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Pentaerithrityl tetranitrate (PETN) for prevention of fetal growth restriction in pregnancy: A systematic review and meta-analysis☆

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ABSTRACT

Background: Fetal Growth Restriction (FGR), often due to placental insufficiency, poses significant risks to perinatal outcomes. This review evaluates the efficacy of pentaerythritol tetranitrate (PETN), a nitric oxide donor, in preventing FGR.

Methods: A systematic review and meta-analysis was conducted by searching PubMed, Embase, and CENTRAL up to July 2024. The inclusion criteria focused on randomized controlled trials comparing PETN to placebo in FGR prevention. Key outcomes were incidences of FGR, perinatal mortality, neonatal mortality, and intrauterine fetal demise (IUFD). Other outcomes were classified as maternal, fetal, neonatal and safety outcomes. We used Cochrane RoB 2.0 tool to assess risk of bias, and GRADE criteria for evidence quality.

Results: Two eligible studies encompassing 417 pregnant women at risk of FGR were included. PETN did not significantly reduce incidence of FGR (RR 0.83, 95 % CI 0.66–1.04, 2 trials, 417 participants, low certainty) or perinatal mortality (RR 0.64, 95 % CI 0.26–1.58, 2 trials, 417 participants, very low certainty) compared to placebo. None of the studies reported neonatal mortality or IUFD. However, PETN treatment was associated with a reduction in preterm birth (RR 0.74, 95 % CI 0.58–0.93, 2 trials, 417 participants, moderate certainty). Other outcomes were similar between the groups.

Conclusion: While PETN does not significantly impact FGR rates or perinatal mortality, it is associated with a reduction in preterm birth, suggesting potential benefits in high-risk pregnancies. Larger trials are necessary to substantiate these findings and clarify the role of PETN in FGR prevention.

1. Introduction

Fetal growth restriction (FGR) is a relatively common pregnancy complication defined by a discrepancy between actual and expected fetal ultrasound biometric measurements for a given gestational age [1]. Fetuses with FGR fail to reach their genetically predetermined growth potential, either, due to maternal factors (such as undernutrition, exposure to toxins, hypoxemia, hypovolemia, and cardiovascular conditions), fetal factors (like chromosomal or genetic abnormalities, malformations, and infections), or placental disorders [2]. Among these, the most common cause of FGR is placental dysfunction. The earlier and more severe the onset of FGR, the greater the risk of declining intrauterine fetal well-being, potentially leading to both short-term and long-term complications [3]. Several international scientific societies have established guidelines for managing FGR, emphasizing the delicate balance between extending the pregnancy to enhance fetal maturity and the risks associated with prolonged intrauterine stress [4]. While additional days or weeks in utero can reduce the likelihood of preterm birth, this approach must be weighed against the increased risk of fetal compromise, including a heightened chance of stillbirth. Although the focus should now shift from managing FGR to preventing it, there is no clear evidence currently which supports the efficacy of any pharmacological interventions to improve placental function [5]. Nitric oxide (NO) donors like pentaerythritol tetranitrate (PETN) decrease the impedance in the uteroplacental vessels and have been shown to have protective effects on the endothelium. In pregnancies complicated by impaired utero-placental perfusion, PETN has been shown to reduce the risk of severe FGR and perinatal death [6]. Exploring the existing literature could shed light on the potential of PETN as a therapeutic strategy for preventing FGR. In this study, we conducted a systematic

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review and meta-analysis to evaluate the effectiveness of PETN in the prevention of FGR during pregnancy.

2. Methods

This systematic review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The study protocol was registered with PROSPERO (registration number CRD42024533652).

2.1. Inclusion and exclusion criteria

All randomized controlled trials (RCTs) or quasi-RCTs that compared PETN with placebo or no treatment for the prevention of FGR during pregnancy were included. Unpublished studies, non-RCT designs, conference abstracts and studies with incomplete or unavailable data were excluded.

2.2. Search strategy

A comprehensive electronic database search was conducted, including PubMed (1946 to July 2024), Embase (1974 to July 2024), and the Cochrane Central Register of Controlled Trials (CENTRAL; 1946 to July 2024). The search encompassed articles published in English with no restriction on publication year. The U.S. National Library of Medicine's ClinicalTrials.gov was searched for registered ongoing trials. Additionally, reference lists of the retrieved articles and any previous systematic reviews on the subject were hand-searched to identify eligible studies. Follow-up reports of included studies were sought by searching for their trial registration numbers in MEDLINE. The search strategies can be found in Appendix S1**.** Additional related studies were identified by reviewing the reference lists of relevant articles.

2.3. Outcome measures

The main outcomes assessed included the incidences of FGR, perinatal mortality, neonatal mortality, and intra-uterine fetal demise (IUFD). Additional outcomes examined were categorized into maternal, fetal, neonatal, and adverse maternal outcomes. Maternal outcomes encompassed preeclampsia (PE), placental abruption, preterm delivery (<37 weeks), instrumental delivery and caesarean section rates. Fetal outcomes examined included the incidence of severe FGR, and utero-placenta-fetal Doppler parameters. Neonatal outcomes included birth weight (BW), gestational age (GA) at birth, Apgar scores at 1 min and 5 min, umbilical cord blood gas parameters, Neonatal Intensive Care Unit (NICU) admission, need for ventilation support and incidences of neonatal morbidities.

2.4. Study selection and data extraction

Two investigators (AH and AD) independently conducted study selection, reviewed primary reports, and extracted pertinent data from the included studies. Any disagreements were resolved through discussion or consultation with a third reviewer (MP). In case of incomplete information from the published studies, we tried to contact the study authors, but unfortunately, we did not receive a response.

2.5. Quality assessment and risk of bias

Two authors (AH and SH) independently assessed the risk of bias in the included trials using the Cochrane 'Risk of Bias' (RoB 2.0) tool, evaluating domains such as bias arising from the randomization process, deviations from intended interventions, missing outcome data, measurement of outcomes, and selection of reported results [7]. Any disagreements were resolved by a third reviewer (MP).

2.6. Data synthesis, statistical analysis and grading of evidence

A preliminary narrative review was conducted. If two or more studies with sufficient similarity and acceptable heterogeneity were identified, meta-analysis was performed using Review Manager 5.4 [8]. Treatment effects were expressed as risk ratios (RR) and 95 % confidence intervals (CI) for categorical data, and mean differences (MD) and 95 % CI for continuous data. For primary analysis, a random-effects model was used to pool the results of individual studies. Statistical heterogeneity among the trials was assessed by inspecting forest plots and quantifying inconsistency using the I^2 statistic. Significant heterogeneity (I^2 >60 % or $P < 0.1$) prompted exploration of possible causes. In cases of non-significant heterogeneity, the meta-analysis results from fixed-effect model were additionally presented. We utilized GRADEpro software to assign the quality of evidence [9].

3. Results

The PRISMA flow diagram is shown in Fig. 1. We identified 50 references through electronic searches of PubMed (n = 9), Embase (n = 23), Cochrane Library (n = 18). After exclusion of non-relevant records (Appendix S2), four reports of two studies recruiting a total of 417 patients were finally included in the review [10–13].

3.1. Study characteristics

The characteristics of the included studies are summarized in Table 1**.** Both studies (Schleussner 2014, Groten 2023) were randomized, double-blinded, placebo-controlled trial recruiting 110 and 307 participants, respectively. These studies aimed to evaluate the role of PETN in prevention of FGR and perinatal death. Both studies included pregnant women 19 + 0 to 23 + 6 weeks of gestation with abnormal uterine artery doppler as defined by bilateral notching or unilateral notching and increased mean resistance index > 90th percentile. These pregnancies were further classified as low- and high-risk. High-risk group was defined as pre-existing hypertension or diabetes or history of adverse pregnancy outcome including FGR, late abortion, stillbirth, placental abruption, preterm delivery, PE, or HELLP syndrome. Groten 2023 included some additional high-risk factors like pre-existing vascular disorders and history of PE in previous pregnancy.

In Schleussner 2014, the intervention included PETN 80 mg twice a day starting at randomization and continued until gestational age of 35 weeks or stopped at the time of preterm delivery (n = 53), while the control group comprised of placebo that was identical in appearance and taste to the one containing PETN (n = 57). Intervention arm in Groten 2023 comprised of PETN 50 mg twice daily starting with enrolment until 36 + 6 weeks of gestation or the day of delivery (n = 151), while control group was administered placebo tablets identical in size, shape, taste, and colour (n = 156).

Both studies reported the incidences of FGR and perinatal mortality, but did not report the other main outcomes (neonatal mortality and IUFD). FGR was defined as BW < 10th percentile and the presence of one of the following criteria: reduced amniotic fluid, deceleration of fetal growth dynamics, impaired fetal perfusion, and/or fetal indication to initiate delivery (pathological cardiotocography monitoring). Schleussner 2014 defined severe FGR as BW < 5th percentile with presence of at least one of the following: PE, preterm birth, or placental abruption. However, the study results mentioned severe FGR as small-for-gestational age (SGA) infants, defined by a BW< 5th percentile. We considered the latter definition for uniformity across both studies.

3.2. Risk of bias of included studies

The assessment indicated "some concerns" for both studies according to RoB 2.0 tool (Appendix S3). Both studies had a low risk of bias for randomization, outcome measurement, missing outcome data, and

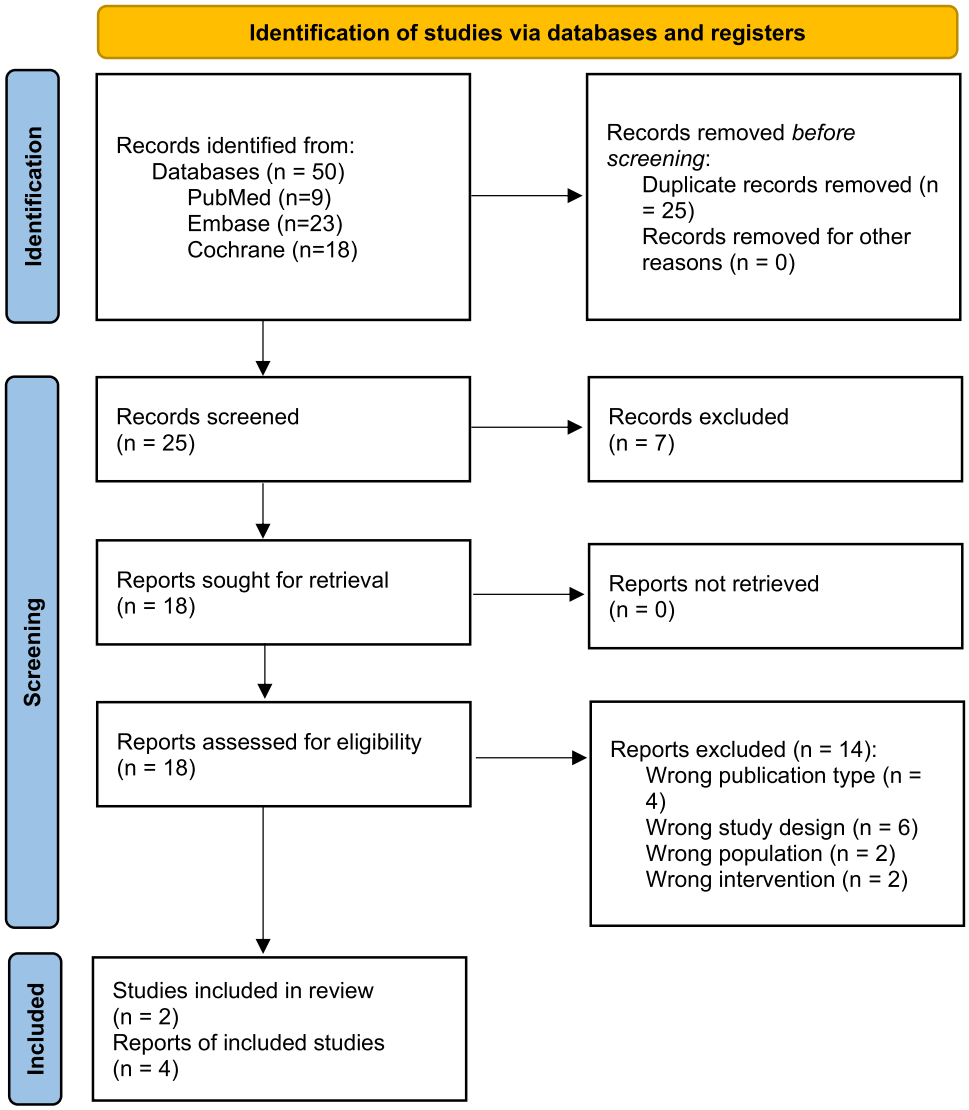

Fig. 1. PRISMA flow chart.

Table 1
Characteristics of the included studies.

Author, year	Setting, country	Study population, sample size	Interventions and control	Primary Outcome	Remarks
Schleussner 2014	Prospective, randomized, double-blinded, placebo-controlled trial (Germany)	Pregnant women 19 + 0 to 23 + 6 weeks of gestation with abnormal uterine artery Doppler as defined by bilateral notching or unilateral notching and increased mean resistance index > 90th percentile (N = 110, intervention=53, control=57)	PETN 80 mg twice a day started at randomization and continued until gestational age of 35 weeks or stopped at the time of preterm delivery **Control-** placebo identical in appearance and taste to the one containing PETN, twice daily	Occurrence of perinatal death and/ or IUGR	This study was a pilot trial. The risk stratification was performed during statistical analysis.
Groten 2023	Multicenter, randomized, double-blind, placebo controlled, parallel group study (Germany)	Pregnant women 19 + 0 to 23 + 6 weeks of gestation with abnormal uterine artery Doppler as defined by bilateral notching or unilateral notching and increased mean resistance index > 90th percentile (N = 307, intervention=151, control=156)	PETN 50 mg twice daily starting with enrolment until 36 + 6 weeks of gestation or the day of delivery **Control-** placebo tablets identical in size, shape, taste, and color	Composite outcome of perinatal death and/or development of FGR	This trial was conducted by the same group of researchers involved in the above study.

selective reporting. However, for deviations from intended interventions, there was some concern as adherence rates to treatment were not mentioned in both included studies.

3.3. Outcomes

3.3.1. Main outcomes

The incidence of FGR was similar between the two groups (RR=0.83; 95 % CI: 0.66–1.04; I^2 =0 %; 2 studies, 417 participants; low certainty,

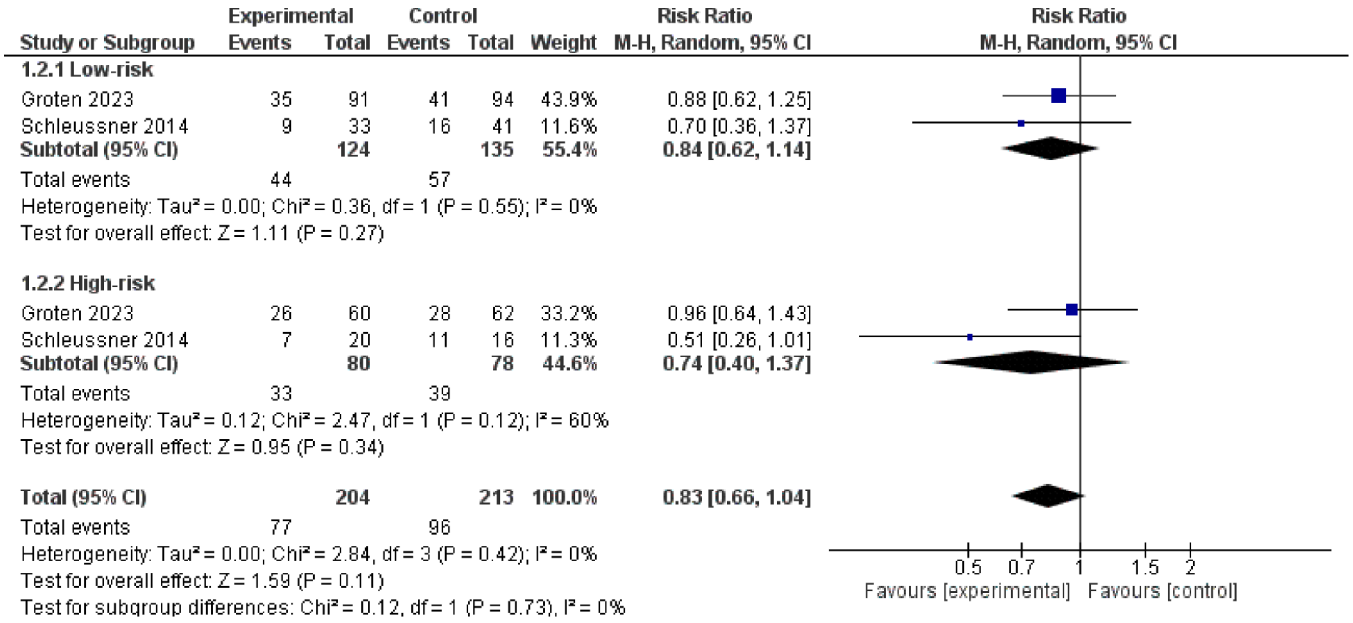

Fig. 2. Forest plot for comparison: PETN vs Placebo term (random effects model). Outcome: Fetal growth restriction.

Fig. 2), as was the incidence of perinatal death (RR=0.64; 95 % CI: 0.26–1.58; I^2 =0 %; 2 studies, 417 participants; very low certainty, Fig. 3). Additionally, there was no significant difference in the combined incidence of FGR or perinatal death (RR=0.81; 95 % CI: 0.64–1.03; I^2 =8 %; 2 studies, 417 participants; low certainty, Fig. 4). This lack of difference persisted across both low-risk and high-risk groups for all these outcomes. The evidence was rated as low certainty due to serious risk of bias and imprecision (Table 2).

3.3.2. *Maternal outcomes*

There were no significant differences in the risk of pre-eclampsia and HELLP syndrome, as well as, in the incidence of placental abruption (Appendix S4). PETN treatment was associated with a significant reduction in preterm delivery (RR=0.74; 95 % CI: 0.58–0.93; I^2 =0 %; 2 studies, 417 participants; moderate certainty). Consequently, GA at birth was significantly higher in the PETN group (MD=1.18 weeks; 95 % CI: 0.29–2.06; I^2 =0 %; 2 studies, 417 participants; moderate certainty), suggesting that PETN may contribute to extending pregnancy duration. Although the rate of instrumental delivery remained similar, caesarean sections were lower in the PETN group (RR=0.81; 95 % CI: 0.68–0.96; I^2 =0 %; 2 studies, 417 participants; moderate certainty).

3.3.3. *Fetal outcomes*

The risk of severe FGR did not differ significantly between the PETN and placebo groups (RR=0.86; 95 % CI: 0.62–1.18; I^2 =0 %; 2 studies, 417 participants; low certainty).

3.3.4. *Neonatal outcomes*

Schleussner 2014 reported no difference in BW between the two groups (2674 ± 889 vs. 2382 ± 1042 g; p = 0.161). Similarly, there was no difference in the APGAR scores at 1 min and 5 mins (7.5 ± 1.8 vs. 7.5 ± 2.1; p = 0.542 and 8.5 ± 1.2 vs. 8.8 ± 1.1; p = 0.323

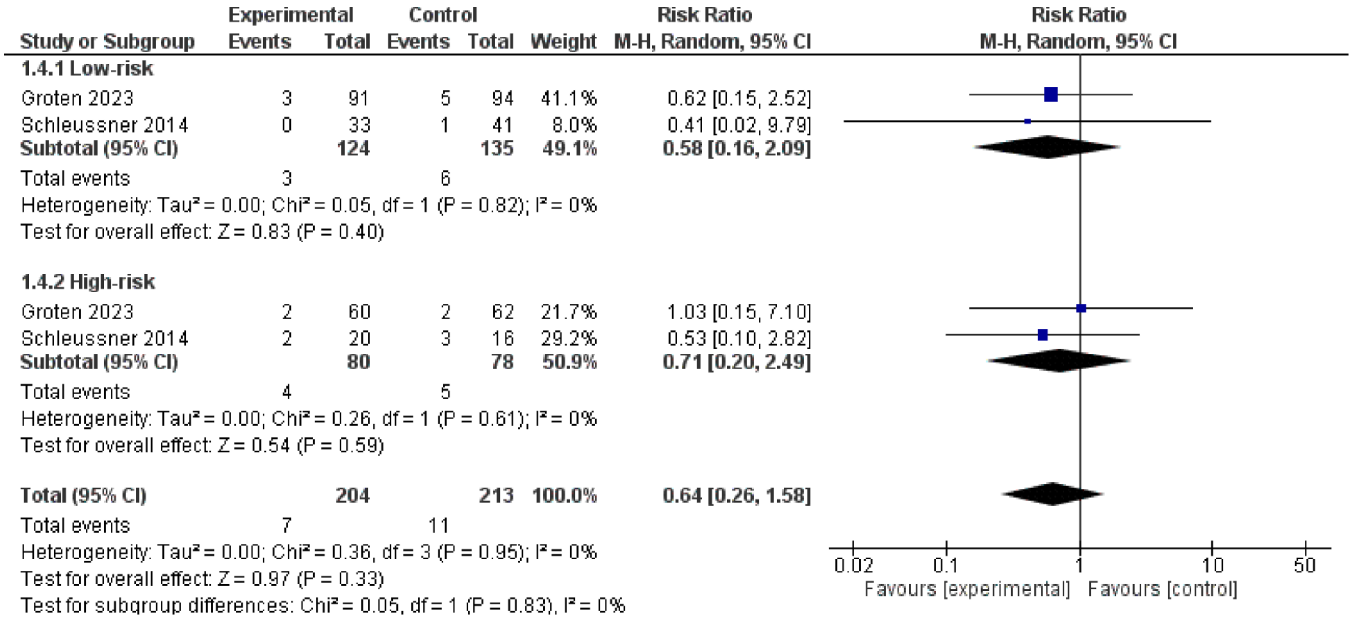

Fig. 3. Forest plot for comparison: PETN vs Placebo term (random effects model). Outcome: perinatal mortality.

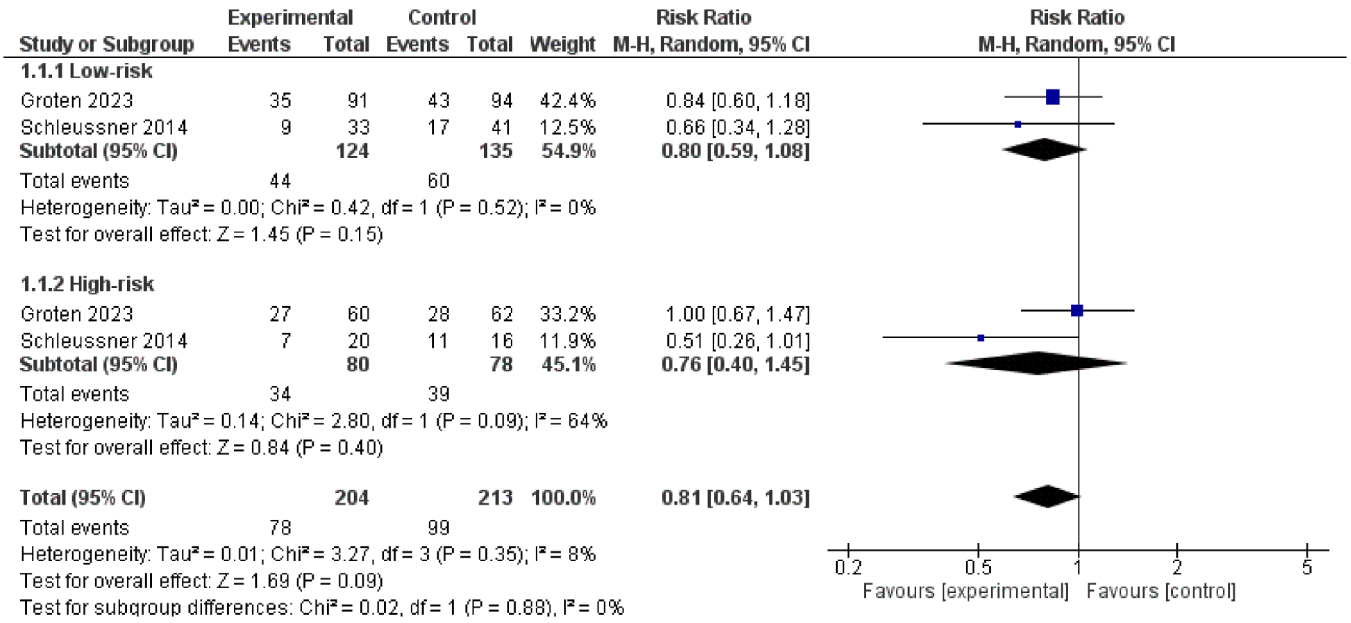

Fig. 4. Forest plot for comparison: PETN vs Placebo term (random effects model). Outcome: Combined outcome of fetal growth restriction or perinatal mortality.

Table 2
Summary of findings.

PETN compared to Placebo for Prevention of FGR during pregnancy					
Patient or population: At-risk pregnancy					
Intervention: PETN					
Comparison: Placebo					
Outcomes	No. of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95 % CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with PETN
FGR or perinatal death	417 (2 RCTs)	⨁⨁◯◯ Low[a,b]	RR 0.81 (0.64 to 1.03)	465 per 1000	88 fewer per 1000 (167 fewer to 14 more)
FGR	417 (2 RCTs)	⨁⨁◯◯ Low[a,b]	RR 0.83 (0.66 to 1.04)	451 per 1000	77 fewer per 1000 (153 fewer to 18 more)
Perinatal death	417 (2 RCTs)	⨁◯◯◯ Very low[a,b,c]	RR 0.64 (0.26 to 1.58)	52 per 1000	19 fewer per 1000 (38 fewer to 30 more)
Severe FGR	417 (2 RCTs)	⨁⨁◯◯ Low[a,b]	RR 0.86 (0.62 to 1.18)	286 per 1000	40 fewer per 1000 (109 fewer to 52 more)
Preterm birth	417 (2 RCTs)	⨁⨁⨁◯ Moderate[a]	RR 0.74 (0.58 to 0.93)	469 per 1000	122 fewer per 1000 (197 fewer to 33 fewer)
Gestational age at birth assessed with: weeks Scale from: 24 to 40	417 (2 RCTs)	⨁⨁⨁◯ Moderate[a]	-	The mean gestational age at birth was 35.3 weeks.	MD 1.18 weeks higher (0.29 higher to 2.06 higher)
Pre-eclampsia and HELLP	417 (2 RCTs)	⨁⨁◯◯ Low[a,b]	RR 0.71 (0.51 to 1.00)	286 per 1000	83 fewer per 1000 (140 fewer to 0 fewer)
Placental Abruption	417 (2 RCTs)	⨁◯◯◯ Very low[a,b,c]	RR 0.48 (0.08 to 2.93)	42 per 1000	22 fewer per 1000 (39 fewer to 82 more)
Cesarean section	417 (2 RCTs)	⨁⨁⨁◯ Moderate[a]	RR 0.81 (0.68 to 0.96)	610 per 1000	116 fewer per 1000 (195 fewer to 24 fewer)
Assisted Ventilation	417 (2 RCTs)	⨁⨁◯◯ Low[a,b]	RR 0.93 (0.68 to 1.25)	296 per 1000	21 fewer per 1000 (95 fewer to 74 more)
Umbilical artery pH	417 (2 RCTs)	⨁⨁◯◯ Low[a,b]	-	The mean umbilical artery pH was 7.3.	MD 0 (0.02 lower to 0.02 higher)

*The risk in the intervention group (and its 95 % confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95 % CI). CI: confidence interval; MD: mean difference; RR: risk ratio

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

a. Downgraded by one point for risk of bias under the domain 'deviations from intended intervention' as the adherence rate was not mentioned in both studies.

b. Downgraded by one point for imprecision because the 95 % confidence interval around the RR failed to exclude important benefit or important harm.

c. Downgraded by one more point for imprecision because the event rate was very low and the sample size was less than 2000 per group.

respectively). Both these outcomes were not reported in Groten 2023. No difference was observed in umbilical artery pH at birth between the groups (MD= 0.00; 95 % CI: −0.02–0.02; I^2 =0 %; 2 studies, 417 participants; low certainty). Groten 2023 did not report any difference in NICU admissions (RR=0.81; 95 % CI: 0.64–1.04), while Schluessner 2014 did not report this outcome. Need for assisted ventilation rates were comparable between the PETN and placebo groups (RR=0.93; 95 % CI: 0.68–1.25; I^2 =0 %; 2 studies, 417 participants; low certainty).

Groten 2023 reported one case of severe intraventricular hemorrhage (IVH) and two cases of necrotising enterocolitis (NEC) in the control group, while no case in the PETN group. In their follow-up report, Groten et al. reported no postnatal deaths in the PETN group but two in the placebo group (RR=0.21; 95 % CI= 0.01–4.27).

Although we were interested in long-term neurodevelopmental outcomes at 2 years of age, Groten 2023 reported that 94.6 % (105/114) cases in the PETN group and 84.6 % (104/126) cases in the control group had normal development at 1 year follow-up (p = 0.018).

3.3.5. *Adverse outcomes in mothers*

While there was one case of maternal headache and dizziness each in Schleussner 2014, Groten 2023 did not mention any maternal side-effects.

3.4. *Meta-analysis with fixed-effect model*

The results essentially remained unchanged with fixed-effect model (Appendix S5).

4. Discussion

In this systematic review, we evaluated the effectiveness of PETN in preventing FGR and associated adverse perinatal outcomes. FGR, often resulting from placental dysfunction, poses significant risks to both the fetus and the mother, underscoring the need for effective preventive strategies. Although PETN has shown promise as a nitric oxide donor that improves uteroplacental blood flow, the evidence supporting its clinical utility remains inconclusive. Our analysis, which included data from two trials involving 417 women, revealed that while PETN did not significantly reduce the incidence of FGR or perinatal death, it did demonstrate potential benefits in reducing preterm delivery and extending gestational age, particularly in high-risk pregnancies.

There is evidence that nitric oxide donors like glyceryl trinitrate (GTN) can improve uterine and umbilical blood flow, and ex vivo studies suggest GTN has protective effects on placental hypoxia-reperfusion injury [14]. However, clinical trials have not shown efficacy in preventing PE or FGR, and additionally, GTN is associated with significant side effects like severe headaches, which limit its use [15]. In contrast, PETN has a more favourable side effect profile and also boosts antioxidant gene expression, offering potential advantages over other NO donors [14]. Although a pilot trial showed promising results [13], our review failed to prove any benefit of PETN on the incidence of FGR or perinatal death. The pilot trial by Schleussner et al. [13] reported a lower incidence of FGR with PETN use (adjusted RR 0.44, CI 0.19–0.97), but the larger trial by Groten et al. [11] could not find any such benefit (adjusted RR 0.92, CI 0.71–1.19). This discrepancy could have been due to differences in methodology (lack of stratified randomization) or dosage of PETN (50 mg vs 80 mg, which may have reduced the therapeutic effect).

Among the pharmacological agents, aspirin is the only recommended treatment for FGR currently [16]. There are several other potential agents in the pipeline for prevention and treatment for FGR [2], with low-molecular-weight heparin (LMWH) as one of the most promising agents. A systematic review of 15 studies and 2795 participants showed that LMWH was associated with a significant reduction in the risk of PE, SGA, and perinatal death [17]. The results are particularly compelling for LMWH combined with low-dose aspirin [17,18]. However, the overall quality of evidence was of low certainty due to lack of blinding, imprecision, and inconsistency. Similarly, the evidence for PETN is of low quality, with mixed results on efficacy in reducing PE and perinatal mortality. This highlights the need for future large multicentric RCTs to fully elucidate the potential benefits and risks of PETN in preventing adverse perinatal outcomes.

To our knowledge, this is the first systematic review to specifically analyse the role of PETN in the prevention of FGR, contributing new insights to the field. However, it included only two studies with a total of 417 participants, which limits the generalizability and strength of the conclusions. Differences in PETN dosage between the included studies could have impacted the outcomes, making it difficult to draw definitive conclusions about the optimal dosage. We attempted to obtain additional data from the included studies but were unsuccessful, which could have enriched the analysis.

5. Conclusion

In conclusion, this review highlights the potential of PETN in reducing preterm delivery and prolonging gestation in high-risk pregnancies, although its effects on preventing FGR and other critical perinatal outcomes remain inconclusive. Future research should focus on evaluation of its clinical efficacy, especially in resource-limited settings with high incidence of FGR.

Conflicts of interest/Competing interests

The authors declare that they have no conflicts of interest or financial relationship with any organization.

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CRediT authorship contribution statement

Mayank Priyadarshi: Conceptualization, Data curation, Formal analysis, Methodology, Project administration, Supervision, Validation, Writing – original draft, Writing – review & editing. **Sakshi Heda:** Conceptualization, Data curation, Formal analysis, Methodology, Resources, Validation, Writing – original draft. **Akanksha Deshwali:** Conceptualization, Data curation, Formal analysis, Methodology, Resources, Writing – original draft, Writing – review & editing. **Ayush Heda:** Conceptualization, Data curation, Formal analysis, Methodology, Project administration, Resources, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.eurox.2024.100350.

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