The nitric oxide donor pentaerythritol tetranitrate lowers hypertension and angiogenic imbalance in pregnancies with impaired uterine perfusion—a secondary analysis of a randomized trial

OBJECTIVE: A multicenter, randomized controlled trial investigated the effects of the nitric oxide donor pentaerythritol tetranitrate (PETN) in pregnant women with impaired uterine perfusion.[1] PETN did not significantly reduce the composite primary outcome of fetal growth restriction (FGR) or perinatal death, but it led to significant reductions of 55% in pregnancy-induced hypertension (PIH) and of 27% in preterm birth. Participants in the PETN group were less likely to be admitted to the hospital during pregnancy (hazard ratio [HR], 0.51; 95% confidence interval [CI], 0.30−0.85; P=.01).[1] A dysfunctional placenta releases antiangiogenic factors, such as soluble fms-like tyrosine kinase-1 (sFlt-1) and soluble endoglin (sEng), while suppressing proangiogenic factors, like placental growth factor (PlGF). This imbalance disrupts endothelial function and vascular health and leads to hypertension and impaired placental perfusion. This secondary analysis focuses on the effect of PETN on maternal outcomes and angiogenic profiles.

STUDY DESIGN: Pregnant women who presented with a mean uterine artery pulsatility index of >95th percentile at 19+0 to 22+6 weeks of gestation were randomized to receive 50 mg PETN or placebo twice daily. The maternal data that were collected upon inclusion, at study visits every 4 weeks, and at delivery included blood pressure, adverse events, serum sample sFlt-1/PlGF ratios, and preeclampsia-related serum parameters. Residual samples were obtained on availability and were used to determine the sEng and PETN metabolite serum concentration. The intent-to-treat principle was used, and continuous outcomes were compared using the Mann-Whitney U test and categorical outcomes were compared using Fisher's exact test.

RESULTS: Of the 317 women who were enrolled in the study, clinical data were available for further analyses for 307 women. The sFlt-1/PlGF ratio values were available for 290 participants. Residual samples for the determination of sEng and PETN metabolite concentrations were available for 100 participants (46 PETN cohort and 55 placebo group). There were no differences noted between the 2 study groups, including in the sFlt-1/PlGF ratio values (Supplemental Table 1).

The incidence of PIH was significantly reduced in the PETN group (23.9%; 37/155 women) when compared with the placebo group (36.6%; 59/161 women) (Table). Preeclampsia, defined as PIH and at least 1 additional feature, such as FGR, liver enzyme alteration, kidney malfunction, or hemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome, was observed in 20% (31/155 women) of the PETN group and in 29.2% (47/161 women) of the placebo group (P=.07). The mean of the maximum reported systolic blood pressure was significantly lower in the PETN group when compared with the placebo group (130 mm Hg vs 135 mm Hg; P=.019), and the proportion of participants whose blood pressure values remained <140 mm Hg systolic and/or <90 mm Hg diastolic was higher in the PETN group (HR, 0.6; CI, 0.397−0.906; P=.013) (Supplemental Figure).

At least 1 adverse outcome was reported in 111 participants (72%) in the PETN group and in 127 participants (78%) in the placebo group with no significant differences between the groups (Supplemental Tables 2 and 3). The sFlt-1/PlGF ratios were determined for 290 participants (150 placebo and 140 PETN). Missing values were because of restrictions in the access to sFlt-1 and PlGF measurements in some centers. The sFlt-1/PlGF ratio remained <85 more often among women in the PETN group (HR, 0.559; CI, 0.376−0.831; P=.003), and there were statistically significantly fewer patients (40; 28.6%) in the PETN group with sFlt-1/PlGF ratio values that exceeded 85 (vs 75; 50% in the placebo group; P<.001) (Table 1). A total of 272 residual serum samples of 100 patients (46 PETN cohort and 55 Placebo group) from 3 study centers were available for further evaluation. Because the baseline characteristics of the subgroup did not differ from those of the overall study population, the subgroup was considered representative of the entire cohort. There was no detection of PETN or its metabolites pentaerytrithylmononitrate and pentaerytrithyldinitrate in samples of the placebo group or samples retrieved at inclusion (study visit 1). In 2 participants in the PETN cohort, PETN metabolites could not be detected. For the analysis of sEng, residual samples were included from participants who provided specimens at study visit 1 and at least 1 additional visit. Across all study visits following the initiation of treatment, sEng concentrations were significantly lower in the PETN group at all time points.

CONCLUSION: This secondary analysis of the PETN trial demonstrates that PETN treatment in women with impaired uterine perfusion at midgestation was associated with a significantly lower incidence of PIH, a reduction in systolic blood pressure, a significant reduction in cesarean deliveries (Table 1), and a shorter duration of hospitalization during pregnancy. This was accompanied by a lower proportion of patients

TABLE
Maternal outcomes by study group[a]

Outcomes	Total (n=307) PETN (n=151)	Placebo (n=156)	*P*
Gestational age at birth (wk), mean ± SEM	36.1±4.7	35.1±4.7	.06
Preterm birth (<37 wk), n (%)	57 (37.7)	81 (51.9)	.02
PIH[b], n (%)	37 (23.9)	59 (36.6)	.02
Preeclampsia[c], n (%)	31 (20.0)	47 (29.2)	.07
Early preeclampsia ≤32+0 wk, n (%)	26 (16.8)	33 (20.5)	.471
Late preeclampsia >32+0 wk, n (%)	5 (3.2)	14 (8.7)	.057
Placental abruption, n (%)	4 (2.7)	4 (2.6)	1.00
Cesarean delivery, n (%)	76 (50.3)	102 (65.4)	.008
Maternal AE, n	111	127	.194
Eclampsia, n (%)	1	0	.492
Hypertensive crisis (RR >170/110 mm Hg) or reported as AE, n (%)	1 (0.7)	2 (1.3)	1.000
Max systolic blood pressure (mm Hg)	130 (122–144)	137 (129–146)	.019
Max Diastolic blood pressure (mm Hg)	85 (80-93)	87 (80-93)	.312
Platelets <100,000/μL, n (%)	3 (2.0)	8 (5.1)	.220
ASAT > 70 U/L, n (%)	6 (4.1)	12 (7.7)	.227
ALAT > 70 U/L n (%)	7 (4.7)	14 (8.9)	.178
LDH > 300 U/L, n (%)	27 (18.6)	29 (18.7)	1.000
Creatinine >150 μmol/L, n (%)	0	0	1.000
sFlt-1/PLGF	47.3 (20.0–120.5)	76.4 (18.6–205)	.073
sFlt-1/PlGF always <38, n (%)	55 (39.3)	53 (35.3)	.544
sFlt-1/PLGF >85 at any time, n (%)	40 (28.6)	75 (50.0)	<.001
sFlt-1/PlGF always < 85 if >38, n (%)	45 (32.1)	22 (14.7)	<.001
sFlt-1/PLGF >85 if <38 at inclusion, n (%)	22 (19.1)	46 (38.3)	.002

AE, adverse event; *ALAT*, alanine aminotransferase; *ASAT*, aspartate aminotransferase; *LDH*, lactate dehydrogenase; *PETN*, pentaerythritol tetranitrate; *PIH*, pregnancy-induced hypertension; *PLGF*, placental growth factor; *RR*, blood pressure; *SEM*, standard error of the mean; *sFlt-1*, soluble fms-like tyrosine kinase-1.

[a] Median and 25th to 75th percentiles are reported for continuous baseline characteristics and absolute and relative frequencies are reported for categorical characteristics; [b] Defined as systolic blood pressure exceeding 140 mm Hg and/or diastolic blood pressure exceeding 90 mm Hg; [c] Defined as PIH and at least 1 additional manifestation of organ malperfusion that lead to either fetal growth restriction, liver enzyme alteration, kidney malfunction, or hemolysis, elevated liver enzymes, and low platelet count syndrome.

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whose sFlt-1/PlGF ratios exceeded the cutoff of 85 at any time during pregnancy. In addition, serum concentrations of sEng were significantly lower in the treatment group throughout the study duration.

Elevated sFlt-1/PlGF ratios are associated with poor pregnancy outcomes, including preterm birth and FGR.[2,3] Our findings suggest that PETN may improve pregnancy outcomes by reducing the anti-angiogenic state in affected women. In addition to the improved balance between sFlt-1 and PlGF, sEng, which plays a crucial role in vascular function, angiogenesis, and endothelial health, was significantly reduced. sEng acts synergistically with sFlt1 to induce severe preeclampsia features and is considered an additional biomarker of endothelial dysfunction.[4]

Our findings are consistent with PETN's known pharmacologic effects of improving endothelial function, reducing oxidative stress, and improving vascular homeostasis. PETN seems to have unique properties in maintaining angiogenic balance. Our group has shown that PETN protects endothelial cells from thrombin-induced ROS production in vitro.[5]

The findings of this secondary analysis of our multicenter trial suggest that PETN treatment may offer significant benefits in reducing the incidence of hypertensive disorders in high-risk pregnancies with impaired uterine perfusion. Adverse events and severe pregnancy-related complications were less frequent in the PETN group, although these did not reach statistical significance. Serum analysis supports the potential benefits of PETN, because participants who

received the treatment exhibited a more favorable angiogenic profile, including lower sEng levels, and a reduced number of cases that exceeded the elevated sFlt-1/PlGF ratio thresholds. It can be speculated that pharmacologic alterations of the sFlt-1/PlGF axis might have clinical implications beyond obstetrical contexts, because elevated circulating sFlt-1 and reduced PlGF levels have also been implicated in cardiovascular and renal disease.[6,7] Further research is necessary to confirm these findings and establish the long-term safety and efficacy of PETN in clinical practice.

CREDIT AUTHORSHIP CONTRIBUTION STATEMENT: **Tanja Groten:** Data curation, Conceptualization. **Mariann Städtler:** Writing — review & editing, Validation, Project administration, Data curation. **Silke Große:** Investigation: performed sample analyses to determine endoglin and PETN metabolites, Writing — review & editing. **Thomas Lehmann:** Writing — original draft, Visualization, Validation, Methodology, Formal analysis, Conceptualization. **Matej Komar:** Writing — review & editing, Investigation. **Jennifer Lucia Winkler:** Writing — review & editing, Investigation. **Mateja Condic:** Writing — review & editing, Investigation. **Brigitte Strizek:** Writing — review & editing, Investigation. **Sven Seeger:** Writing — review & editing, Investigation. **Yvonne Jäger:** Writing — review & editing, Investigation. **Ulrich Pecks:** Writing — review & editing, Writing — original draft, Investigation. **Christel Eckmann-Scholz:** Writing — review & editing, Investigation. **Karl Oliver Kagan:** Writing — review & editing, Investigation. **Markus Hoopmann:** Writing — review & editing, Investigation. **Constantin S. von Kaisenberg:** Writing — review & editing, Investigation. **Lars Brodowski:** Writing — review & editing, Investigation. **Anne Tauscher:** Writing — review & editing, Investigation. **Susanne Schrey-Petersen:** Writing — review & editing, Investigation. **Ulrike Friebe-Hoffmann:** Writing — review & editing, Investigation. **Krisztian Lato:** Writing — review & editing, Investigation. **Christoph Hübener:** Writing — review & editing, Investigation. **Maria Delius:** Writing — review & editing, Investigation. **Stefan Verlohren:** Writing — review & editing, Investigation. **Dorota Sroka:** Writing — review & editing, Investigation. **Dietmar Schlembach:** Writing — review & editing, Writing — original draft, Investigation. **Laura de Vries:** Writing — review & editing, Investigation. **Katrina Kraft:** Writing — review & editing, Writing — original draft, Investigation. **Gregor Seliger:** Writing — review & editing, Investigation. **Ekkehard Schleußner:** Writing — review & editing, Writing — original draft, Supervision, Resources, Investigation, Conceptualization. ■

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

The data set will be available to appropriate academic parties on request from the Chief Investigator, Tanja Groten, in accordance with the data sharing policies of the Jena University Hospital and the German research foundation. Input from the co-investigator group will be evaluated when applicable. The study protocol is available at https://europepmc.org/article/PMC/PMC6744635.


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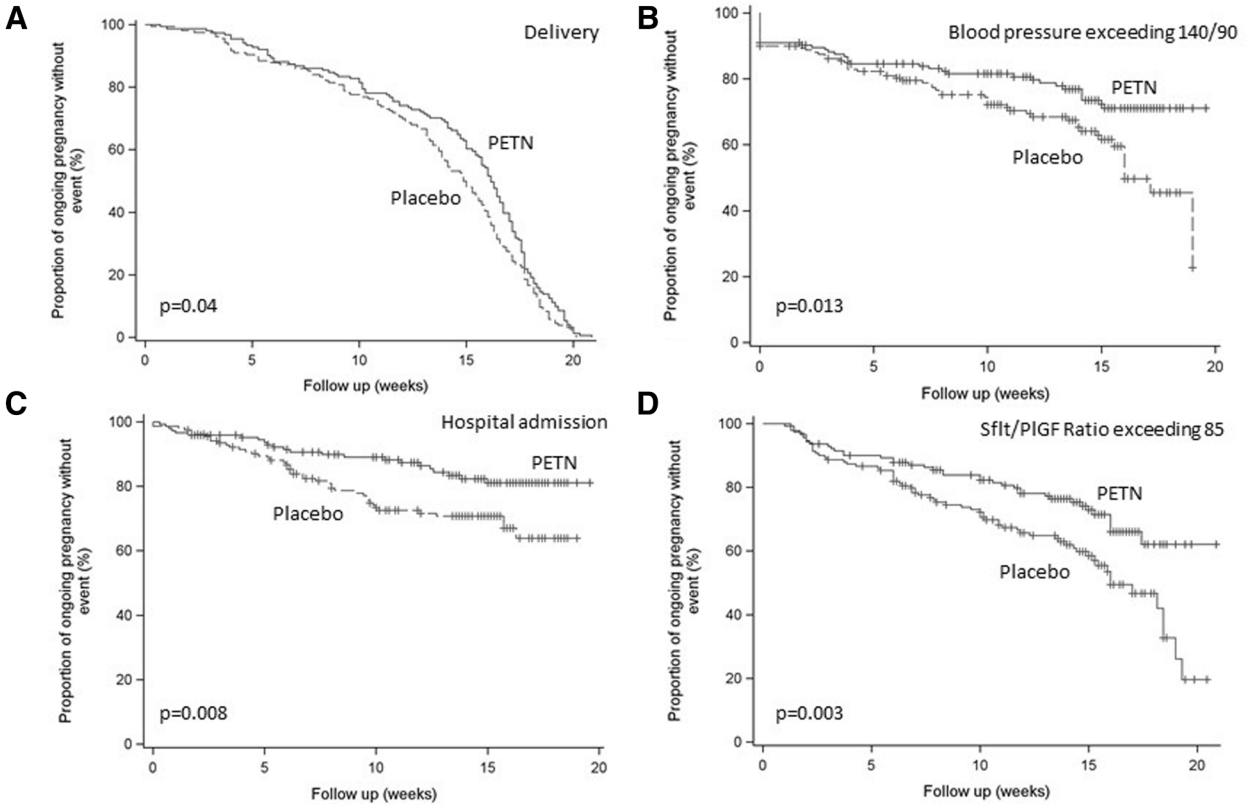
SUPPLEMENTAL FIGURE

Kaplan–Meier curves of cumulative event-free rates



Kaplan Meier Plot of cumulative percentage of ongoing pregnancies (HR, 0.795; CI, 0.635-0.997; *P*=.04) (**A**), of participants who did not develop blood pressure values >140 mmHg systolic and/or >90 mmHg diastolic (HR, 0.6; CI, 0.397-0.906; *P*=.013) (**B**), who were not admitted to the hospital (HR, 0.411; CI, 0.308-0.846; *P*=.008) (**C**), who remained with their sFlt/PlGF ratio below 85 (HR, 0.559; CI, 0.376-0.831; *P*=.003) (**D**).

HD, hazard ratio.

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SUPPLEMENTAL TABLE 1
Maternal characteristics at baseline[a]

Characteristic	PETN (n = 155)	Placebo (n = 162)	*P*
Age (y)	33 (30–36)	34 (29–37)	.170
BMI (kg/m^2)	24.6 (22–30.9)	25.7 (21.6–31.5)	.571
Weight before pregnancy	74 (64.9–86.6)	76.6 (65–91)	.559
BMI >30, n (%)	43 (27.7)	48 (29.8)	.711
Gestational age at randomization (wk)	21.7 (21–22.4)	21.7 (20.9–22.3)	.436
Preexisting diagnosed hypertension	20 (12.9)	25 (15.4)	.630
RR >140/90 mm Hg and/or diagnosed hypertension at randomization, n (%)	30 (19.4)	33 (20.6)	.888
Systolic blood pressure (mm Hg) at randomization	122 (111–134)	120 (112.5–133.5)	.818
Diastolic blood pressure (mm Hg) at randomization	78 (70–85)	78 (70–85)	.960
Hypertensive medication[b] yes	35 (22.6)	57 (35.4)	.013
Nulliparous	67 (43.2)	85 (52.8)	.093
Number of previous deliveries	1 (0–1)	0 (0–1)	.070
ASS at inclusion, n (%)	57 (36.8)	56 (34.8)	.726
PI Arteria uterina (mean)	1.84 (1.69–2.11)	1.82 (1.68–2.04)	.416
Angiogenic marker at baseline			
sFlt/PlGF	6.5 (4.0–14.2)	8.0 (4.2–26.4)	.075
sFlt/PlGF >38, n (%)	26 (17.7)	36 (22.8)	.319
sFlt/PlGF >85, n (%)	17 (11.6)	25 (15.8)	.320
PlGF <100 pg/mL	42 (28.6)	57 (36.1)	.179
PlGF <12 pg/mL	2 (1.4)	8 (5.1)	.106

ASS, acetylsalicylic acid; *BMI*, body mass index; *PETN*, pentaerythritol tetranitrate; *PI*, pulsatility index; *PlGF*, placental growth factor; *RR*, blood pressure; *sFlt-1*, soluble fms-like tyrosine kinase-1.

[a] The median and 25th to 75th percentiles are reported for continuous baseline characteristics and absolute and relative frequencies are reported for categorical characteristics; [b] Antihypertensive medications include Adalat, alpha methyldopa, amlodipin, Bayotensin akut, Beloc, bisoprolol, Dopegyt, Ebrantil, Ebrantil Perfusor, Ebrantil intravenous, methyldopa, MetoHexal, metoprolol, Nepresol, nifedipin, Nitrendipin Phiole Akutmedikation, Presinol, urapidil.

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SUPPLEMENTAL TABLE 2
Maternal adverse events

Adverse events	PETN, n = 155 Frequency	PETN, n = 155 Participants with AE, n (%)	Placebo, n = 162 Frequency	Placebo, n = 162 Participants with AE, n (%)	*P*
Occurrence of any AE		111 (71.6)		127 (78.4)	.194
Cardiac disorders[a]	4	3 (1.9)	3	3 (1.9)	.718
Ear and labyrinth disorders[b]	3	3 (1.9)	1	1 (0.6)	.362
Endocrine disorders: goitre	—		1	1 (0.6)	1.000
Eye disorders[c]	7	4 (2.6)	2	2 (1.2)	.439
Gastrointestinal disorders[d]	63	28 (18.1)	40	27 (16.7)	.768
General disorders and administration site conditions[e]	5	5 (3.2)	3	3 (1.9)	.494
Cholestasis in pregnancy	—		2	2 (1.2)	.499
Infections and infestations[f]	34	29 (18.7)	44	29 (17.9)	.885
Injury, poisoning, and procedural complications[g]	1	1 (0.6)	2	2 (1.2)	1.000
Medical observation	1	1 (0.6)	3	2 (1.2)	1.000
Metabolism and nutrition disorders: impaired glucose tolerance	—		1	1 (0.6)	1.000
Musculoskeletal and connective tissue disorders[h]	8	8 (5.2)	12	9 (5.6)	1.000
Nervous system disorders[i]	132	51 (32.9)	98	49 (30.2)	.630
Pregnancy, puerperium, and perinatal conditions[j]	86	71 (45.8%)	132	100 (61.7%)	.004[n]
Psychiatric disorders: restlessness	3	2 (1.3)	—		.238
Renal and urinary disorders[k]	—		3	3 (1.9)	.248
Reproductive system and breast disorders[l]	1	1 (0.6)	4	3 (1.9)	.623
Respiratory, thoracic, and mediastinal disorders: epistaxis	8	5 (3.2)	5	4 (2.5)	.746
Skin and subcutaneous tissue disorders[m]	4	4 (2.6)	12	7 (4.3)	.543
Vascular disorders: hypotension	—		1	1 (0.6)	1.000

AE, adverse event; *PETN*, pentaerythritol tetranitrate.

[a] Bradycardia, extrasystoles, palpitations; [b] Ear pain, vertigo; [c] Altered visual depth perception, vision blurred; [d] Abdominal pain, constipation, diarrhoea, dry mouth, gastrointestinal disorder, gastrooesophageal reflux disease, mouth hemorrhage, oral mucosal blisterin; [e] Facial pain, fatigue, peripheral swelling, pyrexia; [f] Bronchitis, gastrointestinal infection, herpes simplex, nasopharyngitis, pyelonephritis, urinary tract infection, vaginal infection; [g] Foot fracture, procedural dizziness, uterine rupture; [h] Arthralgia, back pain, groin pain, muscle spasms, musculoskeletal pain, pain in jaw, pubic pain; [i] Carpal tunnel syndrome, dizziness, dysgeusia, epilepsy, headache, migraine, paraesthesia, syncope; [j] Eclampsia, gestational diabetes, gestational hypertension, gestational oedema, hemolysis, elevated liver enzymes and low platelet count syndrome, hemorrhage in pregnancy, placental insufficiency, preeclampsia, premature delivery, premature labor, premature separation of placenta; [k] Dysuria, renal pain, urine abnormality; [l] Breast pain, vaginal hemorrhage; [m] Alopecia, pruritus, rash; [n] Significant differences between study groups.

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SUPPLEMENTAL TABLE 3
Serious adverse events (SAE) reported in the mothers

	PETN, n = 155		Placebo, n = 162		
Severe adverse events	Frequency of AE	Individuals involved, n (%)	Frequency of AE	Individuals involved, n (%)	*P*
Participants without SAE		90 (58.1)		70 (43.2)	.010[a]
Cardiac disorders			1	1 (0.6)	1.000
Ear and labyrinth disorders	1	1 (0.6)			.489
General disorders and administration site conditions	1	1 (0.6)			.489
Infections and infestations	1	1 (0.6)	1	1 (0.6)	1.000
Nervous system disorders			1	1 (0.6)	1.000
Pregnancy, puerperium, and perinatal conditions	68	63 (40.6)	105	91 (56.2)	.007[a]
Reproductive system and breast disorders	1	1 (0.6)	2	2 (1.2)	1.000

AE, adverse event; *PETN*, pentaerythritol tetranitrate.

[a] Significant differences between groups.

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