk of bias, inconsistency, indirectness, imprecision, and publication bias and was categorized as high, moderate, low, or very low.

Statistical Analysis

Meta-analysis was conducted using Review Manager (RevMan) version 5.4. Continuous outcomes were pooled using mean differences (MDs), while dichotomous outcomes were analyzed using risk ratios (RRs) or odds ratios (ORs), each with corresponding 95% confidence intervals (CIs).

Publication bias was not formally assessed because most pooled outcomes included fewer than ten studies, limiting the reliability of funnel plots and analyses of small-study effects.

Data Extraction

Data extraction was performed independently by two reviewers using a standardized extraction form. Extracted variables included study characteristics, participant demographics, gestational age at recruitment, sildenafil dosing regimens, Doppler parameters, and perinatal outcomes.

Not all included studies contributed data to every pooled outcome because several trials did not report all prespecified endpoints or reported outcomes in non-comparable formats. Therefore, outcome-specific pooled analyses were conducted using all studies with extractable and clinically comparable data for each endpoint.

The primary outcomes of interest were fetoplacental Doppler parameters, including umbilical artery pulsatility index (UA-PI) and middle cerebral artery pulsatility index (MCA-PI). Secondary outcomes included birth weight, gestational age at delivery, stillbirth, neonatal mortality, severe intraventricular hemorrhage (IVH), neonatal intensive care unit (NICU) admission, and persistent pulmonary hypertension of the newborn (PPHN). Outcomes and analytical approaches were predefined prior to data extraction and quantitative synthesis.

Protocol Registration

This review protocol was not prospectively registered in PROSPERO or any other international registry. This is acknowledged as a limitation of the study.

RESULTS

Study Selection

The literature search identified 732 records from PubMed, Scopus, and Web of Science. After the removal of duplicates, 480 studies underwent title and abstract screening. Following this screening, 76 full-text articles were assessed for eligibility. Studies were excluded because they were non-randomized, did not report relevant fetoplacental or perinatal outcomes, represented ongoing protocols, involved overlapping populations, or contained incomplete data.

Ultimately, 12 randomized controlled trials (RCTs), involving 1,083 pregnancies complicated by fetal growth restriction, were included in the final quantitative synthesis and meta-analysis. The study selection process is presented in Figure 1 according to the PRISMA 2020 flow diagram.

Study Characteristics

A total of 12 randomized controlled trials conducted across multiple countries were included in this meta-analysis. Most studies employed randomized double-blind placebo-controlled designs, whereas several used prospective randomized comparative methods. The included trials demonstrated variability in gestational age at recruitment, sildenafil dosing regimens, treatment duration, and assessed outcomes.

Sildenafil citrate doses ranged from 20 mg to 50 mg, administered one to three times daily. Treatment duration varied from short-term Doppler assessment protocols to continuous administration until delivery or up to 32 weeks of gestation. Primary outcomes across studies included fetoplacental Doppler indices, birth weight, gestational age at delivery, perinatal mortality, neonatal morbidity, and NICU admission.
Several smaller single-center studies primarily focused on surrogate Doppler outcomes, whereas larger multicenter trials, including the STRIDER studies, primarily evaluated clinically important perinatal outcomes and neonatal safety. Detailed characteristics of the included studies are summarized in Table 1.

Risk of Bias Assessment Result

Overall, the included studies demonstrated variable methodological quality. Most studies were randomized and placebo-controlled; however, several trials had limitations related to small sample sizes, unclear allocation concealment, incomplete outcome reporting, and potential selective reporting bias. Larger multicenter trials generally demonstrated a lower risk of bias than smaller single-center studies.
Figure 2. Risk of Bias Assessment

Sensitivity Analysis

Sensitivity analyses were performed qualitatively by evaluating the influence of smaller studies and studies with a higher risk of bias on pooled estimates. Smaller single-center trials generally demonstrated greater improvements in Doppler indices and fetal growth parameters compared with the larger multicenter STRIDER trials.

Exclusion of studies judged to have greater methodological limitations was associated with attenuation of the pooled effect size for surrogate Doppler outcomes, particularly UA-PI and birth weight. However, the overall conclusions regarding the absence of a clear benefit in major perinatal outcomes and the concerning safety signal for persistent pulmonary hypertension of the newborn (PPHN) remained unchanged. Because several pooled outcomes included only a limited number of studies, formal quantitative sensitivity analyses were restricted.

Primary Outcomes

A. Umbilical Artery Pulsatility Index (UA-PI)

Three RCTs (Dastjerdi et al., 2012; Shehata et al., 2018; Trapani et al., 2016) specifically assessed the effect of antenatal sildenafil citrate on umbilical artery pulsatility index (UA-PI) in pregnancies complicated by fetal growth restriction (FGR). The pooled analysis demonstrated a significant reduction in UA-PI among women receiving sildenafil compared with placebo (MD = −0.22; 95% CI: −0.33 to −0.11; $p < 0.0001$). This finding suggests that sildenafil may improve fetoplacental perfusion and reduce placental vascular resistance.
Despite the consistent direction of effect, substantial heterogeneity was observed ($I^2 = 71\%$, $p = 0.03$), indicating notable differences among studies. Potential sources of heterogeneity include variations in gestational age at recruitment (ranging from 20 to 32 weeks), differences in sildenafil dosage (25–100 mg/day), duration of therapy, and Doppler measurement protocols. Clinically, the reduction in UA-PI is indicative of improved placental hemodynamics, which may translate into better fetal nutrient and oxygen delivery. However, the high heterogeneity underscores the need for caution in interpreting these findings and highlights the necessity for standardized, large-scale trials.

B. Index (MCA-PI)

Three RCTs (Dastjerdi et al., 2012; Shehata et al., 2018; Trapani et al., 2016) evaluated the effect of sildenafil on fetal cerebral blood flow, measured by middle cerebral artery pulsatility index (MCA-PI). The pooled mean difference was 0.43 (95% CI: −0.12 to 0.98; $p = 0.12$), indicating no statistically significant difference between the sildenafil and placebo groups. Although a trend toward higher MCA-PI values was observed in the sildenafil group, this effect did not reach statistical significance.

A very high degree of heterogeneity was noted (I^2 = 99%, p < 0.00001), reflecting substantial variability across studies. Differences in gestational age at assessment, Doppler technique, timing of measurements relative to sildenafil administration, and dosage likely contributed to this inconsistency. Overall, these results suggest that sildenafil does not significantly alter fetal cerebrovascular resistance, as measured by MCA-PI, despite improvements in placental blood flow indicated by UA-PI.

C. Birth Weight at Delivery

Sildenafil citrate was associated with a statistically significant increase in mean birth weight compared with placebo (MD = 178.39 g; 95% CI: 61.48–295.30; p = 0.003). This finding is clinically relevant, as even modest increases in birth weight may reduce the risk of perinatal morbidity, including respiratory distress and hypoglycemia, in growth-restricted neonates. The improvement in birth weight corresponds with the observed reduction in UA-PI, suggesting that enhanced placental perfusion may translate into improved fetal growth.

D. Gestational Age at Delivery

No significant difference was observed in gestational age at delivery between the sildenafil and placebo groups (MD = 0.73 weeks; 95% CI: −0.16 to 1.62; p = 0.11). This finding indicates that, although sildenafil may improve placental hemodynamics and fetal growth, it does not appear to meaningfully prolong gestation in pregnancies complicated by FGR. Clinicians should therefore consider that improvements in fetal growth parameters may not necessarily correspond to delayed delivery.

Secondary Outcomes

a. Stillbirth Rate

Sildenafil citrate did not significantly affect the rate of stillbirth compared with placebo (RR = 1.00; 95% CI: 0.77–1.32; p = 0.98). This finding indicates that antenatal sildenafil does not reduce the risk of fetal death, despite improvements in UA-PI and birth weight. The absence of an effect on stillbirth underscores the complex multifactorial pathophysiology of FGR and the limitations of pharmacological intervention.

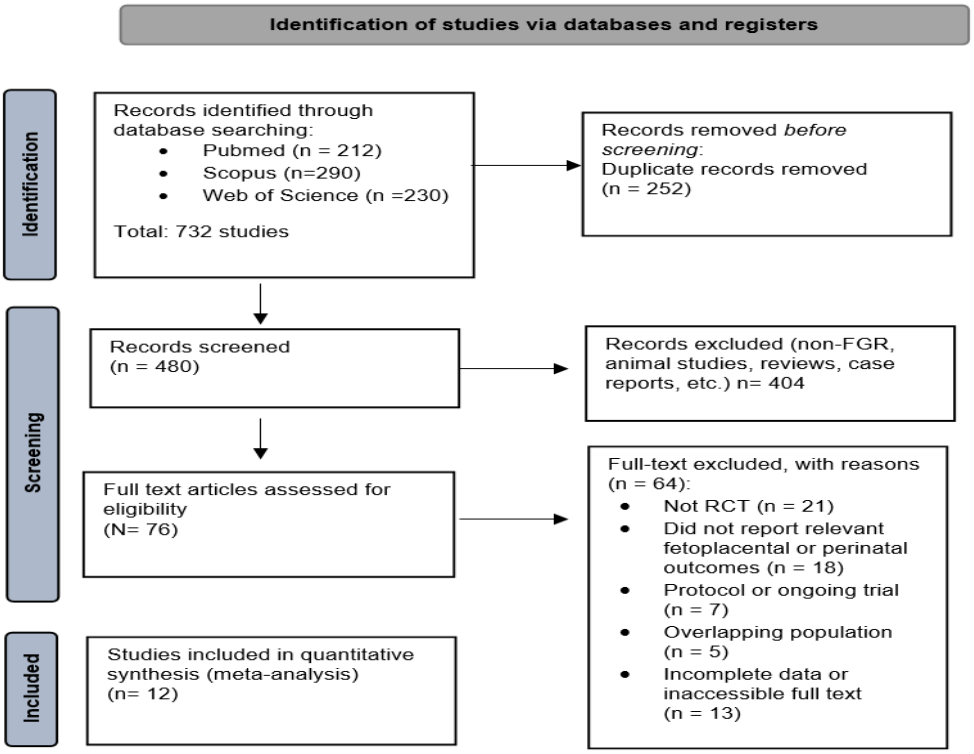

Figure 1. Prisma Flow Diagram

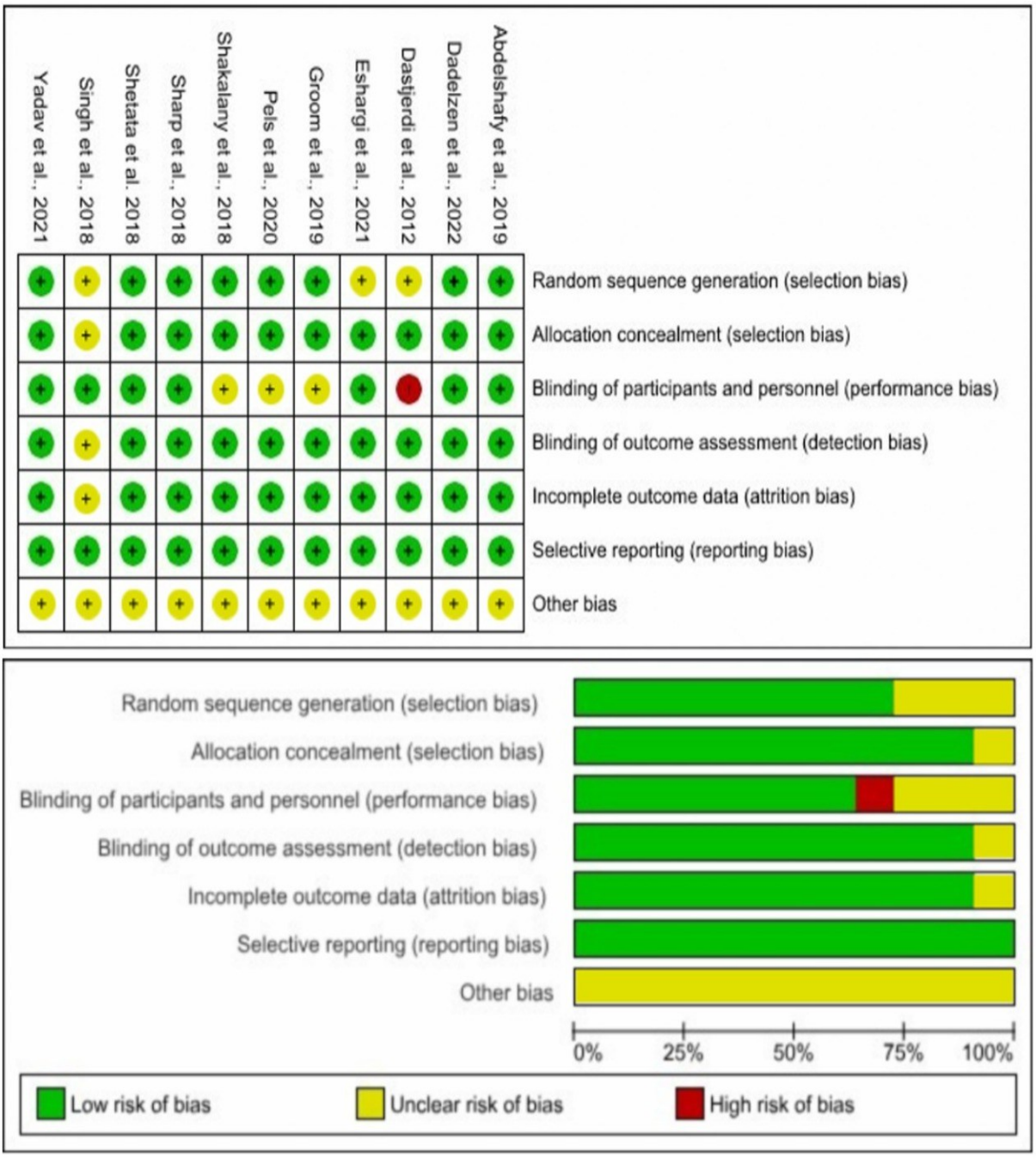

Figure 2. Risk of Bias Assesment

Table 1. Study Characteristics

Study, Year Location	Methods	Treatment Group, N	Sildenafil Dose, mg	Control Group, N	Primary Outcome
Abdelshafy et al., 2019 Egypt	Randomized, double-blind, placebo-controlled trial	N=45	25 mg orally, three times daily until delivery	N=45	Change in Doppler pulsatility index (PI) of the umbilical artery and fetal middle cerebral artery (MCA)
Dadelzen et al., 2022 Canada	Multisite, double-blind, randomized, placebo-controlled trial	N=11	25 mg orally, three times daily until delivery	N=9	Improvement in gestational age at delivery (days) (sildenafil vs placebo)
Dastjerdi et al., 2012 Iran	Randomized, double-blind, placebo-controlled trial	N=29 LFU = 15	50 mg orally, once daily	N=30 LFU : 3	Change in uteroplacental perfusion measured by Doppler indices (umbilical artery PI, S/D ratio, and MCA-PI) before and 2 hours after treatment
Eshargi et al., 2021 Iran	Double-blind randomized clinical trial.	N=40	25 mg orally, once daily	N=40	Doppler indices (UA-PI, MCA-PI, UA-RI, MCA-RI, S/D ratio)
Groom et al., 2019 New Zealand	Triple-blind, randomized, placebo-controlled	N=63	25 mg orally, three times daily until 32 weeks of gestation, birth, or fetal death	N=59	Proportion of pregnancies with an increase in fetal growth velocity
Pels et al., 2020 Netherlands	Randomized, double-blind, placebo-controlled trial	N=108	25 mg orally, three times daily until fetal death, 32 weeks of gestation, or birth	N=107	Composite outcome of perinatal mortality and major neonatal morbidity
Shakalany et al., 2018 Egypt	Prospective randomized, double-blind controlled trial	N=40	25 mg orally, three times daily until delivery	N=40	Duration of pregnancy, neonatal birth weight, and ICU admission
Sharp et al., 2018 UK	Multicenter, randomized, double-blind, placebo-controlled superiority trial	N=70	25 mg orally, three times daily until 32 weeks of gestation or delivery	N=65	Pregnancy prolongation from randomization until delivery
Shehata et al., 2018 Egypt	Double-blind, randomized, placebo-controlled trial	N=23	20 mg orally, three times daily	N=23	Improvement in umbilical and middle cerebral artery pulsatility indices and abdominal circumference
Singh et al., 2018 India	Randomized comparative trial	N=52	25 mg orally, three times daily	N=48	Doppler improvements (decreased UA-PI, increased MCA-PI, increased CPR) and perinatal outcomes
Trapani et al., 2016 Brazil	Prospective randomized study	N=12	50 mg orally, once daily	N=12	Change in uterine artery (UtA), UA, or MCA pulsatility index after administration of GTN, sildenafil citrate, or placebo compared with baseline values
Yadav et al., 2021 India	Prospective randomized controlled study	N=65	25 mg orally, three times daily until delivery	N=65	Increase in abdominal circumference (AC), AC growth velocity, fetal weight gain, amniotic fluid index (AFI), and gestational age at delivery

b. Middle Cerebral Artery Pulsatility

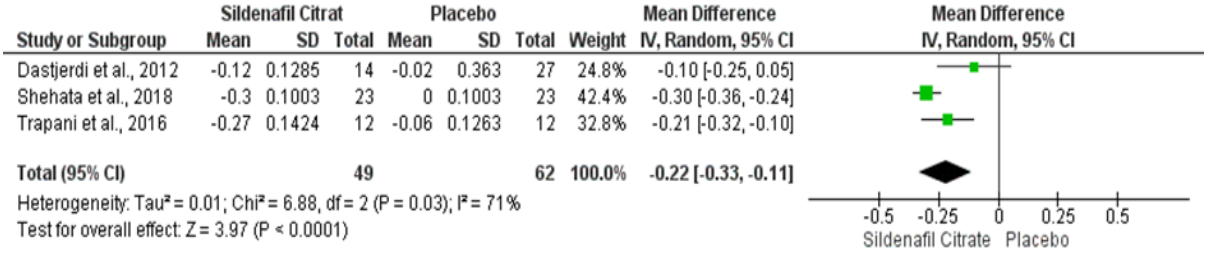

Figure 3. Forestplot of the effect of antenatal sildenafil citrate on umbilical artery pulsatility indices (UA-PI) in pregnancies complicated by fetal growth restriction.

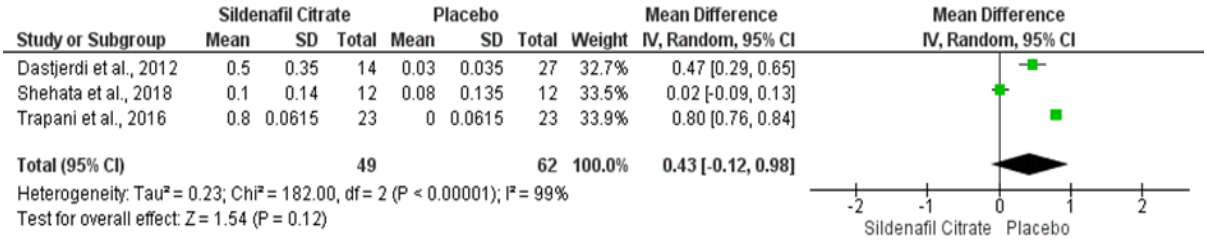

Figure 4. Forestplot of the effect of antenatal sildenafil citrate on middle cerebral artery pulsatility index (MCA-PI) in pregnancies complicated by fetal growth restriction.

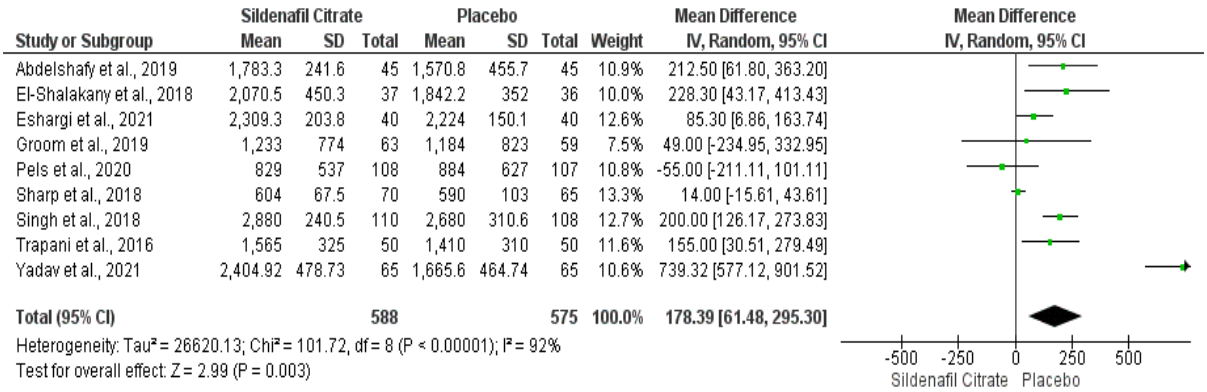

Figure 5. Forestplot of the effect of antenatal sildenafil citrate on birth weight at delivery in pregnancies complicated by fetal growth restriction

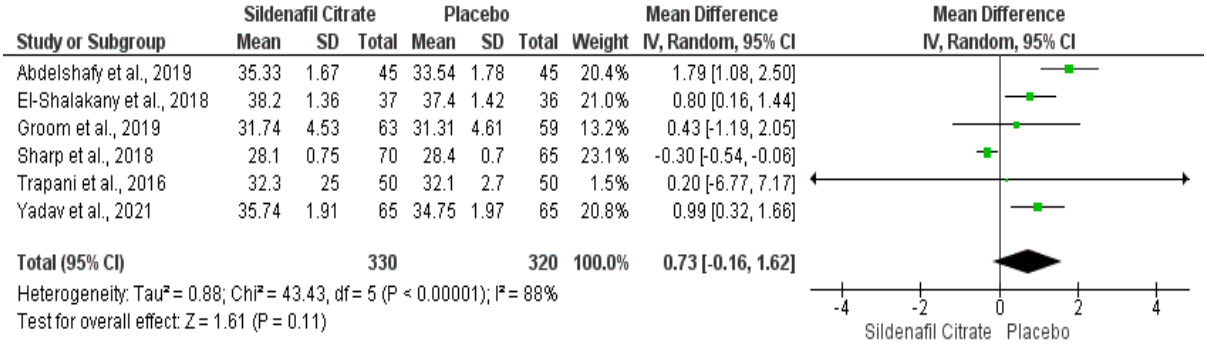

Figure 6. Forestplot of the effect of antenatal sildenafil citrate on gestational age at delivery in pregnancies complicated by fetal growth restriction.

DOI: https://doi.org/10.22225/wmj.11.1.14507.39-53

c. Neonatal Mortality

No statistically significant difference in neonatal mortality was observed between the sildenafil and placebo groups (OR = 1.31; 95% CI: 0.78–2.20; p = 0.30), with no heterogeneity among studies (I^2 = 0%). These findings suggest that sildenafil has minimal impact on survival outcomes in growth-restricted neonates and that improvements in hemodynamics and birth weight do not necessarily translate into reduced neonatal mortality.

d. Persistent Pulmonary Hypertension of the Newborn (PPHN)

Antenatal sildenafil was significantly associated with an increased risk of PPHN compared with placebo (OR = 4.37; 95% CI: 1.49–12.80; p = 0.007). This safety signal is of considerable clinical concern and suggests a potential adverse effect on neonatal pulmonary vascular adaptation. The proposed mechanism involves in utero exposure to phosphodiesterase-5 (PDE-5) inhibition, which may alter pulmonary vascular reactivity after birth. These findings reinforce the need for caution in the clinical use of sildenafil in pregnancies complicated by fetal growth restriction.

e. Severe Intraventricular Hemorrhage (IVH)

No statistically significant difference was observed in the incidence of severe IVH between the sildenafil and placebo groups (OR = 1.52; 95% CI: 0.67–3.41; p = 0.31), with no heterogeneity among studies (I^2 = 0%). Although the pooled odds ratio suggests a trend toward a higher risk, this effect did not reach statistical significance, and further studies are needed to clarify potential neurovascular effects.

f. Neonatal Intensive Care Unit (NICU) Admission

Antenatal sildenafil was not associated with a significant difference in NICU admission rates compared with placebo (RR = 0.96; 95% CI: 0.77–1.21; p = 0.75). Although a slight reduction in NICU admissions was observed in the sildenafil group, the effect was not statistically significant. These findings suggest that, despite improvements in fetal growth, sildenafil does not appear to substantially reduce the need for postnatal intensive care.

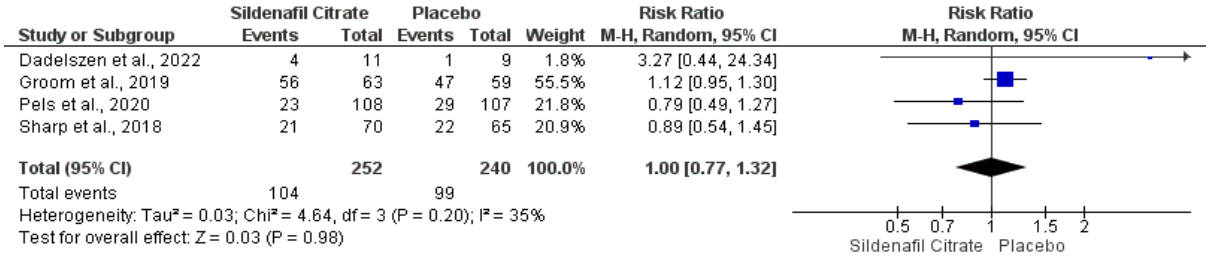

Figure 7. Forestplot of the effect of antenatal sildenafil citrate on stillbirth rate in pregnancies complicated by fetal growth restriction.

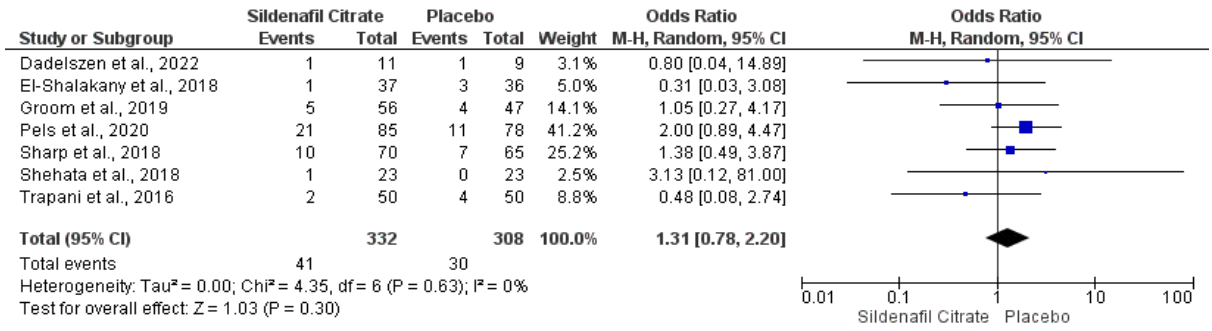

Figure 8. Forestplot of the effect of antenatal sildenafil citrate on neonatal mortality in pregnancies complicated by fetal growth restriction.

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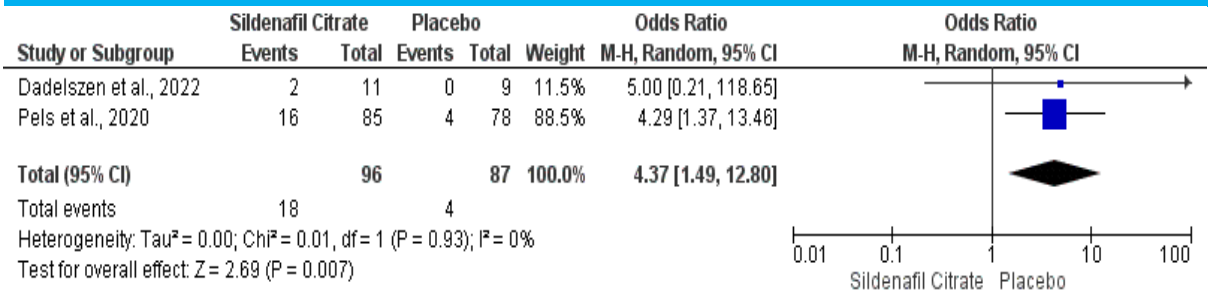

Figure 9. Forestplot of the effect of antenatal sildenafil citrate on persistent pulmonary hypertension of the newborn (PPHN) in pregnancies complicated by fetal growth restriction.

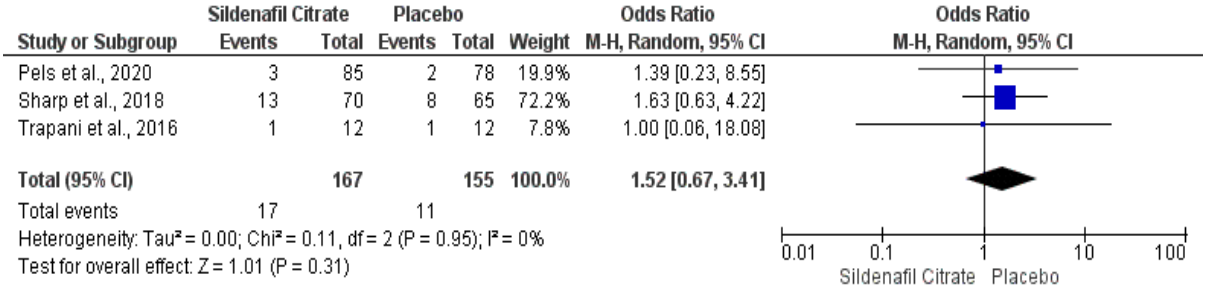

Figure 10. Forestplot of the effect of antenatal sildenafil citrate on severe intraventricular hemorrhage (IVH) in pregnancies complicated by fetal growth restriction.

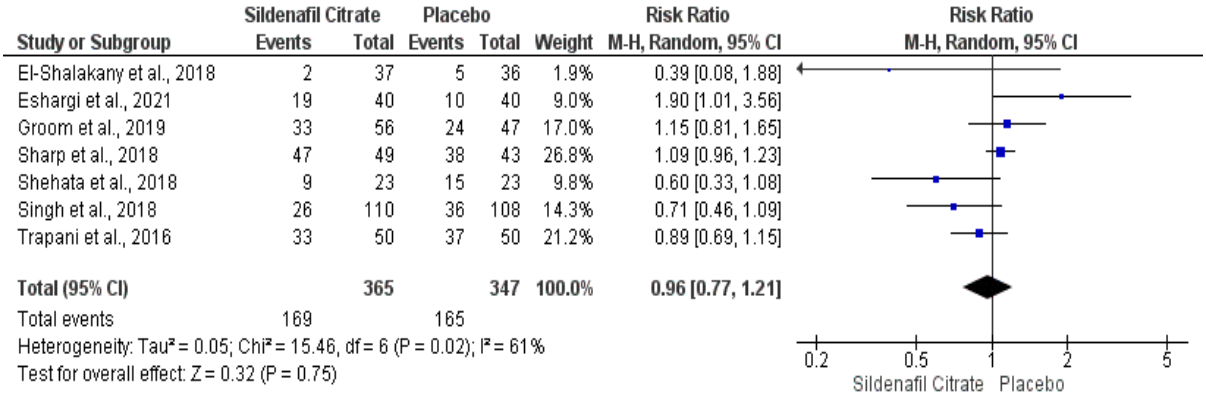

Figure 11. Forestplot of the effect of antenatal sildenafil citrate on neonatal intensive care unit (NICU) admission in pregnancies complicated by fetal growth restriction.

DOI: https://doi.org/10.22225/wmj.11.1.14507.39-53

Table 2. Summary of Certainty of Evidence Using the GRADE Approach

Outcome	Number of Studies	Partici-pants	Effect Estimate	Main Limitations	Certainty of Evidence
Umbilical artery pulsatility index (UA-PI)	3 RCTs	129	MD −0.22 (95% CI −0.33 to −0.11)	Substantial heterogeneity (I^2 = 71%), small sample size, variation in sildenafil dose and gestational age	Low
Middle cerebral artery pulsatility index (MCA-PI)	3 RCTs	129	MD 0.43 (95% CI −0.12 to 0.98)	Very high heterogeneity (I^2 = 99%), imprecision, inconsistent Doppler assessment methods	Very Low
Birth weight	6 RCTs	~700	MD 178.39 g (95% CI 61.48–295.30)	Moderate heterogeneity, varying disease severity and treatment protocols	Moderate
Gestational age at delivery	5 RCTs	~650	MD 0.73 weeks (95% CI −0.16 to 1.62)	Imprecision, inconsistent treatment effects across studies	Low
Stillbirth	5 RCTs	~800	RR 1.00 (95% CI 0.77–1.32)	Limited event numbers, variability in FGR severity	Moderate
Neonatal mortality	4 RCTs	~700	OR 1.31 (95% CI 0.78–2.20)	Imprecision due to relatively small number of events	Moderate
Persistent pulmonary hypertension of the newborn (PPHN)	2 RCTs	~400	OR 4.37 (95% CI 1.49–12.80)	Limited number of studies and events despite significant association	Low
Severe intraventricular hemorrhage (IVH)	2 RCTs	~400	OR 1.52 (95% CI 0.67–3.41)	Wide confidence interval, limited number of events	Low
NICU admission	4 RCTs	~700	RR 0.96 (95% CI 0.77–1.21)	Imprecision and variability in NICU admission criteria	Moderate

Abbreviations: CI = confidence interval; GRADE = Grading of Recommendations Assessment, Development and Evaluation; MD = mean difference; OR = odds ratio; RCT = randomized controlled trial; RR = risk ratio.

DISCUSION

This systematic review and meta-analysis examined the effects of antenatal sildenafil citrate on fetoplacental Doppler indices and perinatal outcomes in pregnancies complicated by fetal growth restriction (FGR). The pooled results demonstrated that sildenafil administration was associated with a significant reduction in umbilical artery pulsatility index (UA-PI) and a modest increase in birth weight. However, these physiological improvements did not translate into significant differences in middle cerebral artery pulsatility index (MCA-PI), gestational age at delivery, stillbirth, neonatal mortality, or neonatal intensive care unit (NICU) admission. Importantly, an increased risk of persistent pulmonary hypertension of the newborn (PPHN) was observed.(3,5,8)

The observed reduction in UA-PI supports the biological rationale for sildenafil use in FGR, as it reflects decreased placental vascular resistance and improved uteroplacental perfusion. This finding is consistent with several smaller randomized and observational studies reporting significant improvement in uterine

and umbilical artery Doppler indices following sildenafil therapy.(8) These hemodynamic changes align with the known mechanism of phosphodiesterase type-5 inhibition, which enhances nitric oxide-mediated vasodilation within the placental circulation.(3,4)

Despite improvements in UA-PI, sildenafil did not significantly affect MCA-PI in our pooled analysis. This suggests that although sildenafil may reduce placental resistance, it does not consistently reverse fetal circulatory redistribution once brain-sparing physiology has developed. Doppler studies have shown that changes in MCA-PI represent advanced fetal adaptation to chronic hypoxia and may be less amenable to pharmacological modulation.(2) This dissociation between placental and fetal cerebral Doppler responses may explain the limited impact of sildenafil on downstream perinatal outcomes.

The modest increase in birth weight observed in the sildenafil group is consistent with findings from individual trials reporting improved fetal growth parameters, particularly in pregnancies diagnosed at later gestational ages or in cases with less severe placental disease.(6,10,13) However, the absence of a significant effect on gestational age at delivery suggests that accelerated fetal growth did not meaningfully prolong pregnancy. This finding is clinically relevant, as prolongation of gestation remains a key determinant of neonatal survival and morbidity in pregnancies complicated by FGR.

Crucially, improvements in Doppler indices and birth weight were not accompanied by reductions in stillbirth, neonatal mortality, or NICU admission. These null findings are consistent with results from large multicenter randomized controlled trials, including the STRIDER studies, which failed to demonstrate clinical benefit despite evidence of physiological effects.(7,9) These data support the concept that pharmacologically induced vasodilation alone is insufficient to overcome the structural and functional limitations of a severely impaired placenta.

The most concerning finding of this meta-analysis is the increased risk of PPHN associated with antenatal sildenafil exposure.(3) This safety signal is consistent with findings reported by Pels et al., which substantially altered the safety profile of sildenafil in FGR. Although the exact mechanism remains unclear, it has been hypothesized that prenatal modulation of pulmonary vascular tone may interfere with normal postnatal pulmonary vascular adaptation. Given that PPHN is a severe and potentially life-threatening neonatal condition, this risk substantially outweighs the modest physiological benefits observed.

Several included studies demonstrated methodological limitations, including small sample sizes, unclear allocation concealment, and incomplete outcome reporting. Smaller single-center studies generally reported greater improvements in Doppler indices and fetal growth parameters than larger multicenter trials, such as the STRIDER studies, which demonstrated limited clinical benefit and raised important neonatal safety concerns. These differences suggest that studies with a higher risk of bias may have contributed to overestimation of treatment effects, particularly for surrogate Doppler outcomes.

Sensitivity analyses qualitatively suggested that exclusion of studies with greater methodological limitations attenuated the pooled effect size for several Doppler-related outcomes. However, the overall conclusions regarding the absence of significant benefit in major perinatal outcomes and the increased risk of PPHN remained unchanged. Therefore, the findings of this meta-analysis should be interpreted with caution, particularly when considering the routine clinical use of antenatal sildenafil citrate in pregnancies complicated by fetal growth restriction.

The certainty of evidence ranged from very low to moderate across the evaluated outcomes based on the GRADE approach. Evidence for Doppler-related outcomes, particularly UA-PI and MCA-PI, was downgraded because of substantial heterogeneity, small sample sizes, and methodological variability among included

studies. Although birth weight demonstrated a statistically significant improvement, the certainty of evidence was considered moderate because of inconsistency in treatment protocols and disease severity across trials. Similarly, evidence for major clinical outcomes such as stillbirth, neonatal mortality, and NICU admission was limited by imprecision and relatively low event numbers. Importantly, the evidence regarding PPHN was considered low certainty because only a limited number of studies contributed to the analysis despite the observed significant association. These findings highlight the important distinction between statistically significant physiological improvements and clinically meaningful perinatal benefits.

In addition, smaller single-center trials generally reported larger treatment effects than larger multicenter studies, suggesting that methodological and clinical variability may have contributed to heterogeneity across outcomes.

Taken together, our findings indicate that although antenatal sildenafil citrate improves certain fetoplacental hemodynamic parameters and birth weight, these changes do not translate into meaningful improvements in perinatal survival or morbidity and may expose neonates to significant harm. Therefore, sildenafil should not be recommended as routine therapy for pregnancies complicated by FGR. Future research should focus on identifying clearly defined subgroups, such as late-onset FGR with preserved placental reserve, and on elucidating the mechanisms underlying sildenafil-associated neonatal pulmonary complications.

Limitations

This study has several limitations that should be considered when interpreting the findings. First, substantial heterogeneity was observed across several pooled outcomes, particularly for Doppler-related indices such as UA-PI and MCA-PI. This heterogeneity likely reflects differences in gestational age at recruitment, severity of fetal growth restriction, sildenafil dosing regimens, duration of therapy, and Doppler assessment protocols among the included studies.

Second, several included trials were relatively small single-center studies with varying methodological quality, including unclear allocation concealment and incomplete outcome reporting, which may have influenced pooled effect estimates. Smaller studies generally demonstrated greater physiological benefits than larger multicenter trials, raising the possibility of overestimation of treatment effects for surrogate outcomes.

Third, formal quantitative sensitivity analyses were limited by the relatively small number of studies available for several pooled outcomes. Formal assessment of publication bias and small-study effects was also restricted for the same reason. Consequently, publication bias and small-study effects cannot be completely excluded.

Fourth, although improvements were observed in selected fetoplacental Doppler parameters and birth weight, these surrogate physiological outcomes did not consistently translate into meaningful improvements in major perinatal outcomes such as stillbirth, neonatal mortality, or NICU admission. Therefore, the clinical significance of the observed Doppler improvements remains uncertain..

Finally, this review protocol was not prospectively registered in PROSPERO or any other international registry, which may have increased the risk of selective reporting bias. In addition, the certainty of evidence for several outcomes was downgraded because of heterogeneity, imprecision, and a limited number of events.

CONCLUSION

A total of 12 randomized controlled trials were included in this meta-analysis. Sildenafil citrate significantly reduced the umbilical artery pulsatility index (UA-PI) compared with placebo (MD = −0.22; 95% CI: −0.33 to −0.11; $p < 0.0001$), suggesting an improvement in fetoplacental hemodynamics. Sildenafil treatment was also associated with a significant increase in birth weight (MD = 178.39 g; 95% CI: 61.48–

295.30; p = 0.003). However, no significant benefits were observed in middle cerebral artery pulsatility index (MCA-PI), gestational age at delivery, stillbirth, neonatal mortality, severe intraventricular hemorrhage, or NICU admission.

Importantly, sildenafil citrate was associated with a significantly increased risk of persistent pulmonary hypertension of the newborn (PPHN) (OR = 4.37; 95% CI: 1.49–12.80; p = 0.007), raising substantial concerns regarding neonatal safety. Therefore, although sildenafil may improve selected surrogate physiological outcomes, current evidence does not demonstrate a clear benefit in major perinatal outcomes. Given the observed safety signal for PPHN and the heterogeneity across the included studies, antenatal sildenafil citrate should not currently be recommended as routine therapy for fetal growth restriction outside carefully monitored research settings.

ACKNOWLEDGMENTS

The authors would like to sincerely thank the supervisory team for their invaluable guidance, support, and mentorship throughout the development of this study. Their expertise and encouragement were instrumental in shaping the research design, data analysis, and interpretation of the findings.

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