Antepartum continuous epidural ropivacaine therapy reduces uterine artery vascular resistance in pre-eclampsia: a randomized, dose-ranging, placebo-controlled study†

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Background. No therapy is currently available to improve the reduced uteroplacental blood flow (UPBF) that characterizes pre-eclampsia. We hypothesized that sympathectomy induced by epidural local anaesthesia reduces uterine vascular resistance (which is inversely correlated with UPBF) in pre-eclampsia.

Methods. Ten pregnant women between 24 and 32 weeks of gestation with pre-eclampsia and uterine artery flow abnormalities were randomized to antepartum continuous epidural therapy (ACET) or control. ACET was initiated by a 5 day dose-ranging trial (ACET-1) of 0.04, 0.06, 0.08, and 0.1% ropivacaine and saline placebo, each at 10 ml h⁻¹ for 24 h. Doses were randomized and double-blind. Doppler ultrasound indices of vascular resistance were assessed at baseline and after each 24 h dosing period in both uterine arteries. Subsequently, these ACET patients were administered 0.1% ropivacaine until delivery (ACET-2), with one additional randomized double-blind placebo day.

Results. Five patients were randomized to ACET. In each patient, one uterine artery exhibited a dose-dependent reduction in vascular resistance (P=0.035), a response that returned to baseline following placebo (P<0.001). The contralateral uterine artery exhibited either increased vascular resistance or no change. In all cases, the uterine artery that responded to ACET had higher baseline resistance than its pair (P=0.043). Baseline right–left difference in resistance between paired uterine arteries was greatly diminished following ACET. Although ACET patients had a mean (SD) duration to delivery of 19 (9) days compared with control 2 (1) days (P=0.008), this should be interpreted with caution because of demographic differences between groups.

Conclusions. ACET reduces uterine artery resistance in pre-eclampsia <32 weeks. Uteroplacental re-distribution is a novel observation and warrants further investigation.

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Pre-eclampsia is an important and common disorder of pregnancy and is associated with reduced uteroplacental blood flow (UPBF) and fetal growth restriction (FGR). As no therapy has been identified to reliably improve UPBF in pre-eclampsia, obstetric management remote from term frequently involves early interventional delivery, which

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may impose the additional burden of prematurity on an already compromised fetus. Pre-eclampsia is associated with 15% of all preterm births in the USA, and US total annual direct costs related to pre-eclampsia and prematurity are $1.9 billion and $7.8 billion, respectively.

In normal pregnancy, uterine spiral arteries are infiltrated by trophoblasts and are transformed into high-calibre, low-resistance vessels unresponsive to sympathetic neural input, thereby increasing blood flow to the developing placenta and fetus. In pre-eclampsia, impaired trophoblast invasion of uterine decidua impedes this pregnancy-related adaptation, causing spiral arteries to retain their endothelial lining and muscular wall and to be abnormally responsive to sympathetic tone. Symphathecy induced by epidural anaesthesia, administered for Caesarean delivery or labour analgesia, improves UPBF in patients with pre-eclampsia, but does not improve UPBF in normal pregnancy. Two small prospective studies assessed the effects of antenatal continuous epidural local anaesthetics on UPBF in patients with pre-eclampsia and FGR. Although these studies demonstrated reduced umbilical and uterine artery vascular resistance, prolongation of gestation, and an increase in birth weight in some patients following treatment, the doses of epidural local anaesthetic used (2 ml h⁻¹ for 0.25% bupivacaine and 5 ml h⁻¹ for 0.175% ropivacaine) were chosen arbitrarily, and neither study was randomized or blinded; the latter had no control group.

Doppler ultrasound is routinely used to assess the uteroplacental circulation; raised uterine artery pulsatility index (PI) (an assessment of vascular resistance) and early diastolic notch in the uterine artery waveform are the best ultrasound predictors for pre-eclampsia and FGR. In this study, we assessed pregnant women remote from term who had raised baseline PI and early diastolic notch in at least one uterine artery, in addition to either pre-eclampsia or FGR.

We hypothesized that symphathecy induced by the epidural local anaesthetic ropivacaine would increase uterine artery blood flow in these patients. We measured Doppler ultrasound indices of vascular resistance, including the PI, which are inversely correlated with blood flow, in the uterine artery. We assessed both a dose–response relationship and an on/off temporal relationship (sustained effect during continuous administration that returned towards baseline during the administration of placebo) as evidence to test the hypothesis.

Methods
This prospective, randomized, dose-ranging, placebo-controlled trial of antepartum continuous epidural therapy (ACET) with ropivacaine was performed in the Hadassah Hebrew University Medical Center (both Ein Karem and Mt Scopus campuses). We received local Institutional Review Board approval, and signed informed consent was obtained from all participants. Pregnant women were approached for enrolment in this study if they met the following criteria:

(i) 24–32 weeks of gestation at the time of enrolment (gestational dates confirmed by ultrasound at 7–14 weeks of gestation);
(ii) raised PI above 1.75 and early diastolic notch in at least one uterine artery and at least one of either:
(iii) pre-eclampsia: defined as resting arterial pressure >140/90 mm Hg, measured twice at least 6 h apart, and proteinuria (at least 0.1 g litre⁻¹ in two random samples at least 6 h apart or at least 0.3 g in a 24 h collection), or
(iii) FGR [either abdominal circumference (AC) or estimated fetal weight below 10th percentile].

Exclusion criteria (at the time of enrolment) were active labour, adverse maternal condition (resting arterial pressure ≥160/110 mm Hg, headache and visual disturbance, coagulopathy), adverse fetal condition (abnormal fetal heart tracing, reversed end-diastolic flow in umbilical artery), contraindications for epidural catheterization, twin pregnancy, intrauterine infection, known fetal or placental anomalies, and refusal of consent. The subjects approached were summarized using a CONSORT flowchart (Fig. 1).

Women were randomized to either ACET or non-ACET controls. Both control and ACET patients received standard therapy: all patients were monitored in hospital, magnesium and anti-hypertensive drugs were administered as appropriate, and obstetric management was decided by the clinical obstetric team on the basis of standard maternal and fetal indications. In addition to standard therapy, ACET patients received a ropivacaine infusion via a tunnelled lumbar epidural catheter, inserted in the operating room under surgical conditions. A 17-gauge Tuohy needle was inserted into the epidural space at the L2/3 interspace using a midline approach. The epidural space was identified by loss of resistance to saline. An 18-gauge multi-orifice epidural catheter was inserted ~4 cm into the epidural space, a negative pressure aspiration test performed, and 5–10 ml 1.5% lidocaine administered in incremental doses, to test the catheter and to provide analgesia for the subcutaneous tunnel. The epidural catheter was then tunnelled subcutaneously for ~10 cm laterally. Sterile transparent dressings were placed over the epidural insertion site and the exit site of the tunnelled epidural catheter. After 24 h, patients were allowed to shower with waterproof protective sheets taped over the sterile dressings. Patients were allowed to ambulate and micturate normally throughout the study. Dressings were examined daily.

There were two consecutive stages of intervention in the ACET group. ACET Stage 1 was a 5 day dose-ranging study (randomized, double-blind, cross-over design). Epidural ropivacaine infusions of 0.04, 0.06, 0.08, and 0.1% and a saline placebo were each administered by
continuous infusion at a rate of 10 ml h \(^{-1}\) for 24 h. Only four dose sequences were randomized; placebo always immediately followed the 0.1% dose. Measurements were made at the end of each 24 h period.

In ACET Stage 2, 0.1% ropivacaine was administered continuously at 10 ml h \(^{-1}\) until delivery. Once during this period, a second 24 h infusion of saline placebo was administered; again the timing of the saline placebo was randomized and blinded.

Randomization and blinding
The dosing sequence of the different ropivacaine concentrations was determined by computer-generated random sequence, and allocation was concealed in consecutive opaque envelopes. Randomization and concealment of dosing sequence in ACET Stage 1 and the second placebo day in ACET Stage 2 used the same method. A blinded investigator enrolled patients. Ultrasound technicians were blinded to group allocation, but patients and obstetricians were not. Dosing sequence (including placebo) in ACET Stage 1 and placebo dose in ACET Stage 2 were double-blinded; drug and placebo were prepared by a non-blinded investigator. Obstetricians were not blinded to the results of ultrasound measurements.

Measurements
Ultrasound measurement was performed in the recumbent position by an ultrasonographer. All measurements used the same protocol; at the Ein Karem campus, measurements were performed under the supervision of S.Y. (see ACET group, Appendix). A Sonos ATL HDI 5000 ultrasound machine with a 2–5 MHz multifrequency curvilinear probe (Phillips Medical Systems, Bothell, WA, USA) was used. The cervical canal and internal cervical os were identified in a sagittal plane. Doppler colour flow mapping was used to highlight both uterine arteries on the sides of the cervix and uterus at the level of the internal os. Pulsed-wave Doppler was used with the sampling volume set at 2 mm to cover the whole vessel at the level where it crossed the external iliac artery. The angle of insonation was <50°. The high-pass

Assessed for eligibility \(n=19\)
Pregnant women at Hadassah Ein Karem and Hadassah Mt Scopus Hospitals, Jerusalem, from 1.8.03 to 1.1.07 who met all the inclusion criteria listed in text: 24–32 completed weeks, raised uterine artery pulsatility index, uterine artery notch, and either pre-eclampsia or FGR.
Excluded \(n=8\)
Exclusion criteria (see text): \(n=4\) (Twins 1, extreme hypertension 1, abnormal fetal heart rate tracing 1, reverse end-diastolic flow 1). Refused to participate: \(n=4\) Other reasons: \(n=0\)
Enrolled \(n=11\)
Allocated to ACET \(n=6\)
Received allocated intervention: \(n=5\)
Did not receive allocated intervention: \(n=1\)
(reason: recently after enrolment, and before intervention, it became known that the patient had prior abnormal fetal heart tracing, which was an established exclusion criteria)
Lost to follow-up: \(n=0\)
Discontinued intervention: \(n=0\)
Analysed in ACET 1: \(n=5\)
Allocated to control \(n=5\)
Received allocated control: \(n=5\)
Did not receive allocated control: \(n=0\)
Lost to follow-up: \(n=0\)
Discontinued intervention: \(n=0\)
Analysed: \(n=5\)
Enrolment–delivery interval, and baseline Doppler velocimetry analysis: \(n=5\)
Note: No control patients had longitudinal Doppler ultrasounds as they all delivered by 1–3 days following enrolment.
Analysed in ACET 2: \(n=3\)
Lost to follow-up: \(n=0\)
Discontinued intervention: \(n=2\)
Reason: one patient delivered before start of ACET 2, one delivered before placebo day in ACET 2.

Fig 1 The CONSORT flowchart for randomized controlled trials.
filter was set at 100 Hz. Standard Doppler indices of vascular resistance were obtained from at least three similar consecutive waveforms. On the basis of the systolic (S), average (A), and diastolic (D) flow velocity, we measured the PI = (S – D)/A, resistance index (RI) = (S – D)/S, and systolic–diastolic ratio (S/D)21 (Fig. 2). Decreased values indicate decreased vascular resistance and correlate with increased flow.20 Measurements were made in the following vessels: right and left uterine arteries, umbilical artery, ductus venosus, and fetal middle cerebral artery. Indices of vascular resistance for each vessel were averaged from triplicate measurements; a printed display was produced for each measurement. We also measured the absolute difference (always a positive value) in these indices between the right and left uterine arteries. Assessments were performed at baseline and at the end of each 24 h dose period in ACET Stage 1; in ACET Stage 2, they were performed at 3 or 4 day intervals and at the end of the second placebo day (timing determined by non-blinded investigator).

The amniotic fluid index, femur length (FL), biparietal diameter (BPD), head circumference, and AC were all averaged from triplicate measurements, and estimated fetal weight was calculated from the BPD, AC, and FL as described by Hadlock and colleagues22 and was referenced to averaged male and female normogram percentiles.23 Unlike the Doppler velocimetry measurements, these ultrasound assessments were made at baseline and at weekly intervals.

Maternal vital signs (arterial pressure, heart rate, ventilatory frequency, temperature) were recorded every 8 h. The patient was weighed and her urine analysed daily. Complete blood count, biochemistry, clotting screen, and creatinine clearance were performed at least weekly. Newly diagnosed obstetric or other medical problems were recorded. Cardiotocography was performed every 8 h.

Statistical analysis
The effect of increasing ropivacaine dose on Doppler indices of uterine artery resistance was assessed using repeated measures analysis of variance (RM-ANOVA) (using the simple contrast function that compared effect with baseline data). The small number of data points prevented the calculation of sphericity, so the conservative Greenhouse-Geisser test was used. RM-ANOVA was also used to assess maternal arterial pressure changes at different doses of epidural ropivacaine. The dose–effect
relationship was also assessed using the Emax model (WinNonlin, Pharsight, Mountainview, CA, USA). The on/off temporal effect (change from 0.1% ropivacaine to placebo) was assessed by Wilcoxon signed rank test for the ACET 1 data and the ACET 2 data separately; the on/off temporal effect for ACET 1 and ACET 2 data combined was assessed using mixed model ANOVA (SAS PROC MIXED version 9.1).

Time until delivery, change in estimated fetal weight during the study, and weight at delivery were compared between ACET and control groups using Mann–Whitney U-test. Statistical analysis of other between-subject outcome data is not appropriate for this sample size and thus fetal and maternal outcome variables were not analysed. All statistical analyses were performed using SPSS version 10.0 (SPSS Inc., Chicago, IL, USA), unless stated otherwise. For the four secondary outcome variables studied (birth weight, gestational age at delivery, enrolment–delivery interval, and Caesarean delivery for maternal vs fetal indications), Bonferroni’s correction for multiple comparisons has been applied (alpha level of 0.0125). For the single primary outcome variable (PI in the responding uterine artery: dose–response effect) and for the demographic and baseline factors presented in Tables 1 and 2, a two-sided alpha level of $P \leq 0.05$ was used. Non-significant $P$-values $\leq 0.2$ are reported.

Sample size calculation

The a priori primary endpoint was the PI of the uterine artery obtained by Doppler flow velocimetry, a measure of vascular resistance that is inversely related to blood flow. Normal mean and 95th percentile uterine artery PI in second trimester are 1.04 and 1.63, respectively. In pregnancies that delivered before 32 weeks of gestation, uterine artery PI above the 95th percentile had a 93% sensitivity and a 95% specificity for pre-eclampsia with FGR. On the basis of these data, an effect measure of 0.75 PI units was chosen. Sample size was determined using the power equation: $\text{Power}(\Delta) = \Phi[\Delta/\sqrt{V}] - Z_{\alpha/2}$, where $\Delta$ is the difference to be detected (effect measure), $V = \sigma^2 (1/n_1 + 1/n_2)$, $\sigma$ the sd ($\sigma^2$ the variance), $n_1$ and $n_2$ the sample sizes of the two study groups, $Z_{\alpha/2}$ the critical $z$-value (1.96 for a two-sided test, where $P = 0.05$), and $\Phi[.]$ the standard normal cumulative distribution function. We drew power against sample size curves using the srs reported in two previous studies using PI (Yoneyama and colleagues SD 0.41; Ochi and colleagues SD 0.32). On the basis of these two studies, a sample size of 10 patients would give 0.82 and 0.96 power, respectively, to detect a difference of 0.75 in the PI between 0.1% ropivacaine and placebo within the ACET subgroup (five per group).

Results

Eleven women were initially enrolled for this study. One patient was rejected shortly after enrolment when it became known that she had a previous abnormal fetal heart rate tracing, which was an a priori exclusion criterion. Of the 10 patients who participated, 5 were randomized to ACET and 5 to control (Fig. 1). Although there were no statistically significant differences in baseline data between groups (Table 1), there was a 17 day difference in the gestational age at enrolment between ACET [187 (SD 19) days] and control [204 (5)]. Accordingly, all comparisons between the ACET group and control have been interpreted with caution. There was also no difference between the ACET group and control group for baseline uterine artery Doppler indices of vascular resistance (Table 2). There was a baseline right–left uterine artery difference present in all 10 subjects enrolled in this study, which was not different between ACET and control (Table 2). The right uterine artery was more severely affected in four subjects, the left in six subjects; there was no association with lateral placental insertion. All patients with prolonged indwelling epidural catheters were mobile and afebrile throughout therapy, there were no cases of infection or inflammation of either the catheter

| Table 1 Patient characteristics at the time of enrolment for patients randomized to the ACET and control groups. See Methods for details of enrolment criteria |
|---------------------------------|----------------|----------------|
|                                | ACET (n=5)     | Control (n=5)  |
| Age (yr)                        | 29 (7)         | 36 (6)         |
| Height (cm)                     | 160 (4)        | 162 (10)       |
| Weight (before pregnancy) (kg)  | 68 (16)        | 70 (7)         |
| Weight gain in pregnancy (kg)   | 11 (6)         | 14 (3)         |
| Gravidity                       | 4 (3)          | 3 (3)          |
| Parity                          | 1 (1)          | 1 (2)          |
| Gestational age at enrolment (days) | 187 (19) | 204 (5) |
| Pre-eclampsia (criterion iiia)  | 2/5            | 3/5            |
| FGR (criterion iiib)            | 4/5            | 3/5            |
| Both pre-eclampsia and FGR (iiia and iiib) | 1/5 | 1/5 |

| Table 2 Baseline uterine artery Doppler indices of vascular resistance in patients randomized to the ACET and control groups. RI, PI, and $S/D$ are the resistance index, pulsatility index, and systolic–diastolic ratio, respectively. There were no statistically significant differences between groups for any of these indices at baseline |
|---------------------------------|----------------|----------------|
|                                | ACET (n=5)     | Control (n=5)  |
| Higher resistance (worse) uterine artery |                   |                 |
| RI                              | 0.81 (0.04)    | 0.82 (0.07)    |
| PI                              | 2.04 (0.15)    | 2.03 (0.25)    |
| $S/D$                           | 5.17 (1.24)    | 4.84 (0.77)    |
| Lower resistance (better) uterine artery |                   |                 |
| RI                              | 0.64 (0.10)    | 0.72 (0.14)    |
| PI                              | 1.26 (0.37)    | 1.46 (0.40)    |
| $S/D$                           | 2.79 (0.67)    | 3.49 (0.99)    |
| Right–left difference           |                   |                 |
| RI                              | 0.16 (0.09)    | 0.10 (0.07)    |
| PI                              | 0.78 (0.32)    | 0.57 (0.19)    |
| $S/D$                           | 2.39 (0.97)    | 1.35 (0.81)    |
or the tunnel insertion sites, and there were no cases of urinary retention requiring urethral catheterization.

Within-subject effects: dose–response effect
In all subjects in the ACET group, there was a dose-dependent reduction in PI in one of the paired uterine arteries (the ‘responding vessel’) with increasing dose of epidural ropivacaine (n=5, P=0.035, Fig. 3a and b). The per cent change from baseline for each dose was as follows: 0.04%: −17.0%; P=0.08; 0.06%: −6.5%; P=0.15; 0.08%: −29.1%; P=0.037; 0.1%: −33.5%; P=0.008. The concentration–effect relationship was also found to fit the E\text{max} model, with EC50 in the range of the concentrations induced by the 0.1% ropivacaine dose. In ACET Stage 2, the reduction in uterine artery vascular resistance was initially sustained but then gradually attenuated over time in all but one patient (the ‘super-responder’, see below).

Within-subject effects: on/off temporal effect
(effect that returned towards baseline during the administration of placebo)

When compared with the 0.1% ropivacaine dose, uterine artery PI returned to baseline during the subsequent placebo day in all five patients in ACET Stage 1 (P=0.043) and in pooled data from ACET Stages 1 and 2 (P<0.001, Fig. 4a). For both assessments, there was no significant difference between placebo and baseline.

Within-subject effects: contralateral vessel and right–left difference

In all cases, the PI in one uterine artery reduced following epidural ropivacaine, and the contralateral vessel displayed either increased PI or no change (Fig. 3c and d). The side of the responding vessel was constant for each individual patient throughout the study. The baseline right–left difference in PI between the paired uterine arteries was almost completely abolished by epidural ropivacaine (Fig. 3e and f). In all five cases, the vessel that responded to ACET had higher baseline PI than its pair (P=0.043, Fig. 5).

There was no significant dose-dependent effect of epidural ropivacaine on vascular resistance in the umbilical artery, fetal middle cerebral artery, or fetal ductus venous. The umbilical artery was an unreliable data source in severe flow abnormalities, as the absence of end-diastolic flow prevents the calculation of indices of resistance. There was no significant effect on maternal arterial pressure throughout the study.

Between-subjects effects

Patients in the ACET group had 19 (9) days of therapy until delivery; by comparison, control patients delivered within 2 (1) days of enrolment (P=0.008). Comparing the ACET and control groups, there was no significant difference in the gestational age at delivery [mean (sd) 205 (24) vs 206 (6) days], or in the birth weight [mean (sd) 835 (427) vs 1022 (269) g, P>0.2]. Except for the ‘super-responder’, ACET Stage 2 patients did not cross percentiles of intrauterine fetal growth (Fig. 6). Non-ACET control patients did not remain in the study long enough for longitudinal ultrasound assessments. All patients had Caesarean deliveries; the indication for surgery was severe pre-eclampsia and deteriorating maternal condition in all ACET patients, even among those who were enrolled to the study with FGR and had not developed pre-eclampsia before enrolment. Two control patients underwent Caesarean delivery for suspected fetal distress.

The super-responder

Only one patient had a sustained response over the entire duration of ACET Stage 2. This patient also had the most marked compensatory changes in the contralateral vessel and had the longest enrolment–delivery interval (28 days).

Discussion

Our data demonstrate that epidural ropivacaine reduces uterine artery vascular resistance in pre-eclampsia, an effect that was dose-dependent, sustained, and that returned towards baseline during the administration of placebo. Our observations contrast with reports that systemic vasodilators, such as nifedipine, although effective at reducing maternal arterial pressure, exert no significant effect on UPBF in pre-eclampsia. We speculate that the lack of effect of systemic vasodilators on UPBF is due, in part, to re-distribution of blood away from the uteroplacental circulation and towards competing vascular beds that also undergo vasodilatation. Unlike ‘systemic’ vasodilators, epidural anaesthesia induces ‘segmental’ vasodilatation. In conscious non-pregnant subjects, epidural anaesthesia has been demonstrated to induce vasodilatation in anaesthetized regions (foot) and cause reflex vasoconstriction in non-anaesthetized regions (hand), presumably as part of a normal sympathetic nervous response to maintain temperature and arterial pressure. Accordingly, ACET might be expected to both induce uterine vasodilatation directly and also re-distribute blood away from competing vascular beds, in favour of the uteroplacental circulation.

Our data also suggest that epidural local anaesthetics initiated a contralateral re-distribution within the uteroplacental circulation, with a selective vasodilatation in the uterine artery which had higher baseline vascular resistance. There was a marked reduction (and occasionally a reversal) of the pre-existing right–left difference in vascular resistance between the paired uterine arteries. Right–left difference in uterine artery vascular resistance has been reported in a small sample of patients with severe pre-eclampsia and was noted to occur in the first
Fig 3 Doppler indices of uterine artery vascular resistance in ACET Stage 1 dose–response effect. Doppler indices of vascular resistance on the y-axis are inversely correlated with blood flow. In (A), (C), and (E), baseline PI is represented as a horizontal dotted line, whereas in (B), (D), and (F), the PI, resistance index, and systolic–diastolic ratio are each expressed as percentage change from baseline. Placebo is represented as the zero dose in the dose–response curve. Error bars represent SD. *Significant difference from baseline (P < 0.05).
trimester but not in second trimester normal pregnancy. Right–left difference in pre-eclampsia may reflect reduced vascular communication between the territories of the paired uterine arteries in pre-eclampsia, or possibly an underlying mechanism for uteroplacental autoregulation. As the uterine vessels arise separately from the paired internal iliac vessels, it is likely that the unilateral improvement in uterine artery vascular resistance observed in this study is associated with an increase in total UPBF. Although contralateral blood flow re-distribution within the uteroplacental circulation has not been previously described, it is a possible explanation of the effects of epidural ropivacaine on the baseline right–left difference in uterine artery resistance observed in this study and warrants further investigation.

This study was designed to assess the effects of ACET on uterine artery vascular resistance. Although women randomized to the ACET protocol also had a considerably longer mean duration from enrolment until delivery than non-ACET controls (19 days vs 2 days; \( P=0.008 \)), this latter observation is limited by three factors. First, the sample size was determined to provide adequate statistical power for uterine artery PI as the endpoint, but not the enrolment–delivery interval. Secondly, there was a 17 day difference in gestational age between the ACET group and control at the time of enrolment; although not statistically significant, this difference may make these groups non-comparable. In addition, patients and obstetricians were not blinded to group allocation or to the results of Doppler vascular resistance studies, and the presence of an alternative to interventional delivery in the ACET group may have influenced obstetric management. Accordingly, comparison between the enrolment–gestation intervals of the

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**Fig 4** Doppler indices of uterine artery vascular resistance in ACET Stage 1-on/off temporal effect. As the placebo dose always followed the 0.1% dose, (A), (B), and (C) represent PI on a continuous time axis corresponding to the baseline, 0.1%, and placebo doses. The three patients who remained in ACET Stage 2 long enough to receive a second placebo dose are also represented in this figure (circles); in those cases, the data for the 0.1% dose are from the last ultrasound before the second placebo dose. *Significant difference from baseline \(( P < 0.05)\).

**Fig 5** The responsive uterine artery had higher baseline PI. Baseline (Day 0) uterine artery PI is represented on the y-axis. In all patients, the vessel that responded to ACET had higher baseline PI than its pair. *Significant difference from non-responding vessel \(( P < 0.05)\).

**Fig 6** Intrauterine fetal growth during ACET. Data from the four patients who participated in ACET Stage 2 (including the patient who delivered before the second placebo day). Estimated fetal weight measurements at time intervals during the study, with reference to the 5th, 10th, 50th, and 90th percentiles, determined by an average of male and female normograms.23
ACET and the control groups is not supported by these data and should be examined in a separate study designed with sufficient power to assess this outcome.

Despite the small size of this study, we were able to demonstrate that ACET induces a dose-dependent reduction in vascular resistance in one uterine artery. If ACET can reliably improve UBPF in pre-eclampsia and FGR remote from term, it may provide an effective therapeutic option to prolong pregnancy in these patients. Increasing UBPF for as little as 48 h might allow time for the administration of steroids to promote fetal lung maturity. Increasing UBPF for 2–4 weeks may promote intrauterine fetal growth, provide an alternative to early premature interventional delivery, and improve fetal outcome.

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Clinical trial registry: This study is registered with www.clinicaltrials.gov, the protocol registration system of the FDA and the NIH, reference number NCT00197340.

Appendix

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