Effect of Pentaerythrityltetranitrate (PETN) on the development of fetal growth restriction in pregnancies with impaired uteroplacental perfusion at mid gestation – a randomised trial

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Trial registration: The trial was registered at, DRKS (DRKS00011374) at the 27th of June 2017 and clinicaltrials.gov (NCT03669185) at the 14th of September 2018 with the clinical trial identification number EudraCT (2016-004396-51). The date of initial participation enrolment was the 15th of August 2017.

Author Contributions: TG, TL and ES conceived the study. TG and MS coordinated the study and the data collection. All other authors were involved in data collection. TL and TG did the study analyses, with input from ES. TG wrote the article. All authors reviewed, contributed to, and approved the final version of the manuscript. TG, ES, TL and MS had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Data sharing: The dataset 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 coinvestigator group will be achieved where applicable. The study protocol is available at https://europepmc.org/article/PMC/PMC6744635.

Word count: 3293
Condensation: PETN could not prove to prevent growth restriction and perinatal death in pregnancies complicated by impaired uterine perfusion at mid gestation in a randomized trial.

Short Title: Effect of PETN on the development of FGR in high-risk pregnancies

AJOG at a Glance:

A. Why was this study conducted? To evaluate and confirm the effect of the NO-donor PETN on the development of fetal growth restriction and perinatal death in high-risk pregnancies.

B. What are the 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 did not prove to impact on primary outcome. Secondary outcomes, like PTB and PIH were reduced.

C. What does this study add to what is already known? Although PETN failed to significantly impact on FGR and fetal death, it does affect maternal blood pressure and prolongs pregnancy.
Abstract page

Background: Fetal growth restriction is strongly associated with impaired placentation and abnormal utero-placental blood flow. NO-donors like PETN 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 PETN to pregnant women at risk, identified by impaired uterine perfusion at mid gestation. Results of this mono-center study retrieved the hypothesis that PETN might have an effect in pregnancies with compromised placental function the sense of secondary prophylaxis.

Objective: To test the hypothesis that the NO-donor PETN reduces fetal growth restriction and perinatal death in pregnant women with impaired placental perfusion at mid gestation in a multicenter trial.

Study Design: In a multicenter, randomized, double-blind, placebo controlled trial with two parallel groups pregnant women presenting with a mean uterine artery Pulsatility Index >95th percentile at 19+0 to 22+6 weeks of gestation were randomized to Pentalong® 50mg or placebo twice daily. Participants were assigned to high or low risk 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 PETN group and 45.5% in the placebo group, (unadjusted RR 0.90, 95%CI 0.69-1.17; adjusted
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Secondary outcomes like preterm birth (unadjusted RR 0.90, 95%CI 0.69-1.17; p=0.43). Secondary outcomes like preterm birth (unadjusted RR 0.73, 95%CI 0.56-0.94; adjusted RR 0.73, 95%CI 0.56-0.94; p=0.01) and pregnancy induced hypertension (unadjusted RR 0.65, 95%CI 0.46-0.93; adjusted RR 0.65, 95%CI 0.46-0.92; p=0.01) were reduced.

Conclusion: Our study failed to show an impact of PETN on the development of fetal growth restriction and perinatal death in pregnant women with impaired uterine perfusion at mid gestation. PETN significantly reduced secondary outcome parameters like the incidence of preterm birth and pregnancy induced hypertension in these pregnancies.

Key words: fetal growth restriction, preterm birth, placental insufficiency, placental perfusion, pentaerithrityltetranitrate.
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. Furthermore, intrauterine malnutrition causes lifelong consequences as developmental origin of adult diseases. In the mother, FGR is associated with vascular pathology, impaired placentation and the failure of decidual spiral artery remodelling, leading to impaired utero-placental perfusion. Abnormal uterine flow, as well as maternal conditions associated with impaired vascular health, including previous FGR, signifies the risk of developing FGR during pregnancy. Consequently, a recent consensus on the definition on FGR incorporates the presence of Doppler abnormalities underscoring the pathophysiologic significance of fetoplacental perfusion. Thus, abnormal placental- and or fetal perfusion differentiates FGR from the terminus SGA for small for gestational age, a constitution were fetal weight below the 10th percentile can still be normal. NO-donors as pentaerithrityltetranitrate (PETN) reduce the impedance in the uteroplacental vessels and have been demonstrated to possess protecting effects on the endothelium. A randomized controlled pilot study suggested a beneficial effect of PETN on pregnancies recognized by impaired utero-placental perfusion at mid gestation. The PETN pilot study revealed a 38% relative risk reduction for the development of FGR or perinatal death (adjusted RR 0.410; 95% 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 placebo. Based on this pilot data we developed the hypothesis that PETN could serve as secondary prophylaxis to prevent FGR in women with impaired placental perfusion at mid gestation. Thus the aim of the PETN-trial was to proof the effect of PETN on the development of fetal growth restriction.
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and perinatal death in patients with placentation failure, identified at mid gestation in a
multicentre, randomized, double-blind, placebo controlled, parallel grouped, trial.  

Methods

Study design

The PETN-study was a multicentre, randomised, double blind, placebo-controlled, parallel-
grouped study to assess the efficacy and safety of 50 mg PETN twice to prevent FGR and
perinatal death in pregnancies recognized with placentation failure at mid gestation. The trial
was performed at fourteen tertiary care hospitals in Germany. Ethical approval has been
obtained from the ethical committee of the University Hospital of Jena as leading committee
(Institutional review board (IRB) Friedrich Schiller University, Jena) (5085-02/17) and each of
the fourteen German study centres obtained ethical approval of their local committees. The
study protocol has been approved by the higher federal authority and was published before. 

Study Participants

Participants were recruited from pregnant women presenting between 19+0 and 22+6 weeks
of gestation for routine or risk guided mid-trimester ultrasound screening for fetal structural
anomalies including the assessment of utero-placental perfusion. Major inclusion criterion
was abnormal uterine Doppler flow defined by a mean pulsatility index (PI) exceeding the 95th
percentile of the reference population.  
Exclusion criteria were, multiple pregnancies,
diagnosed or suspected foetal chromosomal or major structural defects and maternal
circumstances predicting adverse pregnancy outcome other than due to impaired placental
function and maternal disease defined as contraindication for intake of PETN. Participants
were assigned to risk groups upon inclusion and before randomization. Women with pre-
existing hypertension, diabetes mellitus, or other vascular diseases, and/or who have had FGR, stillbirth, premature placental abruption, HELLP (haemolysis-elevated-liver-enzymes-low-platelet)-syndrome, or preeclampsia in a previous pregnancy are classified as "high risk", 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 randomisation software. Randomization was performed block-wise with a fixed block length stratified by centre and risk group. PETN containing and placebo tablets were manufactured by Aesica Pharmaceuticals GmbH (Zwickau, Germany). The two types of tablet appeared identical in size, shape, taste and colour. Packs were labelled 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 labelled as study medication and thus verum and placebo were indistinguishable to participants, study nurses and clinicians. Following randomisation, oral intake of PETN or placebo was two times daily starting with enrolment 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 four weeks during the treatment period. Upon delivery, data on neonatal and maternal outcome were collected. Data capture were 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 recorded via an encrypted data link (HTTPS) by use of data entry masks.

Outcomes
The primary outcome was pre-specified as a composite outcome of perinatal death and/or development of FGR. Perinatal death is defined as in utero fetal death after randomization or neonatal death within the first week of life. FGR is defined by abnormal uterine Doppler flow and a birth weight of the newborn below the 10th centile according to population growth charts.\textsuperscript{9}

As a key secondary endpoint we report severe neonatal morbidity and mortality as a composite of severe FGR (defined by birth weight below the 3rd and the 5th centile according to population growth charts\textsuperscript{9} and/or perinatal death and/or placental abruption. Additionally, we report a combined outcome parameter of “severe neonatal morbidity” as composite outcome in cases were one of the following occurred the need of ventilation, intraventricular haemorrhage III – IV° or necrotising enterocolitis requiring surgery.

Additional secondary outcome parameters were birth weight below the 3rd, 5th and 10th centile, development of FGR requiring delivery before 30, 34 and 37 weeks, preterm birth before 30, 34 weeks and 37 weeks, rate of neonatal intensive care unit (NICU) admission and neonatal complications like the need of assisted ventilation, occurrence of intraventricular haemorrhage II–IV° or necrotized enterocolitis. Maternal secondary outcome measures were the development of pregnancy induced hypertension (PIH), defined as occurrence of blood pressure exceeding 140mmHg for the systolic and/or 90mmHg for the diastolic measurements during the study period, preeclampsia, defined as PIH and at least one additional manifestation of organ malperfusion leading to either FGR, liver enzyme alteration, kidney malfunction.\textsuperscript{10} Occurrence of a HELLP syndrome was subsumed to preeclampsia.

To document, including the reporting of adverse and serious adverse events we followed the requirements of the 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 has met on a regular basis and did not find any peculiarities and did not make any recommendations on protocol changes.

**Statistical analysis**

Sample size considerations were based on the results of a pilot study. Since additional risk factors increase the risk of FGR a stratified randomisation and analysis was planned with two strata. From the pilot study observed a 2:1 ratio for low and 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 vs. placebo in the pilot study resulted in an estimated odds ratio of 0.41. Thus, for the planning of the PETN trial, we aimed at detecting at a more conservative, clinically relevant 50% risk reduction in the PETN group compared to placebo. 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 two-sided significance level alpha of 0.05 (nQuery 7.0). Assuming a dropout rate of about 10% a total of 324 patients were planned to be randomized. Primarily, data were analysed according to the intent-to-treat (ITT) principle.

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

Results

Between August 2017 and March 2020 317 women have been enrolled in the study. Because we observed a dropout rate of less than 5%, staying far below the expected one 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 two treatment groups.

The cumulative incidence of the primary outcome was 41.1% (62 of 155 infants) in the PETN group and 45.5% (71 of 161 infants) in the placebo group, the difference between both groups was not statistically significant (adjusted RR 0.90, 95% CI 0.69-1.17, p=0.43). The estimated treatment effect was supported by a generalized linear model with adjustment for study centre effects (adjusted RR 0.90, 95% CI 0.69-1.15, p=0.38) and also after the multiple imputation of missing values (RR 0.90, 95% CI 0.70-1.17, p=0.43). Five perinatal deaths (3.3%) occurred in the PETN group compared to seven cases (4.5%) in the placebo group (adjusted RR 0.74, 95% CI 0.23-2.28, p=0.6). (table 2, figure 2)
The cumulative incidence of the combined endpoint of birth weight below the 3rd centile, intrauterine or neonatal death or placental abruption was 25.2% (38 of 155 infants) in the PETN group and 26.3% (41 of 161 infants) in the placebo group (adjusted RR 0.90, 95% CI 0.65-1.40, p=0.82). Birth weight of 61 infants (40.7%) in the PETN group and 69 infants (44.2%) in the placebo group was below the 10th percentile (adjusted RR 0.92, 95% CI 0.71-1.20, p=0.5). 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=0.01) (table 2, figure 2). Severe neonatal morbidity reported as “combined neonatal morbidity” as a composite of need of ventilation and/or necrotising enterocolitis and/or intraventricular haemorrhage of grade III/IV occurred in 30.1% (44 of 155 infants) in the PETN group and 35.8% (53 of 161 infants) in the placebo group (adjusted RR 0.84, 95% CI 0.61-1.7, p=0.3). (table 3, figure 2)

The cumulative incidence of PIH was 23.9% (37 of 155 women) in the PETN group and 36.6% (59 of 161 women) in the placebo group (adjusted RR 0.65, 95% CI 0.46-0.92, p=0.01) (table 2, figure 2). Preeclampsia was observed in 20% (31 of 155 women) of the PETN and 29.2% (47 of 161 women) of the placebo group women (adjusted RR 0.68, 95% CI 0.46-1.03, p=0.05) (table 2, figure 2). Outcome according to gestational age did not reveal statistically significant results (supplemental figure 1). 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 mmHg systolic and/or 90 mmHg 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
Among pregnant women with impaired utero-placental perfusion at mid gestation, using the NO-donor PETN compared to 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 utero-placental pulsatility index > 95th percentile predicts FGR with a sensitivity of 18% and a specificity of 95% in a general population and a sensitivity of 58% for any FGR in a high risk population with a specificity of 75%. More recent data confirm, the higher risk for FGR in women with a medical history of chronic hypertension, diabetes mellitus, systemic lupus erythematoses or antiphospholipid antibody syndrome and in those with prior history of adverse pregnancy outcome associated with FGR. According to these data, at least one 3rd of the pregnant women diagnosed with impaired perfusion of the uterine arteries at mid gestation 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 mal-perfusion of
the placenta is recognized to cause, maintain and worsen the development of FGR. While, in our previous trial utero-placental and fetal perfusion was significantly improved in the PETN group, Doppler measurements during the current trial did not reveal any changes. (figure 3) The failure to improve utero-placental 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=0.055) was similar in the treatment groups, the maternal outcome indicate improvement favoring PETN for a reduced rate of PIH. These beneficial maternal effects were also reflected in a reduced need to be admitted to the hospital 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% of the low-risk group. However, in the Pilot study stratification was done during statistical analysis while randomisation has not been stratified. The extent to which undetected high-risk patients, which may have been assigned to the low-risk group, may have contributed to the results cannot be determined.

Preterm birth before 37 weeks could be reduced by 30% (RR 0.7, 95% CI 0.6-0.9; p=0.01). Accordingly, Kaplan-Meier-analysis revealed that during the course of pregnancy participants in the treatment group delivered later (p=0.007) revealing a risk reduction of 25% (HR 0.767, 95% CI 0.612-0.961). (figure 4d)

Clinical and Research implications
The actual and future burden of being born with a birth weight below the 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. 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 and obesity. Regardless, there have been only a few studies on pharmacological treatment of FGR so far. To date the PETN trial is the only RCT whose design defined the reduction of FGR as primary outcome in a cohort recognized to be at risk for the development of placenta associated pregnancy complications by impaired utero-placental perfusion at mid gestation. The most recent international RCT including cases where severe FGR has been diagnosed before 30 weeks of gestation investigated the effect of the phosphodiesterase-5-inhibitor sildenafil on neonatal outcome. Although, there was extensive evidence in appropriate animal models of FGR and human evidence suggesting beneficial effect on uterine and fetal perfusion, the 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. The frequency of the most severe outcome perinatal death (15 to 30%) observed during the STRIDER trial impressively demonstrates the risk and danger associated with FGR, clearly emphasizing the importance of finding an effective therapy for FGR. 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 of those born growth restricted. Of 121 children born with FGR 73 (60.3%) were admitted to NICU of whom 47 (64.4%) developed severe neonatal morbidity, emphasizing the importance to achieve clinical progress regarding FGR treatment and prevention.
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In this study investigating the immediate neonatal outcome of pregnancies complicated by impaired uterine perfusion we failed to proof a beneficial effect PETN. Follow-up studies of the infants born in this study at the age of 12 months and five years are prearranged and may still reveal beneficial effects for the offspring. Furthermore, our study show an impact on maternal outcome and data retrieved will be analysed post-hoc, to further evaluate whether PETN might serve as a reasonable option to complement the treatment of high blood pressure in pregnancy in high-risk pregnancies. Finally, our study demonstrated that interventional clinical trials are feasible and safe to be performed in an obstetric population. Which is of particular important to overcome the STRIDER trauma.

Strength and Limitations

A key strength of the 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 to a pre-specified protocol without changes. Additionally, the results of our study clearly demonstrate 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%. As the inclusion criterion to our study was impaired uterine perfusion defined by mean PI of the arteriae uterinae exceeding the 95th centile all infants born with a birth weight below the 10th percentile are FGR in accordance with the consensus definition of FGR published by Gordijn in 2016, which requires fetal weight < 10th centile combined with UtA-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- as well as in the low-risk group, suggesting that criteria for stratification were not appropriate or not adequately applied. Furthermore, in 20% of the cases FGR was already diagnosed at enrolment. Although these cases were equally distributed between groups
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(20.6% vs 19.3%) it is still possible that this condition influences the effect of PETN treatment.

Finally, dosage of PETN was 80mg in the pilot study. Since, in between, PETN is only available as Pentalong® 50mg tablets we decided to stay with this dosage. This might have decreased the effect.

**Conclusion**

We failed to show 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 to develop FGR by impaired uterine perfusion at mid gestation.
References

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Figure legends

**Figure 1.** Trial Profile

**Figure 2:** Effect of PETN on primary and secondary outcome parameters.

**Supplemental Figure 1:** Effect of PETN on secondary outcome parameters according to gestational age.

**Figure 3:** Changes mean PI Aa. uterinae (A), PI A. umbilicalis (B), CPR (ratio PI A. umbilicalis/PI A. cerebri media) (C) and estimated fetal weight (Hadlock IV) (D) during the course of pregnancy following randomisation in the study groups. PETN grey lines, Placebo black lines. Dotted lines represent the 95th percentile (for mean PI Aa. uterinae, PI A. umbilicalis 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.

**Figure 4:** Kaplan Meier Plot of cumulative percentage of participants who developed blood pressure > 140 mmHg systolic and > 90 mmHg diastolic (HR 0.623, CI:0.413-0.940, p=0.019) (A), preeclampsia (HR 0.648, CI:0.411-1.020, p=0.054) (B), who were admitted to the hospital (HR 0.511, CI:0.308-0.846, p=0.008) (C) and who had delivered (HR 0.767, CI:0.612-0.961, p=0.007) (D).
Table 2. Outcomes according to Study Group

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<td>28 (29.8)</td>
</tr>
<tr>
<td>percentile and/or</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>perinatal death and/or</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>placental abruption</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Birth weight &lt; 5th</td>
<td>21 (35.0)</td>
<td>18 (29.0)</td>
<td>0.56</td>
<td>22 (24.2)</td>
<td>29 (30.9)</td>
</tr>
<tr>
<td>percentile and/or</td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>perinatal death and/or</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>placental abruption</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Birthweight percentile</td>
<td>18.1±20.7</td>
<td>19.3±19.0</td>
<td>0.89</td>
<td>19.3±19.0</td>
<td>17.5±18.3</td>
</tr>
<tr>
<td>Birth weight &lt; 10&lt;sup&gt;th&lt;/sup&gt; percentile</td>
<td>Mean (SD)</td>
<td>95% CI</td>
<td>95% CI</td>
<td>95% CI</td>
<td>95% CI</td>
</tr>
<tr>
<td>------------------------------------------</td>
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<td>--------</td>
</tr>
<tr>
<td>&lt; 5&lt;sup&gt;th&lt;/sup&gt; percentile</td>
<td>16 (27.1)</td>
<td>0.65</td>
<td>19 (20.9)</td>
<td>0.49</td>
<td>32 (21.3)</td>
</tr>
<tr>
<td>&lt; 3&lt;sup&gt;rd&lt;/sup&gt; percentile</td>
<td>13 (22.0)</td>
<td>0.65</td>
<td>19 (20.9)</td>
<td>0.49</td>
<td>32 (21.3)</td>
</tr>
<tr>
<td>Gestational age at birth (weeks)</td>
<td>35.7±4.9</td>
<td>0.28</td>
<td>36.3±4.6</td>
<td>0.13</td>
<td>36.1±4.7</td>
</tr>
<tr>
<td>Preterm birth (&lt; completed 37 weeks)</td>
<td>23 (38.3)</td>
<td>0.11</td>
<td>34 (37.4)</td>
<td>0.08</td>
<td>57 (37.7)</td>
</tr>
<tr>
<td>PIH&lt;sup&gt;2&lt;/sup&gt;</td>
<td>17 (27.9)</td>
<td>0.01</td>
<td>20 (21.3)</td>
<td>0.61</td>
<td>37 (23.9)</td>
</tr>
<tr>
<td>Preeclampsia&lt;sup&gt;3&lt;/sup&gt;</td>
<td>17 (27.9)</td>
<td>0.06</td>
<td>14 (14.9)</td>
<td>0.56</td>
<td>31 (20.0)</td>
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<tr>
<td>Placental abruption</td>
<td>4 (6.7)</td>
<td>0.20</td>
<td>0 (0)</td>
<td>0.25</td>
<td>4 (2.6)</td>
</tr>
</tbody>
</table>

Data are in n (%) or mean ± STDW, *outcome data were available of 307 patients included in the ITT analysis; **Unadjusted analysis: Estimate of the relative risk with 95% CI *** Mantel-Haenszel estimate of the stratified relative risk with 95% confidence interval (CI) was reported to assess the treatment effect.

1 Participants with pre-existing 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 are classified as "high risk", otherwise as "low risk". 2 pregnancy induced hypertension (PIH) defined as blood pressure exceeding 140mmHg for the systolic and/or 90mmHg for the diastolic; 3 defined as PIH and at least one additional manifestation of organ malperfusion leading to either FGR, liver enzyme alteration, kidney malfunction or HELLP-syndrome.
Table 3. Additional Outcome parameters according to Study Group

<table>
<thead>
<tr>
<th></th>
<th>High-Risk(^1) (n=122)</th>
<th>Low-Risk(^1) (n=185)</th>
<th>Total (n=307(^*))</th>
<th>unadjusted**</th>
<th>adjusted***</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PETN (n=60)</td>
<td>Placebo (n=62)</td>
<td>p</td>
<td>PETN (n=91)</td>
<td>Placebo (n=94)</td>
</tr>
<tr>
<td>Neonatal Outcome(^2) according to study group</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Combined neonatal outcome(^3)</td>
<td>18 (31.0)</td>
<td>24 (40.7)</td>
<td>0.34</td>
<td>27 (30.7)</td>
<td>29 (32.6)</td>
</tr>
<tr>
<td>Additional Outcome parameters</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Female</td>
<td>18 (30.0)</td>
<td>26 (41.9)</td>
<td>0.19</td>
<td>36 (39.6)</td>
<td>46 (48.9)</td>
</tr>
<tr>
<td>Apgar score &lt; 7 at 5 min after birth</td>
<td>3 (5.3)</td>
<td>6 (9.8)</td>
<td>0.49</td>
<td>5 (5.7)</td>
<td>7 (7.7)</td>
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<tr>
<td>Umbilical artery pH</td>
<td>7.3±0.1</td>
<td>7.3±0.1</td>
<td>0.69</td>
<td>7.3±0.1</td>
<td>7.3±0.1</td>
</tr>
<tr>
<td>Mode of delivery</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaginal delivery</td>
<td>25 (41.7)</td>
<td>17 (27.4)</td>
<td>0.13</td>
<td>45 (49.5)</td>
<td>34 (36.2)</td>
</tr>
<tr>
<td>Assisted vaginal delivery</td>
<td>2 (3.3)</td>
<td>1 (1.6)</td>
<td>0.62</td>
<td>3 (3.3)</td>
<td>2 (2.1)</td>
</tr>
<tr>
<td>Elective caesarean</td>
<td>22 (36.7)</td>
<td>31 (50.0)</td>
<td>0.15</td>
<td>27 (29.7)</td>
<td>31 (33.0)</td>
</tr>
<tr>
<td>Emergency caesarean</td>
<td>11 (18.3)</td>
<td>13 (21.0)</td>
<td>0.82</td>
<td>16 (17.6)</td>
<td>27 (28.7)</td>
</tr>
<tr>
<td>Additional neonatal outcome parameters</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Assisted ventilation</td>
<td>18 (30.0)</td>
<td>24 (38.7)</td>
<td>0.35</td>
<td>27 (29.7)</td>
<td>29 (30.9)</td>
</tr>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td>p-value</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>------------------</td>
<td>-------------</td>
<td>-----------</td>
<td>---------</td>
<td>-------------</td>
<td>-----------</td>
</tr>
<tr>
<td>IVH III-IV</td>
<td>0 (0.0)</td>
<td>1 (1.6)</td>
<td>1.00</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>NEC</td>
<td>0 (0.0)</td>
<td>2 (3.3)</td>
<td>0.50</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Admission to NICU</td>
<td>25 (43.1)</td>
<td>34 (56.7)</td>
<td>0.20</td>
<td>38 (43.2)</td>
<td>16 (51.7)</td>
</tr>
<tr>
<td>Nights on NICU</td>
<td>46.6±56.5</td>
<td>16.2±24.0</td>
<td>0.42</td>
<td>32.5±33.5</td>
<td>2.6±28.3</td>
</tr>
<tr>
<td>Joint discharge of mother and child</td>
<td>36 (60.0)</td>
<td>31 (50.0)</td>
<td>0.28</td>
<td>54 (60.0)</td>
<td>47 (50.0)</td>
</tr>
</tbody>
</table>

Data are in n (%) or mean ± STDW, *outcome data were available of 307 patients included in the ITT analysis; **Unadjusted analysis: Estimate of the relative risk with 95% CI
*** Mantel-Haenszel estimate of the stratified relative risk with 95% confidence interval (CI) was reported to assess the treatment effect.
1 Participants with pre-existing 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 are classified as "high risk", otherwise as "low risk", 2 outcome data of 297 life born of 307 cases included in the ITT analysis; 3 need of ventilation and/or necrotising enterocolitis and/or intraventricular haemorrhage of grade III/IV
Table 1: Baseline Characteristics of the trial Participants*

<table>
<thead>
<tr>
<th></th>
<th>PETN group (n=155)</th>
<th>Placebo group (n=162)</th>
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</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>33 (30-36)</td>
<td>34 (29-37)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.6 (22-30.9)</td>
<td>25.7 (21.6-31.5)</td>
</tr>
<tr>
<td>Gestational age at randomisation (weeks)</td>
<td>21.7 (21-22.4)</td>
<td>21.7 (20.9-22.3)</td>
</tr>
<tr>
<td>Body mass index at start of pregnancy (kg/m²)</td>
<td>74 (64.9-86.6)</td>
<td>76.6 (65-91)</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>122 (111-134)</td>
<td>120 (112.5-133.5)</td>
</tr>
<tr>
<td>Nulliparous</td>
<td>78 (70-85)</td>
<td>78 (70-85)</td>
</tr>
<tr>
<td>Number of previous deliveries</td>
<td>1 (0-1)</td>
<td>0 (0-1)</td>
</tr>
<tr>
<td>High risk</td>
<td>61 (39.4)</td>
<td>64 (39.8)</td>
</tr>
<tr>
<td>Reason for High risk</td>
<td></td>
<td></td>
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<tr>
<td>Pre-existing hypertension</td>
<td>20 (32.8)</td>
<td>25 (39.1)</td>
</tr>
<tr>
<td>Pre-existing diabetes</td>
<td>6 (9.8)</td>
<td>6 (9.4)</td>
</tr>
<tr>
<td>Previous FGR</td>
<td>23 (37.7)</td>
<td>20 (31.3)</td>
</tr>
<tr>
<td>Previous Preeclampsia</td>
<td>14 (23.0)</td>
<td>14 (21.9)</td>
</tr>
<tr>
<td>Previous HELLP syndrome</td>
<td>10 (16.4)</td>
<td>10 (15.6)</td>
</tr>
<tr>
<td>Previous Stillbirth</td>
<td>4 (6.6)</td>
<td>4 (6.3)</td>
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<tr>
<td>Previous Placental abruption</td>
<td>5 (8.2)</td>
<td>3 (4.7)</td>
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<tr>
<td>Other diseases affecting the endothelium</td>
<td>7 (11.5)</td>
<td>3 (4.7)</td>
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<tr>
<td>Sonographic data at randomisation</td>
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<tr>
<td>EFW (g)</td>
<td>416 (352-474)</td>
<td>411 (344-458)</td>
</tr>
<tr>
<td>EFW percentile</td>
<td>30 (12-50)</td>
<td>29 (13-48)</td>
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<tr>
<td>EFW percentile &lt; 10</td>
<td>32 (20.6)</td>
<td>31 (19.3)</td>
</tr>
<tr>
<td>Abdominal circumference (mm)</td>
<td>162 (152-172)</td>
<td>163 (151-170)</td>
</tr>
<tr>
<td>Head circumference (mm)</td>
<td>189 (180-199)</td>
<td>188 (179-196)</td>
</tr>
<tr>
<td>PI A. uterina (mean)</td>
<td>1.84 (1.69-2.11)</td>
<td>1.82 (1.68-2.04)</td>
</tr>
<tr>
<td>PI A. cerebri media</td>
<td>1.64 (1.44-1.84)</td>
<td>1.62 (1.48-1.83)</td>
</tr>
<tr>
<td>PI A. umbilicalis</td>
<td>1.25 (1.11-1.41)</td>
<td>1.28 (1.15-1.45)</td>
</tr>
<tr>
<td>CPR</td>
<td>1.32 (1.10-1.57)</td>
<td>1.27 (1.08-1.50)</td>
</tr>
</tbody>
</table>

*Median and 25th to 75th percentile are reported for continuous baseline characteristics, absolute and relative frequencies for categorical characteristics.
Figure 1. Trial Profile

* Analysis of the primary endpoint
<table>
<thead>
<tr>
<th>Endpoint</th>
<th>PETN</th>
<th>Placebo</th>
<th>RR</th>
<th>p value</th>
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<tr>
<td><em>Primary endpoint</em></td>
<td>62 (41.1)</td>
<td>71 (45.5)</td>
<td>0.9 (0.7–1.2)</td>
<td>0.433</td>
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<tr>
<td>Secondary endpoints</td>
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<tr>
<td>combined perinatal death</td>
<td>38 (25.2)</td>
<td>41 (26.3)</td>
<td>1.0 (0.7–1.4)</td>
<td>0.824</td>
</tr>
<tr>
<td>PPH</td>
<td>6 (3.3)</td>
<td>7 (4.5)</td>
<td>0.7 (0.2–2.5)</td>
<td>0.696</td>
</tr>
<tr>
<td>PE/HELLP</td>
<td>37 (23.9)</td>
<td>59 (36.6)</td>
<td>0.7 (0.5–0.9)</td>
<td>0.013</td>
</tr>
<tr>
<td>FGR &lt; 10</td>
<td>31 (20.0)</td>
<td>47 (29.2)</td>
<td>0.7 (0.5–1.0)</td>
<td>0.055</td>
</tr>
<tr>
<td>FGR &lt; 5</td>
<td>61 (43.7)</td>
<td>69 (44.2)</td>
<td>0.9 (0.7–1.2)</td>
<td>0.531</td>
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<tr>
<td>FGR &lt; 3</td>
<td>30 (20.0)</td>
<td>36 (22.4)</td>
<td>1.0 (0.6–1.5)</td>
<td>0.814</td>
</tr>
<tr>
<td>preterm birth &lt; 37 weeks</td>
<td>67 (42.3)</td>
<td>81 (51.9)</td>
<td>0.7 (0.5–0.9)</td>
<td>0.013</td>
</tr>
<tr>
<td>preterm birth &lt; 34 weeks</td>
<td>30 (20.0)</td>
<td>49 (31.4)</td>
<td>0.8 (0.6–1.2)</td>
<td>0.281</td>
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<tr>
<td>preterm birth &lt; 30 weeks</td>
<td>21 (13.9)</td>
<td>29 (17.8)</td>
<td>0.8 (0.5–1.3)</td>
<td>0.333</td>
</tr>
<tr>
<td>**</td>
<td>46 (30.0)</td>
<td>53 (35.8)</td>
<td>0.8 (0.6–1.2)</td>
<td>0.300</td>
</tr>
<tr>
<td>**</td>
<td>62 (42.5)</td>
<td>80 (53.7)</td>
<td>0.8 (0.6–1.0)</td>
<td>0.055</td>
</tr>
</tbody>
</table>

*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 necrotizing enterocolitis requiring surgery.

Figure 2: Effect of PETN on primary and secondary outcome parameters.
Figure 3: Changes in mean PI A. uterinae (A), PI A. umbilicalis (B), CPR (ratio PI A. umbilicalis/PI A. cerebri media) (C) and estimated fetal weight (Hadlock IV) (D) during the course of pregnancy following randomisation in the study groups. PETN grey lines, Placebo black lines. Dotted lines represent the 95th percentile (for mean PI A. uterinae, PI A. umbilicalis 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.
Figure 4: Kaplan Meier Plot of cumulative percentage of participants who developed blood pressure > 140 mmHg systolic and > 90 mmHg diastolic (HR 0.623, CI 0.415-0.940, p=0.019) (A), preeclampsia (HR 0.648, CI 0.411-1.020, p=0.054) (B), who were admitted to the hospital (HR 0.511, CI 0.308-0.846, p=0.008) (C) and who had delivered (HR 0.767, CI 0.612-0.961, p=0.007) (D).