OBSTETRICS

Effect of pentaerythritol tetranitrate (PETN) on the development of fetal growth restriction in pregnancies with impaired uteroplacental perfusion at midgestation—a randomized trial

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BACKGROUND: Fetal growth restriction is strongly associated with impaired placentation and abnormal uteroplacental blood flow. Nitric oxide donors such as pentaerythritol tetranitrate are strong vasodilators and protect the endothelium. Recently, we demonstrated in a randomized controlled pilot study a 38% relative risk reduction for the development of fetal growth restriction or perinatal death following administration of pentaerythritol tetranitrate to pregnant women at risk, identified by impaired uterine perfusion at midgestation. Results of this monocenter study prompted the hypothesis that pentaerythritol tetranitrate might have an effect in pregnancies with compromised placental function as a secondary prophylaxis.

OBJECTIVE: This study aimed to test the hypothesis that the nitric oxide donor pentaerythritol tetranitrate reduces fetal growth restriction and perinatal death in pregnant women with impaired placental perfusion at midgestation in a multicenter trial.

STUDY DESIGN: In this multicenter, randomized, double-blind, placebo-controlled trial, 2 parallel groups of pregnant women presenting with a mean uterine artery pulsatility index >95th percentile at 19+0 to 22+6 weeks of gestation were randomized to 50-mg Pentalong or placebo twice daily. Participants were assigned to high- or low-risk groups according to their medical history before randomization was performed block-wise with a fixed block length stratified by center and risk group. The primary efficacy endpoint was the composite outcome of perinatal death or development of fetal growth restriction. Secondary endpoints were neonatal and maternal outcome parameters.

RESULTS: Between August 2017 and March 2020, 317 participants were included in the study and 307 were analyzed. The cumulative incidence of the primary outcome was 41.1% in the pentaerythritol tetranitrate group and 45.5% in the placebo group (unadjusted relative risk, 0.90; 95% confidence interval, 0.69—1.17; adjusted relative risk, 0.90; 95% confidence interval, 0.69—1.17; P=.43). Secondary outcomes such as preterm birth (unadjusted relative risk, 0.73; 95% confidence interval, 0.56—0.94; adjusted relative risk, 0.73; 95% confidence interval, 0.56—0.94; P=.01) and pregnancy-induced hypertension (unadjusted relative risk, 0.65; 95% confidence interval, 0.46—0.93; adjusted relative risk, 0.65; 95% confidence interval, 0.46—0.92; P=0.01) were reduced.

CONCLUSION: Our study failed to show an impact of pentaerythritol tetranitrate on the development of fetal growth restriction and perinatal death in pregnant women with impaired uterine perfusion at midgestation. Pentaerythritol tetranitrate significantly reduced secondary outcome parameters such as the incidence of preterm birth and pregnancy-induced hypertension in these pregnancies.

Key words: fetal growth restriction, pentaerythritol tetranitrate, placental insufficiency, placental perfusion, preterm birth

Introduction

Fetal growth restriction (FGR) remains a major cause of perinatal mortality and morbidity. FGR is defined as the pathologic restriction of intrauterine supply and the failure of the fetus to achieve its genetic growth potential.[1] Furthermore, intrauterine malnutrition causes lifelong consequences as a developmental origin of adult diseases.[2] In the mother, FGR is associated with vascular pathology, impaired placentation, and failure of decidual spiral artery remodeling, leading to impaired uteroplacental perfusion. Abnormal uterine flow and maternal conditions associated with impaired vascular health, including previous FGR, signify the risk of developing FGR during pregnancy.[3] Consequently, a recent consensus on the definition of FGR incorporates the presence of Doppler abnormalities, underscoring the pathophysiological significance of fetoplacental perfusion.[4] Thus, abnormal placental and/or fetal perfusion differentiates FGR from the term "small for gestational age," according to which fetal weight below the 10th percentile can still be considered normal. Nitric oxide (NO) donors such as pentaerythritol tetranitrate (PETN) reduce the impedance in the uteroplacental vessels and have been demonstrated to possess protecting effects on the endothelium.[5] A randomized controlled pilot study suggested a beneficial effect of PETN on pregnancies with impaired uteroplacental perfusion at midgestation.

Cite this article as: Groten T, Lehmann T, Städtler M, et al. Effect of pentaerythritol tetranitrate (PETN) on the development of fetal growth restriction in pregnancies with impaired uteroplacental perfusion at midgestation—a randomized trial. Am J Obstet Gynecol 2023;228:84.e1-12.

0002-9378

https://doi.org/10.1016/j.ajog.2022.07.028

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AJOG at a Glance

Why was this study conducted?

This study aimed to evaluate and confirm the effect of the nitric oxide donor pentaerythritol tetranitrate (PETN) on the development of fetal growth restriction (FGR) and perinatal death in high-risk pregnancies.

Key findings

Our inclusion criteria identified a high-risk cohort with 41% FGR, 44% preterm birth (PTB), 31% pregnancy-induced hypertension (PIH), and 25% preeclampsia. PETN was not proven to affect the primary outcome. Secondary outcomes such as PTB and PIH were reduced.

What does this add to what is known?

Although PETN failed to affect FGR and fetal death, it did affect maternal blood pressure and prolong pregnancy.

A PETN pilot study revealed a 38% relative risk (RR) reduction of FGR or perinatal death (adjusted RR, 0.410; 95% confidence interval [CI], 0.184−0.914) and a 70% reduction of preterm birth before 32 weeks of gestation (adjusted RR, 0.436; 95% CI, 0.196−0.970) in the PETN intervention group relative to the placebo group.[6] On the basis of this pilot data we developed the hypothesis that PETN could serve as secondary prophylaxis to prevent FGR in women with impaired placental perfusion at midgestation. Thus, the aim of this PETN trial was to assess the effect of PETN on the development of FGR and perinatal death in patients with placentation failure, identified at midgestation in a multicenter, randomized, double-blind, placebo-controlled, parallel-group trial.[7]

Materials and Methods

Study design

This PETN study was a multicenter, randomized, double-blind, placebo-controlled, parallel-group study to assess the efficacy and safety of 50-mg PETN twice a day to prevent FGR and perinatal death in pregnancies with placentation failure at midgestation. The trial was performed at 14 tertiary-care hospitals in Germany. Ethical approval was obtained from the ethical committee of the Jena University Hospital as the leading committee (institutional review board of Friedrich Schiller University Jena; 5085-02/17), and each of the 14 German study centers obtained ethical approval from their local committees. The study protocol was approved by the higher federal authority and was published previously.[7]

Study participants

Participants were recruited from pregnant women presenting at 19+0 to 22+6 weeks of gestation for routine or risk-guided midtrimester ultrasound screening for fetal structural anomalies including the assessment of uteroplacental perfusion. The major inclusion criterion was abnormal uterine Doppler flow defined by a mean pulsatility index (PI) exceeding the 95th percentile of the reference population.[8] Exclusion criteria were multiple pregnancies, diagnosed or suspected fetal chromosomal or major structural defects, and maternal circumstances indicating adverse pregnancy outcome other than impaired placental function and maternal disease defined as a contraindication for intake of PETN. Participants were assigned to risk groups on inclusion and before randomization. Women with preexisting hypertension, diabetes mellitus, or other vascular diseases, and/or who have had FGR, stillbirth, premature placental abruption, HELLP (hemolysis, elevated liver enzymes, and low platelet count) syndrome, or preeclampsia in a previous pregnancy were classified as "high-risk," and otherwise as "low-risk."

Treatment

Following verification of eligibility, patients were randomly assigned in a 1:1 ratio to receive PETN or placebo using an internet-based randomization software. Randomization was performed block-wise with a fixed block length stratified by center and risk group. PETN and placebo tablets were manufactured by Aesica Pharmaceuticals GmbH (Zwickau, Germany). The 2 types of tablets appeared identical in size, shape, taste, and color. Packs were labeled with unique pack identifiers linked to the randomly generated sequence known only to the manufacturing unit and the trial unit programmers. All tablets were blistered and labeled as study medication, and thus verum and placebo were indistinguishable to participants, study nurses, and clinicians. Following randomization, PETN or placebo were taken orally 2 times daily starting with enrollment until 36+6 weeks of gestation or the day of delivery. Participants were asked to record tablet intake and side effects in patient ID−assigned study diaries. Maternal and fetal status and condition were assessed every 4 weeks during the treatment period. On delivery, data on neonatal and maternal outcomes were collected. Data capture was done via a secure web application on the servers of the Jena University Hospital with OpenClinica. This study management software meets all regulatory requirements and records data via an encrypted data link (HTTPS) by use of data entry masks.

Outcomes

The primary outcome was prespecified as a composite outcome of perinatal death and/or development of FGR. Perinatal death was defined as in utero fetal death after randomization or neonatal death within the first week of life. FGR was defined by abnormal uterine Doppler flow and a birthweight <10th centile according to population growth charts.[9]

As a key secondary endpoint, we reported severe neonatal morbidity and mortality as a composite of severe FGR (defined by birthweight below the third and the fifth centile according to population growth charts[9]) and/or perinatal death and/or placental abruption. In addition, we reported a combined

outcome parameter of "severe neonatal morbidity" as a composite outcome in cases in which one of the following occurred: need for ventilation, intraventricular hemorrhage grade III to IV, or necrotizing enterocolitis requiring surgery.

Additional secondary outcome parameters were birthweight <3rd, <5th, and <10th centile, development of FGR requiring delivery before 30, 34, and 37 weeks' gestation, preterm birth before 30, 34, and 37 weeks, rate of neonatal intensive care unit (NICU) admission, and neonatal complications such as the need for assisted ventilation, occurrence of intraventricular hemorrhage grade II to IV, and necrotizing enterocolitis. Maternal secondary outcome measures were the development of pregnancy-induced hypertension (PIH), defined as occurrence of blood pressure exceeding 140 mm Hg for the systolic and/or 90 mm Hg for the diastolic measurements during the study period; and preeclampsia, defined as PIH and at least 1 additional manifestation of organ malperfusion leading to either FGR, liver enzyme alteration, or kidney malfunction.[10] Occurrence of HELLP syndrome was subsumed to preeclampsia.

In reporting data, including the reporting of adverse and serious adverse events, we followed the requirements of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use—Good Clinical Practice (ICH-GCP). A data safety monitoring board (DSMB) was established to supervise safety events and outcome data of the neonates born during the ongoing study. The DSMB met on a regular basis and did not find any peculiarities nor make any recommendations on protocol changes.

Statistical analysis

Sample size considerations were based on the results of a pilot study.[6] Because additional risk factors increase the risk of FGR, a stratified randomization and analysis were planned with 2 strata. The pilot study observed a 2:1 ratio of low- to high-risk patients and estimated the proportion of FGR or perinatal death to be 0.42 in the low-risk and 0.69 in the high-risk stratum of the placebo group. Comparing PETN with placebo in the pilot study resulted in an estimated odds ratio of 0.41. Thus, for the planning of the PETN trial, we aimed to detect a more conservative, clinically relevant 50% risk reduction in the PETN group compared with the placebo group. Accordingly, a sample size of 290 patients was needed to detect this treatment effect by a Mantel–Haenszel test with a power of 80% at a 2-sided significance level alpha of 0.05 (nQuery 7.0; Statsols, Cork, Ireland). Assuming a dropout rate of approximately 10%, a total of 324 patients were planned to be randomized. Primarily, data were analyzed according to the intent-to-treat (ITT) principle.

Regarding the primary endpoint, the Mantel–Haenszel test was chosen as a confirmatory test to address the stratified analysis of the primary endpoint, and the Mantel–Haenszel estimate of the RR with 95% CI was reported to assess the treatment effect, applying a 2-sided significance level alpha of 0.05. In addition, to check the robustness of the primary test, a generalized mixed linear model with treatment and risk group as the fixed and canter as the random factor was fitted to adjust for variability between study centers. Estimated RRs with 95% CI were also reported for the primary endpoint in this model. In a subsequent sensitivity analysis checking the robustness of the main results, we performed multiple imputation of missing primary endpoint data (fully conditional specification approach with m=20 imputations) and reran the aforementioned analyses. For all secondary endpoint or subgroup (in both low- and high-risk patients) analyses there were no adjustments for multiple testing because they are all considered as exploratory. Thus, we reported nominal 2-sided *P* values for all exploratory tests in addition to point and interval.

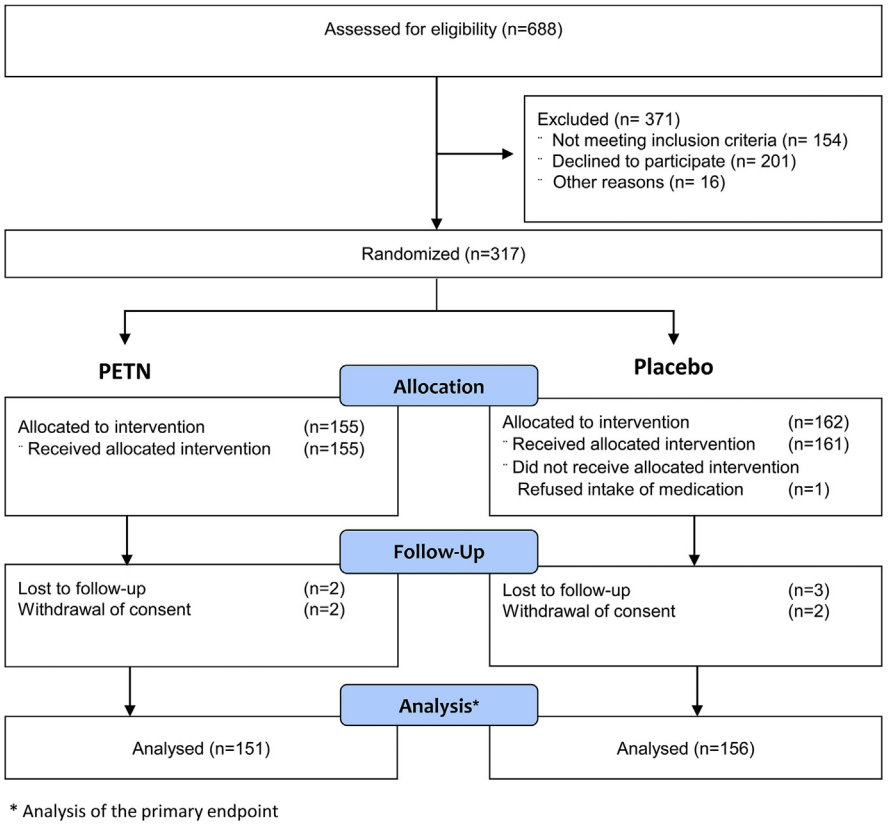
Results

Between August 2017 and March 2020, 317 women were enrolled in the study. Because we observed a dropout rate of <5%, far below the expected rate of 10%, we decided to stop recruitment in April 2020, when constraints caused by the COVID-19 pandemic started influencing study performance and 317 participants had been enrolled (Figure 1). Primary outcome data of 307 patients were included in the ITT analysis, exceeding the required number of 290. Sensitivity analyses including all 317 patients had no impact on our main statements. Table 1 displays the baseline characteristics of the 2 treatment groups.

The cumulative incidence of the primary outcome was 41.1% (62/155 infants) in the PETN group and 45.5% (71/161 infants) in the placebo group, and the difference between the groups was not statistically significant (adjusted RR, 0.90; 95% CI, 0.69–1.17; *P*=.43). The estimated treatment effect was supported by a generalized linear model with adjustment for study center effects (adjusted RR, 0.90; 95% CI, 0.69–1.15; *P*=.38) and also after multiple imputation of missing values (RR, 0.90; 95% CI, 0.70–1.17; *P*=.43). Five perinatal deaths (3.3%) occurred in the PETN group vs 7 cases (4.5%) in the placebo group (adjusted RR, 0.74; 95% CI, 0.23–2.28; *P*=.6) (Table 2 and Figure 2).

The cumulative incidence of the combined endpoint of birthweight below the third centile, intrauterine or neonatal death, and placental abruption was 25.2% (38/155 infants) in the PETN group and 26.3% (41/161 infants) in the placebo group (adjusted RR, 0.90; 95% CI, 0.65–1.40; *P*=.82). Birthweight of 61 infants (40.7%) in the PETN group and 69 infants (44.2%) in the placebo group was <10th percentile (adjusted RR, 0.92; 95% CI, 0.71–1.20; *P*=.5). Preterm birth before completed 37 weeks of gestation occurred in 138 cases—57 (37.7%) in the PETN group and 81 (51.9%) in the placebo group. Expressed as risk reduction for preterm birth, the estimated RR was 0.73 (95% CI, 0.56–0.94; *P*=.01) (Table 2 and Figure 2). Severe neonatal morbidity reported as "combined neonatal morbidity" as a composite of need for ventilation and/or necrotizing enterocolitis and/or intraventricular hemorrhage grade III to IV occurred in 30.1% (44/155) of infants in the PETN group and 35.8% (53/161) in the placebo

FIGURE 1
Trial profile



* Analysis of the primary endpoint

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group (adjusted RR, 0.84; 95% CI, 0.61−1.7; *P*=.3) (Table 3 and Figure 2).

The cumulative incidence of PIH was 23.9% (37/155 women) in the PETN group and 36.6% (59/161 women) in the placebo group (adjusted RR, 0.65; 95% CI, 0.46−0.92; *P*=.01) (Table 2 and Figure 2). Preeclampsia was observed in 20% (31/155 women) of the PETN and 29.2% (47/161 women) of the placebo group (adjusted RR, 0.68; 95% CI, 0.46−1.03; *P*=.05) (Table 2 and Figure 2). Outcome according to gestational age did not reveal statistically significant results (Supplemental Figure). Additional outcome data are displayed in Table 3. Longitudinal monitoring of Doppler parameters and fetal growth during the study period also revealed no evidence for group differences (Figure 3).

Figure 4 displays the cumulative percentage of participants who developed blood pressure exceeding 140 mm Hg systolic and/or 90 mm Hg diastolic or preeclampsia, who delivered, and who were admitted to the hospital. Explorative Kaplan−Meier analyses revealed in these secondary endpoints that participants in the PETN group seemed to be less likely to have increased blood pressure (hazard ratio [HR], 0.62; 95% CI, 0.41−0.94; *P*=.02), to deliver preterm (HR, 0.77; 95% CI, 0.61−0.96; *P*=.01), and to be admitted to the hospital (HR, 0.51; 95% CI, 0.30−0.85; *P*=.01) (Figure 4).

Comment

Principal findings

Among pregnant women with impaired uteroplacental perfusion at midgestation, using the NO-donor PETN vs placebo did not reduce the cumulative incidence of the primary composite outcome of perinatal death and/or development of FGR. Several sensitivity analyses underlined the robustness of this claim. However, the secondary endpoints revealed that PETN reduced both hypertension in the pregnant women and the rate of preterm births. These observations require subsequent confirmation in independent studies.

Results in the context of what is known

A mean uteroplacental PI >95th percentile predicts FGR with a sensitivity of 18% and a specificity of 95% in general populations, and a sensitivity of 58% for any FGR in high-risk populations with a specificity of 75%.[11] More recent data confirm the higher risk of FGR in women with a medical history of chronic hypertension, diabetes mellitus, systemic lupus erythematodes, or antiphospholipid antibody syndrome and in those with history of adverse pregnancy outcomes associated with FGR.[12] According to these data, at least one-third of pregnant women diagnosed with impaired perfusion of the uterine arteries at midgestation will develop FGR and associated adverse pregnancy outcomes. Consistently, in our study FGR occurred in 110 of 307 (35.8%) cases. Poor placental function and malperfusion of the placenta are recognized to cause, maintain, and worsen the development of FGR. Although in our previous trial uteroplacental and fetal perfusion were significantly improved in the PETN group,[13] Doppler measurements during the current trial did not reveal any changes (Figure 3). The failure to improve uteroplacental resistance and consecutive fetal perfusion indices during this trial could explain the inability to reproduce beneficial effects on fetal growth. Concordantly, short-term neonatal outcome data did not differ between groups.

Whereas risk reduction for preeclampsia (20% vs 29.2%; RR, 0.7; *P*=.055) was similar between the treatment groups, the maternal outcomes indicated improvement favoring PETN for a reduced rate of PIH. These beneficial maternal effects were also reflected in a reduced need for hospital admission during the course of pregnancy (Figure 4).

In our study cohort, 125 of 317 randomized women were high-risk (39.4%) (Table 1). Unexpectedly, the rate of FGR was similar in the high- and the low-risk group (44% and 41%), whereas in our previous study the proportion of FGR was 50% in the high-risk and 34% in the low-risk group. However, in the pilot study stratification was done during statistical analysis, whereas randomization was not stratified. The extent to which undetected high-risk patients who may have been assigned to the low-risk group may have contributed to the results cannot be determined.

Preterm birth before 37 weeks' gestation could be reduced by 30% (RR, 0.7; 95% CI, 0.6–0.9; P=.01). Accordingly, Kaplan–Meier analysis revealed that during the course of pregnancy participants in the treatment group delivered later (P=.007), revealing a risk reduction of 25% (HR, 0.767; 95% CI, 0.612–0.961) (Figure 4, D).

TABLE 1
Baseline characteristics of the trial participants[a]

Characteristic	PETN group (n=155)	Placebo group (n=162)
Age (y)	33 (30–36)	34 (29–37)
BMI (kg/m^2)	24.6 (22–30.9)	25.7 (21.6–31.5)
Gestational age at randomization (wk)	21.7 (21–22.4)	21.7 (20.9–22.3)
BMI at start of pregnancy (kg/m^2)	74 (64.9–86.6)	76.6 (65–91)
Systolic blood pressure (mm Hg)	122 (111–134)	120 (112.5–133.5)
Nulliparous	78 (70–85)	78 (70–85)
Number of previous deliveries	1 (0–1)	0 (0–1)
High risk	61 (39.4)	64 (39.8)
Reason for high risk		
Preexisting hypertension	20 (32.8)	25 (39.1)
Preexisting diabetes mellitus	6 (9.8)	6 (9.4)
Previous FGR	23 (37.7)	20 (31.3)
Previous preeclampsia	14 (23.0)	14 (21.9)
Previous HELLP syndrome	10 (16.4)	10 (15.6)
Previous stillbirth	4 (6.6)	4 (6.3)
Previous placental abruption	5 (8.2)	3 (4.7)
Other diseases affecting the endothelium	7 (11.5)	3 (4.7)
Sonographic data at randomization		
EFW (g)	416 (352–474)	411 (344–458)
EFW percentile	30 (12–50)	29 (13–48)
EFW percentile <10	32 (20.6)	31 (19.3)
Abdominal circumference (mm)	162 (152–172)	163 (151–170)
Head circumference (mm)	189 (180–199)	188 (179–196)
PI arteria uterina (mean)	1.84 (1.69–2.11)	1.82 (1.68–2.04)
PI arteria cerebri media	1.64 (1.44–1.84)	1.62 (1.48–1.83)
PI arteria umbilicalis	1.25 (1.11–1.41)	1.28 (1.15–1.45)
CPR	1.32 (1.10–1.57)	1.27 (1.08–1.50)

BMI, body mass index; *CPR*, cerebroplacental ratio; *EFW*, estimated fetal weight; *FGR*, fetal growth restriction; *HELLP*, hemolysis, elevated liver enzymes, and low platelet count; *PETN*, pentaerythritol tetranitrate; *PI*, pulsatility index.

[a] Median and 25th to 75th percentile are reported for continuous baseline characteristics, and absolute and relative frequencies for categorical characteristics.

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Clinical and research implications

The actual and future burden of being born with a birthweight <10th percentile, leading to adverse outcomes at any period of life, including increased rates of neurologic delay, chronic diseases, and mortality, makes FGR a general health problem for the society.[14,15] Treatment and even just mitigation of intrauterine growth restriction would have tremendous impact on public health and would help to reduce the burden of diabetes mellitus and obesity.[14,16,17] Nevertheless, there have been only a few studies on pharmacologic treatment of FGR thus far. This PETN randomized controlled trial (RCT) made the relevant contribution of defining reduction of FGR as the primary outcome in a cohort recognized to be at risk for the development of placenta-associated pregnancy complications because of impaired uteroplacental perfusion at midgestation. The most recent international RCT including cases where severe FGR was diagnosed before 30 weeks of gestation investigated the effect of the phosphodiesterase-5 inhibitor sildenafil on neonatal outcomes. Although there was extensive evidence in appropriate animal models of FGR and human evidence suggesting beneficial effects on uterine and fetal perfusion,[18,19] the Sildenafil TheRapy In Dismal prognosis Early onset fetal growth Restriction (STRIDER) studies failed to show any effect on the outcome of the affected pregnancies. Beyond the lack of effect, the Dutch STRIDER trial had to be discontinued in 2018 because of suspected excess mortality in the sildenafil group.[20] The frequency of the most severe outcome of perinatal death (15%–30%) observed during the STRIDER trial impressively demonstrated the risk and danger associated with FGR, clearly emphasizing the importance of finding an effective therapy for FGR.[21,22] The outcome in our study was associated with a stillbirth rate of 3.8%, a high rate of NICU admission, and severe combined neonatal morbidity

TABLE 2
Outcomes according to study group

Outcome	High-risk[a] (n=122)			Low-risk[a] (n=185)			Total (n=307[b])			Unadjusted[c]		Adjusted[d]		
	PETN (n=60)	Placebo (n=62)	*P* value	PETN (n=91)	Placebo (n=94)	*P* value	PETN (n=151)	Placebo (n=156)	*P* value	RR[c]	CI[c]	RR[d]	CI[d]	*P* value[d]
Primary outcome														
Combined endpoint of perinatal death or FGR	27 (45.0)	28 (45.2)	1.00	35 (38.5)	43 (45.7)	.37	62 (41.1)	71 (45.5)	.49	0.90	0.69–1.17	0.90	0.69–1.17	.43
Secondary outcome parameter														
Perinatal death	2 (3.3)	2 (3.2)	1.00	3 (3.3)	5 (5.3)	.23	5 (3.3)	7 (4.5)	.77	0.74	0.23–2.28	0.74	0.24–2.27	.60
Birthweight below third percentile and/or perinatal death and/or placental abruption	19 (31.7)	13 (21.0)	.22	19 (20.9)	28 (29.8)	.18	38 (25.2)	41 (26.3)	.90	0.96	0.65–1.41	0.96	0.65–1.41	.82
Birthweight below fifth percentile and/or perinatal death and/or placental abruption	21 (35.0)	18 (29.0)	.56	22 (24.2)	29 (30.9)	.33	43 (28.5)	47 (30.1)	.80	0.95	0.66–1.34	0.95	0.67–1.34	.75
Birthweight percentile	18.1±20.7	19.1±20.3	.89	19.3±19.0	17.5±18.3	.53	18.8±19.6	18.2±19.1	.77	0.64	−3.8 to 5.0	0.64	−3.8 to 5.0	.93
Birthweight <10th percentile	26 (44.1)	28 (45.2)	1.00	35 (38.5)	41 (43.6)	.55	61 (40.7)	69 (44.2)	.56	0.92	0.70–1.20	0.92	0.71–1.19	.53
Below fifth percentile	16 (27.1)	16 (25.8)	1.00	22 (24.2)	25 (26.6)	.74	38 (25.3)	41 (26.3)	0.	0.96	0.65–1.41	0.96	0.65–1.41	.85
Below third percentile	13 (22.0)	11 (17.7)	.65	19 (20.9)	24 (25.5)	.49	32 (21.3)	35 (22.4)	.89	0.95	0.62–1.46	0.95	0.61–1.46	.81
Gestational age at birth (wk)	35.7±4.9	34.7±4.9	.28	36.3±4.6	35.3±4.6	.13	36.1±4.7	35.1±4.7	.06	1.00	−0.1 to 2.1	1.00	−0.1 to 2.1	.06
Preterm birth (before completed 37 wk)	23 (38.3)	33 (53.2)	.11	34 (37.4)	48 (51.1)	.08	57 (37.7)	81 (51.9)	.02	0.73	0.56–0.94	0.73	0.56–0.94	.01
PIH[e]	17 (27.9)	35 (54.7)	<.01	20 (21.3)	24 (24.7)	.61	37 (23.9)	59 (36.6)	.02	0.65	0.46–0.93	0.65	0.46–0.93	.01
Preeclampsia[f]	17 (27.9)	29 (45.3)	.06	14 (14.9)	18 (18.6)	.56	31 (20.0)	47 (29.2)	.07	0.69	0.46–1.02	0.69	0.46–1.02	.06
Placental abruption	4 (6.7)	1 (1.6)	.20	0 (0)	3 (3.2)	.25	4 (2.6)	4 (2.6)	1.00	1.03	0.26–4.06	1.03	0.26–4.09	.96

Data are in number (percentage) or mean±standard deviation.

CI, confidence interval; *FGR*, fetal growth restriction; *HELLP*, hemolysis, elevated liver enzymes, and low platelet count; *PETN*, pentaerythritol tetranitrate; *PIH*, pregnancy-induced hypertension; *RR*, relative risk.

[a] Participants with preexisting hypertension, diabetes mellitus, or other vascular diseases, and/or who have had FGR, stillbirth, premature placental abruption, HELLP syndrome, or preeclampsia in a previous pregnancy were classified as "high-risk," and otherwise as "low-risk"; [b] Outcome data were available for 307 patients included in the intention-to-treat analysis; [c] Unadjusted analysis: estimate of the RR with 95% CI; [d] Mantel–Haenszel estimate of the stratified RR with 95% CI was reported to assess the treatment effect; [e] PIH defined as blood pressure exceeding 140 mm Hg for the systolic and/or 90 mm Hg for the diastolic; [f] Defined as PIH and at least 1 additional manifestation of organ malperfusion leading to either FGR, liver enzyme alteration, kidney malfunction, or HELLP syndrome.

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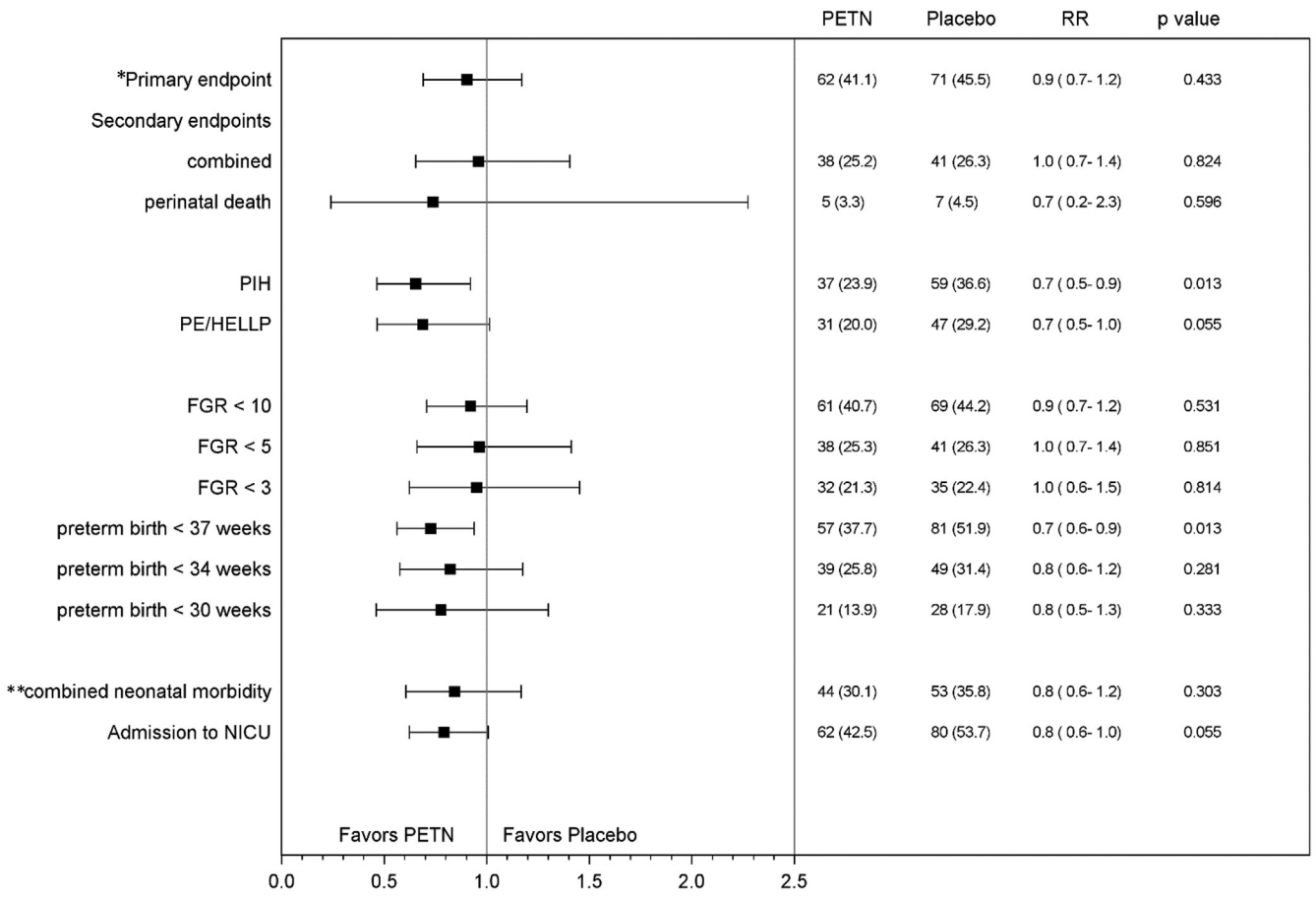
FIGURE 2
Effect of PETN on primary and secondary outcome parameters



*The primary endpoint was defined as combined endpoint of perinatal death or FGR **Combined neonatal morbidity was defined as composite outcome of the need of ventilation, occurrence of intraventricular hemorrhage III – IV ° or necrotized enterocolitis requiring surgery.

PETN, pentaerythritol tetranitrate.

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of those born growth-restricted. Of the 121 children born with FGR, 73 (60.3%) were admitted to the NICU, of whom 47 (64.4%) developed severe neonatal morbidity, emphasizing the importance of achieving clinical progress regarding FGR treatment and prevention.

In this study investigating the immediate neonatal outcome of pregnancies complicated by impaired uterine perfusion, we failed to prove a beneficial effect of PETN. Follow-up studies of the infants born in this study at the age of 12 months and 5 years are prearranged and may still reveal beneficial effects for the offspring. Furthermore, our study showed an impact on maternal outcome, and data retrieved will be analyzed post hoc to further evaluate whether PETN might serve as a reasonable option to complement the treatment of high blood pressure in high-risk pregnancies. Finally, our study demonstrated that interventional clinical trials are feasible and safe to be performed in obstetrical populations, which is of particular importance to overcome the STRIDER trauma.

Strengths and limitations

A key strength of this trial is the prospective, randomized, double-blind, placebo-controlled design matched to our successful pilot study, enabling informed caseload planning. The trial was rigorously conducted according to a prespecified protocol without changes. In addition, the results of our study clearly demonstrated that by applying our inclusion criteria, we were able to identify a cohort of high-risk pregnancies developing FGR in 41%, prematurity in 44%, PIH in 31%, and preeclampsia in 25% of cases. Given that the inclusion criterion of our study was impaired uterine perfusion defined by mean PI of the arteriae uterinae exceeding the 95th centile, all infants with birthweight <10th percentile were considered to have FGR in accordance with the consensus definition of FGR published by Gordijn[4] in 2016, which

TABLE 3
Additional outcome parameters according to study group

Outcome	High-risk[a] (n=122)			Low-risk[a] (n=185)			Total (n=307[b])			Unadjusted[c]		Adjusted[d]		
	PETN (n=60)	Placebo (n=62)	*P* value	PETN (n=91)	Placebo (n=94)	*P* value	PETN (n=151)	Placebo (n=156)	*P* value	RR[c]	CI[c]	RR[d]	CI[d]	*P* value[d]
Neonatal outcome[e] according to study group														
Combined neonatal outcome[f]	18 (31.0)	24 (40.7)	.34	27 (30.7)	29 (32.6)	.87	45 (30.8)	53 (35.8)	.39	0.86	0.62–1.20	0.86	0.62–1.20	.37
Additional outcome parameters														
Female	18 (30.0)	26 (41.9)	.19	36 (39.6)	46 (48.9)	.24	54 (35.8)	72 (46.2)	.08	0.77	0.58–1.02	0.78	0.59–1.02	.06
Apgar score <7 at 5 min after birth	3 (5.3)	6 (9.8)	.49	5 (5.7)	7 (7.7)	.77	8 (5.6)	13 (8.6)	.37	0.65	0.27–1.53	0.65	0.27–1.53	.32
Umbilical artery pH	7.3±0.1	7.3±0.1	.69	7.3±0.1	7.3±0.1	.32	7.3±0.1	7.3±0.1	.31	-0.01	−0.1 to 0.2	-0.01	−0.1 to 0.2	.30
Mode of delivery														
Vaginal delivery	25 (41.7)	17 (27.4)	.13	45 (49.5)	34 (36.2)	.08	70 (46.4)	51 (32.7)	.02	1.42	1.06–1.89	1.42	1.07–1.88	.01
Assisted vaginal delivery	2 (3.3)	1 (1.6)	.62	3 (3.3)	2 (2.1)	.68	5 (3.3)	3 (1.9)	.50	1.72	0.41–7.08	1.72	0.42–7.08	.45
Elective cesarean delivery	22 (36.7)	31 (50.0)	.15	27 (29.7)	31 (33.0)	.64	49 (32.5)	62 (39.7)	.19	0.82	0.60–1.11	0.82	0.61–1.10	.18
Emergency cesarean delivery	11 (18.3)	13 (21.0)	.82	16 (17.6)	27 (28.7)	.08	27 (17.9)	40 (25.6)	.13	0.70	0.45–1.08	0.70	0.45–1.08	.10
Additional neonatal outcome parameters														
Assisted ventilation	18 (30.0)	24 (38.7)	.35	27 (29.7)	29 (30.9)	.87	45 (29.8)	53 (34.0)	.46	0.88	0.63–1.22	0.88	0.63–1.22	.43
IVH III-IV	0 (0.0)	1 (1.6)	1.00	0 (0.0)	0 (0.0)	1.00	0 (0.0)	1 (0.6)	1.00	0.34	0.01–8.16	0.34	0.01–8.16	.32
NEC	0 (0.0)	2 (3.3)	.50	0 (0.0)	0 (0.0)	1.00	0 (0.0)	2 (1.3)	.50	0.21	0.01–4.22	0.21	0.01–4.22	.16
Admission to NICU	25 (43.1)	34 (56.7)	.20	38 (43.2)	46 (51.7)	.29	63 (43.2)	80 (53.7)	.08	0.80	0.63–1.03	0.80	0.63–1.03	.07
Nights on NICU	46.6±56.5	36.2±24.0	.42	32.5±33.5	32.6±28.3	1.00	38.1±44.2	34.1±31.3	.55	4.00	−8.6 to 16.6	4.25	−8.3 to 16.8	.20
Joint discharge of mother and child	36 (60.0)	31 (50.0)	.28	54 (60.0)	47 (50.0)	.19	90 (60.0)	78 (50.0)	.09	1.20	0.97–1.48	1.20	0.98–1.47	.08

Data are in number (percentage) or mean±standard deviation.

CI, confidence interval; *FGR*, fetal growth restriction; *HELLP*, hemolysis, elevated liver enzymes, and low platelet count; *IVH*, intraventricular hemorrhage; *NEC*, necrotizing enterocolitis; *NICU*, neonatal intensive care unit; *PETN*, pentaerythritol tetranitrate; *RR*, relative risk.

[a] Participants with preexisting hypertension, diabetes mellitus, or other vascular diseases, and/or who have had FGR, stillbirth, premature placental abruption, HELLP syndrome, or preeclampsia in a previous pregnancy were classified as "high-risk," and otherwise as "low-risk"; [b] Outcome data were available for 307 patients included in the intention-to-treat analysis; [c] Unadjusted analysis: estimate of the RR with 95% CI; [d] Mantel–Haenszel estimate of the stratified RR with 95% CI was reported to assess the treatment effect; [e] 297 life born infants born to 307 patients included in the intention-to-treat analysis; [f] Need for ventilation and/or NEC and/or IVH grade III to IV.

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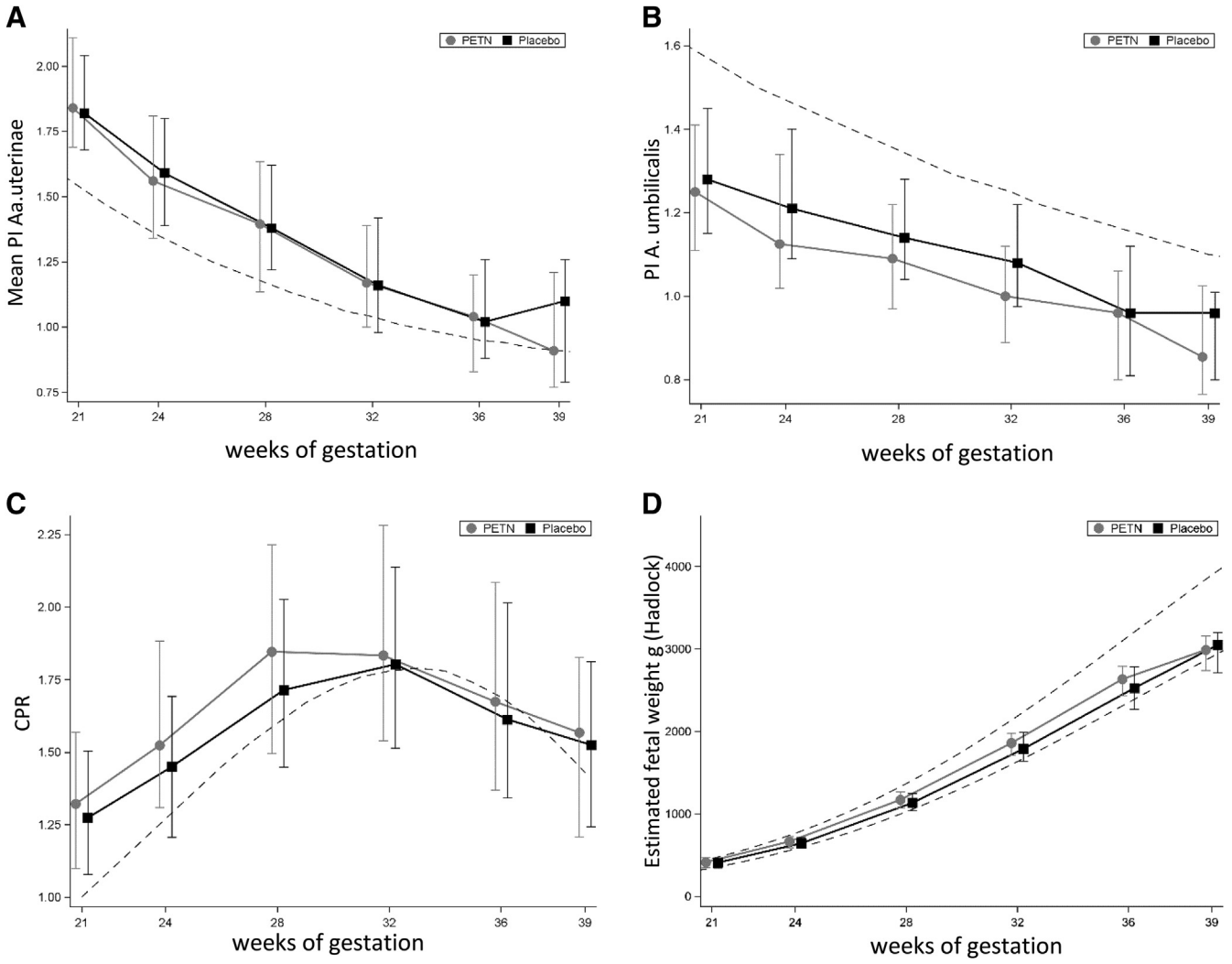
FIGURE 3
Changes in Doppler parameters and development of estimated fetal weight during pregnancy



Changes in **A,** arteriae uterinae mean PI, **B,** arteriae umbilicalis PI, **C,** CPR (ratio of arteriae umbilicalis PI to arteriae cerebri media PI), **D,** and estimated fetal weight (Hadlock IV) during the course of pregnancy following randomization in the study groups. PETN represented with *gray lines* and placebo with *black lines. Dotted lines* represent the 95th percentile (for arteriae uterinae mean PI, arteriae umbilicalis PI, and estimated fetal weight) and the 10th percentile for estimated fetal weight and CPR. Mean values per group and study visit time point are shown.

CPR, cerebroplacental ratio; *PI*, pulsatility index.

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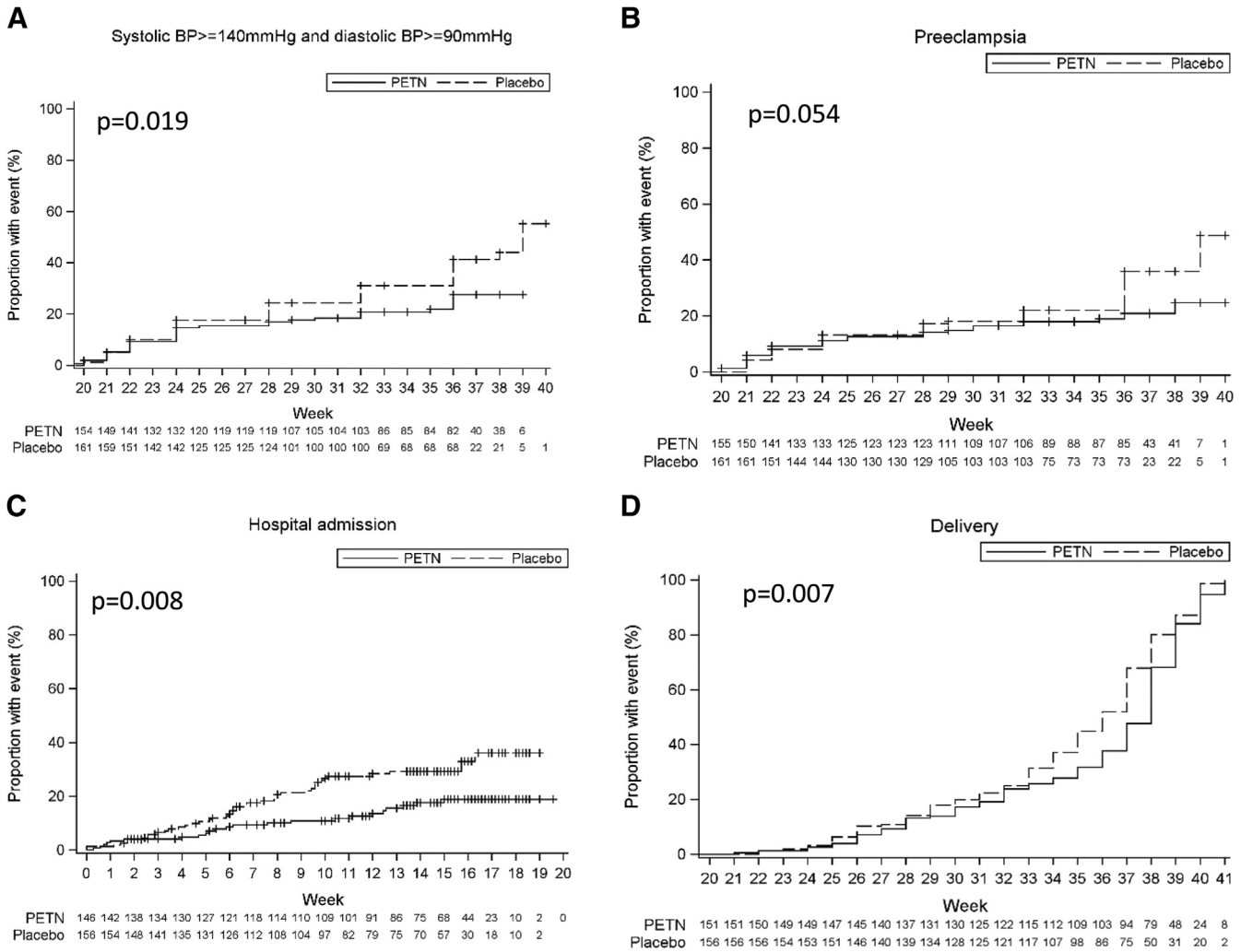
requires fetal weight <10th centile combined with uterine artery PI >95th centile. This can be considered a further strength of the study. A key limitation of this study was the unexpected even incidence of the primary outcome in the high- and low-risk groups, suggesting that criteria for stratification were not appropriate or not adequately applied. Furthermore, in 20% of the cases FGR was already diagnosed at enrollment. Although these cases were equally distributed between groups (20.6% vs 19.3%), it is still possible that this condition influences the effect of PETN treatment. Finally, dosage of PETN was 80 mg in the pilot study, but we used a dosage of 50 mg because PETN is now only available in Pentalong 50-mg tablets (PUREN Pharma GmbH & Co KG, München, Germany), which might have decreased the effect.

Conclusion

We failed to demonstrate the designated impact of PETN on the development of FGR and perinatal mortality and morbidity. However, we observed that PETN was able to reduce prematurity and might improve maternal outcome in a pregnant population identified to be at risk of developing FGR because of impaired uterine perfusion at midgestation. ■

FIGURE 4
Trends in the incidence of pregnancy induced hypertension, preeclampsia, hospitalization, and delivery in the two treatment groups



Kaplan–Meier plot of cumulative percentage of participants who developed **A,** blood pressure >140 mm Hg systolic and >90 mm Hg diastolic (HR, 0.623; CI, 0.413–0.940; *P*=.019) or **B,** preeclampsia (HR, 0.648; CI, 0.411–1.020; *P*=.054), **C,** who were admitted to the hospital (HR, 0.511; CI, 0.308–0.846; *P*=.008), and **D,** who had delivered (HR, 0.767; CI, 0.612–0.961; *P*=.007).

CI, confidence interval; *HR*, hazard ratio.

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Received Jan. 4, 2022; revised July 12, 2022; accepted July 16, 2022.

The authors report no conflict of interest.

Funding for this trial was provided by the German Research Foundation (DFG) to T.G. (GR1955/4-1). The funding organization is a public institution and had no role in the design and conduct of the study; collection, management, and analysis of the data; or preparation, review, approval of the manuscript, or decision to submit the manuscript for publication.

The trial was registered at the Deutsches Register Klinischer Studien (DRKS00011374) on June 27, 2017 https://www.drks.de/drks_web/navigate.do?navigationId=trial.HTML&TRIAL_ID=DRKS00011374 and ClinicalTrials.gov (NCT03669185) https://clinicaltrials.gov/ct2/show/NCT03669185 on September 14, 2018 with the clinical trial identification number EudraCT (2016-004396-51). The date of initial participation enrollment was August 15, 2017.

The dataset will be available to appropriate academic parties on request to the Chief Investigator, T. G., in accordance with the data sharing policies of the Jena University Hospital and the German Research Foundation. Input from the coinvestigator group will be obtained where applicable. The study protocol is available at https://europepmc.org/article/PMC/PMC6744635.

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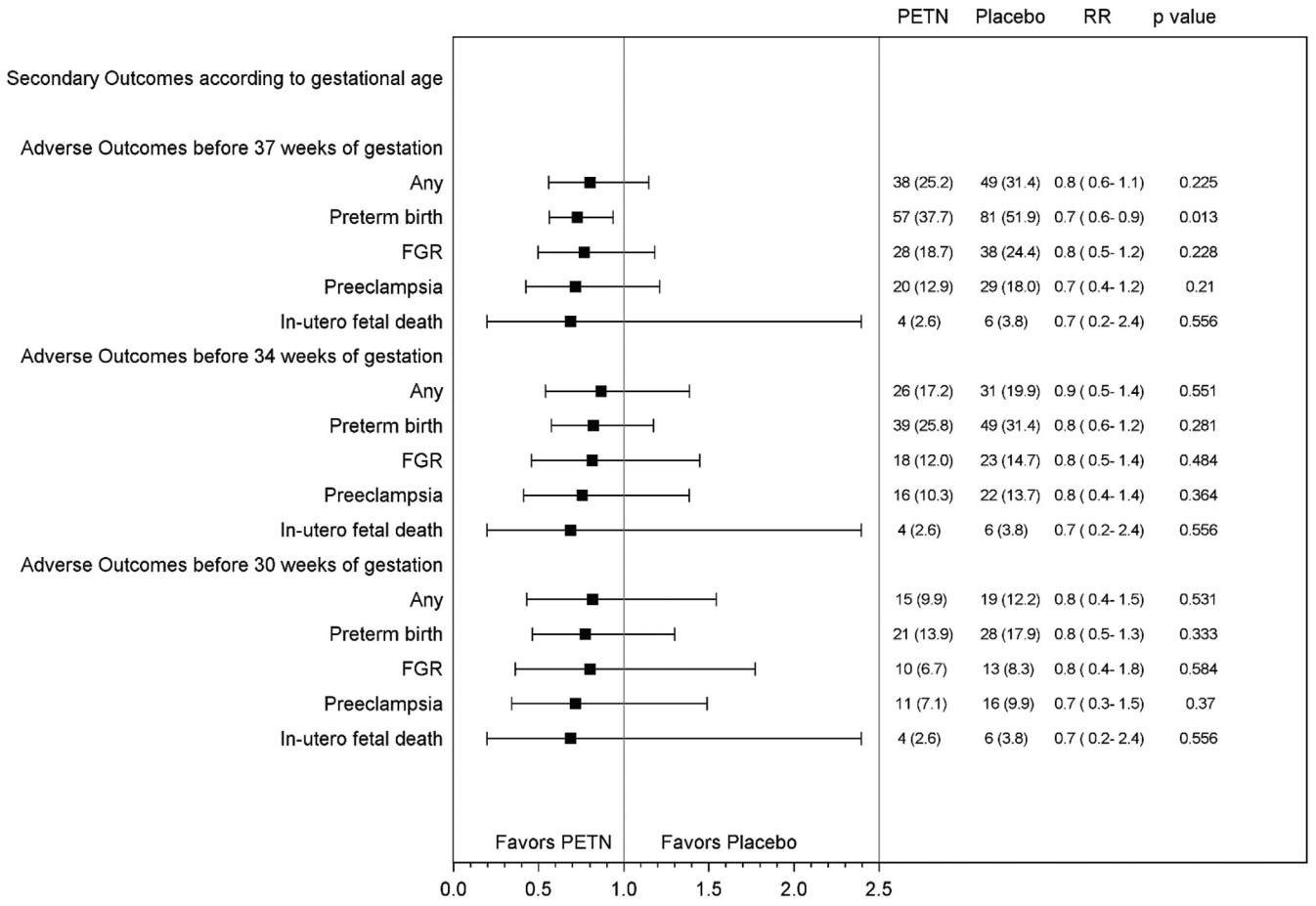
SUPPLEMENTAL FIGURE

PETN effect on secondary outcome parameters according to gestational age



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