OBSTETRICS

Enoxaparin for the prevention of preeclampsia and intrauterine growth restriction in women with a history: a randomized trial

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BACKGROUND: Preeclampsia and small-for-gestational-age pregnancy are major causes of maternal and perinatal morbidity and mortality. Women with a previous pregnancy affected by these conditions are at an increased risk of recurrence in a future pregnancy. Past trials evaluating the effect of low-molecular-weight heparin for the prevention of recurrence of preeclampsia and small-for-gestational-age pregnancy have shown conflicting results with high levels of heterogeneity displayed when trials were compared.

OBJECTIVE: We sought to assess the effectiveness of enoxaparin in addition to high-risk care for the prevention of preeclampsia and small-for-gestational-age pregnancy in women with a history of these conditions.

STUDY DESIGN: This was an open-label randomized controlled trial in 5 tertiary care centers in 3 countries. Women with a viable singleton pregnancy were invited to participate between $>6^{+0}$ and $<16^{+0}$ weeks if deemed to be at high risk of preeclampsia and/or small for gestational age based on their obstetric history. Eligible participants were randomly assigned in a 1-to-1 ratio to standard high-risk care or standard high-risk care plus enoxaparin 40 mg (4000 IU) by subcutaneous injection daily from recruitment until 36^{+0} weeks or delivery, whichever occurred sooner. Standard high-risk care was defined as care coordinated by a high-risk antenatal clinic service, aspirin 100 mg daily until 36^{+0} weeks, and—for women with prior preeclampsia—calcium 1000-1500 mg daily until 36^{+0} weeks. In a subgroup of participants serum samples were taken at recruitment and at 20 and 30 weeks' gestation and later analyzed for soluble fms-like tyrosine kinase-1, soluble endoglin, endothelin-1, placental growth factor, and soluble vascular cell adhesion molecule 1. The primary outcome was a composite of preeclampsia and/or small-for-gestational-age <5th customized birthweight percentile. All data were analyzed on an intention-to-treat basis. The trial is registered with the Australian New Zealand Clinical Trials Registry (ACTRN12609000699268).

RESULTS: Between July 26, 2010, and Oct. 28, 2015, a total of 156 participants were enrolled and included in the analysis. In all, 149 participants were included in the outcome analysis (72 receiving standard high-risk care plus enoxaparin and 77 receiving standard high-risk care only). Seven women who miscarried <16 weeks' gestation were excluded. The majority of participants (151/156, 97%) received aspirin. The addition of enoxaparin had no effect on the rate of preeclampsia and/or small-for-gestational-age <5th customized birthweight percentile: enoxaparin 18/72 (25%) vs no enoxaparin 17/77 (22.1%) (odds ratio, 1.19; 95% confidence interval, 0.53—2.64). There was also no difference in any of the secondary outcome measures. Levels of soluble fms-like tyrosine kinase-1 and soluble endoglin increased among those who developed preeclampsia, but there was no difference in levels of these antiangiogenic factors (nor any of the other serum analytes measured) among those treated with enoxaparin compared to those receiving standard high-risk care only.

CONCLUSION: The use of enoxaparin in addition to standard high-risk care does not reduce the risk of recurrence of preeclampsia and small-for-gestational-age infants in a subsequent pregnancy.

Key words: enoxaparin, fetal growth restriction, intrauterine growth restriction, low-molecular-weight heparin, preeclampsia, randomized trial, small for gestational age

Introduction

Preeclampsia and intrauterine growth restriction (IUGR) are common causes of maternal and perinatal morbidity and mortality. Preeclampsia complicates 3-5% of pregnancies. IUGR is more difficult to define and measure but approximately 10% of infants will be born small for gestational age (SGA) defined as birthweight <10th customized birthweight percentile. At least two thirds of these infants will have had evidence of abnormal uterine and umbilical artery Doppler waveforms if diagnosed prior to birth suggesting significant uteroplacental disease.[1] Thus SGA is used as the most reliable surrogate marker for IUGR.

There are a wide variety of identified risk factors for preeclampsia and/or SGA but risk prediction models, at best, remain modest.[2,3] Until relatively recently it has been suggested that inherited thrombophilias are associated with preeclampsia and SGA, however, more recent evidence from prospective cohort studies suggests this association,

EDITORS' CHOICE

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if present, is only weak.[4] Obstetric history remains the most commonly used method for risk assessment in current clinical practice. Women with previous preeclampsia and/or SGA are at significant risk of recurrence especially when the disease was severe and occurred early in pregnancy.[5-8]

Preeclampsia and IUGR are considered placental diseases and there is likely to be considerable overlap in pathological mechanisms. This fact has led investigators to research common therapeutic and preventative strategies for both diseases. Aspirin and calcium have been studied in a large number of randomized trials in a variety of populations and although effect sizes are only modest both significantly reduce the incidence of preeclampsia,[9,10] and aspirin also decreases the incidence of SGA.[11] Their use should be considered standard practice for women at high risk of these conditions.[12-14]

Heparin and low-molecular-weight heparin (LMWH) have potential as preventative therapies. Their presumed benefit may relate to their anticoagulant properties although it is likely that additional effects on trophoblast development may be more important.[15-17] Small observational and nonrandomized trials[18-21] reporting benefit have led to a variety of randomized controlled trials. These initially focused specifically on populations with or without thrombophilia,[22-24] but trials commenced more recently have included women regardless of thrombophilia status. Results from individual trials of LMWH are conflicting,[22-28] possibly reflecting the heterogeneity of the populations being examined, the type of heparin/LMWH being tested, prolonged trial recruitment phases,[23,24] and early trial discontinuation due to presumed overwhelming effect[22] or futility of ability show any effect.[25] Recent meta-analysis[29] and individual patient data meta-analysis[30] also failed to conclusively demonstrate that LMWH reduces the risk of placenta-mediated complications in subsequent pregnancies for those deemed to be at high risk.

The aim of the Enoxaparin for the Prevention of Preeclampsia and IUGR (EPPI) trial was to assess the effectiveness of LMWH for the prevention of recurrence of preeclampsia and SGA. The trial aimed to be more precise, and clinically relevant, with its inclusion criteria and primary outcome measures specific to women at high risk of preeclampsia and/or SGA. Account was made of each participant's thrombophilia status but this status did not define the study population. All participants received high-risk care including the use of low-dose aspirin and, where appropriate, calcium.

The EPPI trial is the first randomized controlled trial of LMWH to report the serial assessment of placentally derived angiogenic growth factors involved in the pathophysiological process of preeclampsia (soluble fms-like tyrosine kinase [sFlt]-1 and soluble endoglin [sEng], which are elevated in preeclampsia[31-34]; placental growth factor [PlGF], which is decreased in preeclampsia) as well as endothelial-derived circulating markers that are associated with maternal endothelial dysfunction (endothelin [ET]-1 and soluble vascular cell adhesion molecule [sVCAM]-1).

Materials and Methods

Study design, setting, and ethics statement

This was a multicenter open-label randomized controlled trial (ACTRN12609000699268) at 5 tertiary care centers in New Zealand, Australia, and The Netherlands. Appropriate ethics and governance approvals were obtained at each center. All women participating in the trial provided written informed consent.

Participants

Through the duration of the trial women referred for antenatal care were screened for eligibility. Women were eligible for inclusion if they were $>6^{+0}$ and $<16^{+0}$ weeks; gestation with a viable singleton pregnancy confirmed by ultrasound scan and at risk of preeclampsia and/or IUGR based on their obstetric history with: (1) previous preeclampsia delivered $<36^{+0}$ weeks in their last ongoing pregnancy reaching >12 weeks; or (2) previous SGA infant <10th customized birthweight percentile delivered $<36^{+0}$ weeks in their last ongoing pregnancy reaching >12 weeks with no major fetal anomaly; or (3) previous SGA infant ≤3rd customized birthweight percentile delivered at any gestation in their last ongoing pregnancy reaching >12 weeks with no major fetal anomaly. Eligibility criteria were checked against medical records. Women were excluded from the trial if they met ≥1 of the exclusion criteria: any contraindication to LMWH use; need for anticoagulant use in pregnancy such as previous thrombosis or antiphospholipid syndrome; previous successful pregnancy with LMWH treatment; multiple pregnancy; known preexisting type 1 or 2 diabetes; renal disease (with serum creatinine >150 umol/L); thrombocytopenia (platelet count $<80 \times 10^9$/L); or known major fetal anomaly/chromosomal abnormality.

We included women with previous preeclampsia and/or SGA as these diseases are both placental in origin with considerable overlap in pathological mechanisms. LMWH is likely to exert any therapeutic benefit via effect(s) on placentation and therefore has potential to impact both diseases, which often coexist, particularly when disease is preterm.

Randomization and interventions

After confirming eligibility and obtaining consent participants were randomly assigned in a 1-to-1 ratio to standard high-risk care or standard high-risk care plus enoxaparin 40 mg (4000 IU) by subcutaneous injection (Clexane, Sanofi-Aventis, Auckland, New Zealand)[35] daily from recruitment until 36^{+0} weeks or delivery, whichever occurred sooner. A 40-mg dose of enoxaparin was selected as the standard dose used for venous thromboembolism prophylaxis and, as per manufacturer's direction, no adjustment was made for body mass index. Standard high-risk care was defined as care coordinated by a high-risk antenatal clinic service, aspirin 100 mg daily until 36^{+0} weeks, and—for women with prior preeclampsia—calcium 1000-1500 mg daily until 36^{+0} weeks. This was an open-label trial with all participants, clinicians, and investigators aware of trial group assignment.

A computer-generated randomization program balanced in blocks of 5 was

used with stratification for recruiting site and thrombophilia status. Participants who were tested prior to trial involvement were assigned to: (1) positive thrombophilia or (2) negative thrombophilia. Women not tested or partially tested (with negative result) were assigned: (3) unknown thrombophilia status. Samples were then taken prior to any use of LMWH and tested for lupus anticoagulant, anticardiolipin antibodies, antithrombin III deficiency, protein C deficiency, protein S deficiency, factor V Leiden, and the prothrombin gene mutation. These results were used in the final analysis but not revealed to participant, clinicians, or investigators during the trial period.

All participants were assigned a sequential trial identifying number according to thrombophilia status. At the lead recruiting site (National Women's Health, Auckland City Hospital) randomization occurred by telephone to the hospital pharmacy clinical trials service and trial group allocation was made by study identifying number. In all other sites sequential sealed opaque envelopes for each study identifying number were opened to reveal treatment allocation.

Procedures

For women receiving LMWH, an educational session regarding injection technique was provided by a research midwife prior to treatment commencement. LMWH was resupplied on a monthly basis from hospital pharmacies. Participants were asked to return sharps disposal boxes with used syringes and any unused treatment. Indications to stop treatment $<36^{+0}$ weeks included: need for delivery $<36^{+0}$ weeks (stopped once decision made for delivery or 12 hours prior to induction of labor or elective cesarean delivery, whichever was later), episode of threatened preterm labor (treatment recommenced if symptoms settled), and clinical evidence of placental abruption or thrombocytopenia with platelet count $<80 \times 10^9$/L.

Serum samples were taken at recruitment (used as baseline) and at 20 and 30 weeks' gestation in a subgroup of participants (n = 127). Samples were centrifuged and stored at −80°C for later assessment of sFlt-1, sEng, PlGF, sVCAM-1, and ET-1 by enzyme-linked immunosorbent assay according to manufacturer's instructions (R&D Systems, Minneapolis, MN). Optical density was determined using X-Mark microplate spectrophotometer (BioRad, Gladesville, Australia) and analyte levels were determined using Microplate manager 6 software (BioRad). Analytes were measured in 1 batch in a blinded fashion with the cases and controls mixed.

Standard fetal growth parameters[36,37] and uterine and umbilical arterial Doppler waveforms[38] were recorded at 20 and 24 weeks' gestation. Data from any additional antenatal ultrasound scans were collected. All participants received care through a high-risk antenatal clinic service including daily aspirin and, for women with prior preeclampsia, daily calcium. Care included regular blood pressure (BP) assessment, urine dipstick analysis for proteinuria, fetal well-being assessment, and review of any adverse events. Intrapartum and postnatal care was provided by local clinicians. Pregnancy, labor, postnatal, and neonatal data were collected by research staff from maternal and infant clinical records up to the time of hospital discharge.

Outcomes

The primary outcome was a composite of preeclampsia and/or SGA <5th percentile. All cases with primary outcome events were reviewed by trial investigators. Secondary outcomes included preeclampsia, severe preeclampsia, HELLP syndrome (hemolysis, elevated liver enzyme, and low platelet count), eclampsia, gestational hypertension, SGA <10th percentile, SGA <5th percentile, SGA <3rd percentile, placental abruption and antepartum hemorrhage, thrombocytopenia (platelet count $<100 \times 10^9$/L) while on LMWH, stillbirth, induction of labor, cesarean delivery, postpartum hemorrhage, gestational age at birth, preterm birth, mean birthweight and mean birthweight percentile, neonatal death, neonatal intensive care admission and duration of admission, a composite outcome of severe neonatal morbidity (evidence of ≥1: intraventricular hemorrhage [grade 3 and 4], cystic periventricular leukomalacia, chronic lung disease, retinopathy of prematurity requiring treatment, or necrotizing enterocolitis requiring surgery), and maternal serum levels of sFlt-1, sEng, PlGF, sVCAM-1, and ET-1.

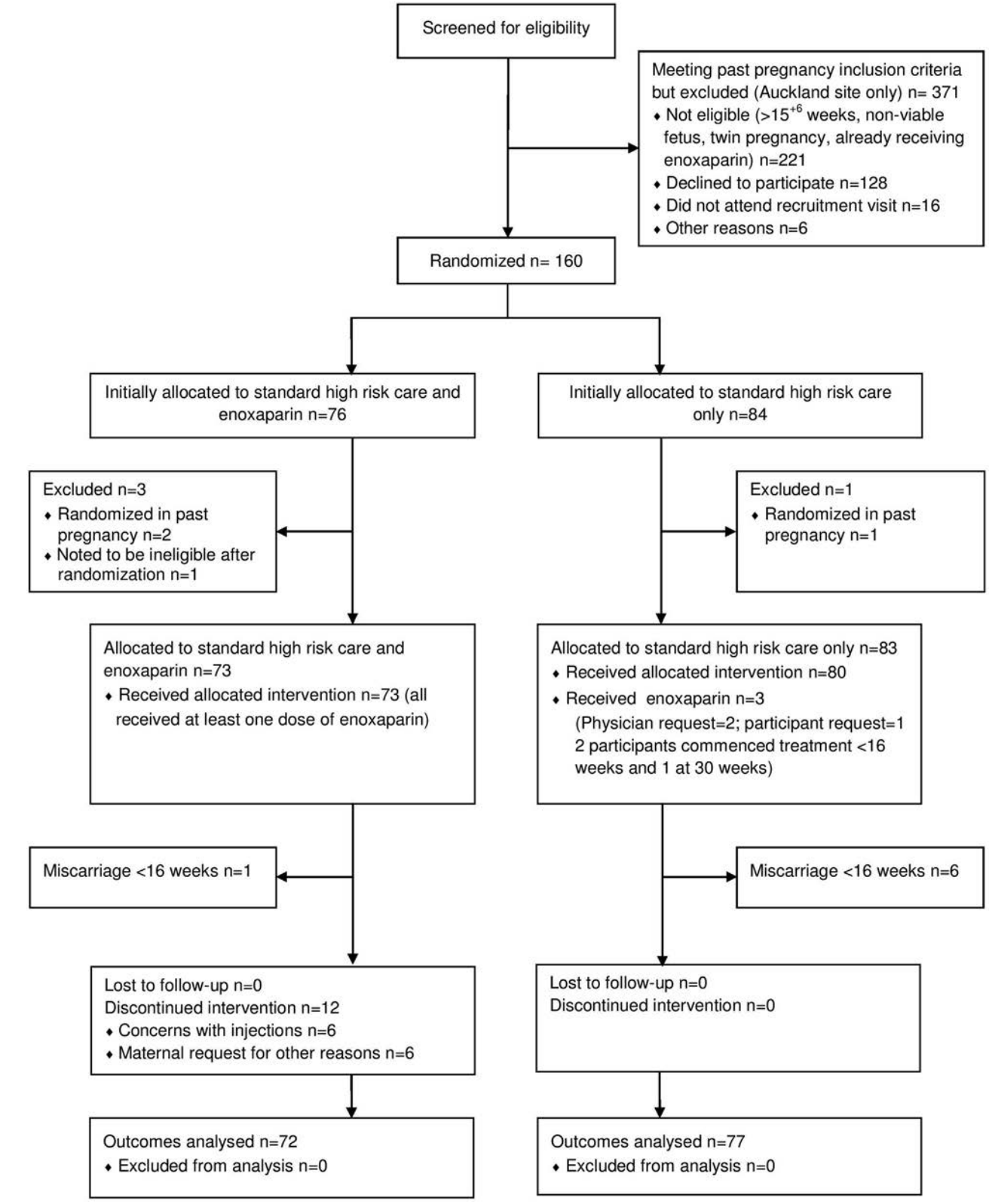
Preeclampsia was defined as new-onset hypertension (systolic BP ≥140 mm Hg and/or diastolic BP ≥90 mm Hg) >20 weeks' gestation with evidence of significant proteinuria or any multisystem complication including hematological, liver, renal, and neurological involvement.[39] Severe preeclampsia included preeclampsia associated with maternal death, persistent severe hypertension (systolic BP ≥170 mm Hg and/or diastolic BP ≥110 mm Hg), or a multisystem complication. Customized birthweight percentiles adjusting for infant sex, gestation at delivery, and maternal variables (parity, ethnicity, height, and early pregnancy weight) were used to identify SGA infants.[40] Nonpregnant- and pregnancy-specific (as appropriate to timing of testing) reference ranges were used to define protein C deficiency, protein S deficiency, and antithrombin III deficiency.[41]

Statistical analysis

A priori we estimated a risk of recurrence of preeclampsia and/or SGA <5th percentile for the included population of 25%. Based on published data we estimated the risk of recurrence would be reduced to 7% with the addition of LMWH therapy.[22] We planned for a sample size of 160 participants (80 participants in each group, including a 5% dropout/early miscarriage rate) to achieve 80% power at a 2-sided significance level of .05 to detect a difference between 25-7%.

An independent data monitoring committee undertook a planned interim analysis once 98 participants were recruited and completed follow-up. Safety and primary outcome data were assessed and reported to the trial investigator group. Early discontinuation of the trial was to be considered if there was an excess of serious adverse events in the LMWH group or if a significant benefit had already been demonstrated (49

FIGURE 1
Enoxaparin for Prevention of Preeclampsia and Intrauterine Growth Restriction (EPPI) trial profile



CONSORT flow diagram of participants in EPPI trial.

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TABLE 1
Maternal and pregnancy characteristics

	Standard high-risk care and enoxaparin, n = 73	Standard high-risk care only, n = 83
Baseline maternal characteristics		
Maternal age, y	34 (21–42)	34 (20–40)
Ethnicity		
European/Caucasian	50 (68.5%)	50 (60.2%)
Far East/South East Asian	7 (9.6%)	5 (6.0%)
Maori/Cook Island	4 (5.5%)	4 (4.8%)
Pacific Island	1 (1.4%)	3 (3.6%)
South Asian	7 (9.6%)	7 (8.3%)
Other	4 (5.5%)	14 (6.9%)
Body mass index, kg/m^2	26.3 (19–48)	25.1 (16–43)
Smoking status at trial entry	3 (4.1%)	4 (4.8%)
Preexisting hypertension	9 (12.3%)	9 (10.8%)
Previous gestational diabetes[a]	1 (1.4%)	3 (3.6%)
Blood pressure at trial entry		
Systolic, mm Hg	110 (80–156)	110 (84–148)
Diastolic, mm Hg	70 (48–98)	69 (40–88)
Thrombophilia status		
FVL heterozygous	6 (7.0%)	7 (8.4%)
Prothrombin gene mutation heterozygous	3 (4.1%)	2 (2.4%)
Protein C deficiency	1 (1.4%)	1 (1.2%)
Protein S deficiency	5 (6.9%)	6 (7.2%)
Antithrombin III deficiency	0	1 (1.2%)
FVL homozygous	0	0
Prothrombin gene mutation homozygous	0	0
Lupus anticoagulant/anticardiolipin antibodies	0	3 (3.6%)
Incomplete screen/unreported result	7 (9.6%)	9 (10.8%)
Obstetric history and reasons for trial inclusion		
Gravidity		
2	36 (49.3%)	43 (51.8%)
3	21 (28.8%)	18 (21.7%)
4–5	12 (16.4%)	16 (19.2%)
≥6	4 (5.5%)	6 (7.2%)
Parity		
0	0	1 (1.2%)[c]
1	63 (86.3%)	63 (75.9%)
2	6 (8.2%)	14 (16.9%)
≥3	4 (5.5%)	5 (6.0%)

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participants in each group to achieve 80% power at a 2-sided significance level of .05 to detect a difference between 25-4%).

All data were analyzed on an intention-to-treat basis. Continuous data are reported as median with minimum–maximum values (range). Categorical data are reported as number and proportion. Unless otherwise stated, statistical models were adjusted for thrombophilia status, recruitment center, inclusion criteria, and number of previous preeclampsia/SGA events (1 vs ≥2) as these variables were deemed the most likely to potentially influence the risk of recurrence and/or the care provided. Multiple logistic regression was used to analyze the binary primary and secondary outcomes. Multiple linear regression was used to analyze the continuous secondary outcomes. No missing data imputation was conducted. No multiple comparison adjustment was made. Two-sided P values $<.05$ were used to determine statistical significance and all confidence intervals (CI) are given at a 2-sided 95% level. Statistical analysis was conducted using software (SAS for Windows 9.4; SAS Institute Inc, Cary, NC). Levels of analytes measured in the serum samples were tested for normal distribution and statistically tested using nonparametric Mann-Whitney test. Data were expressed as mean ± SEM. Biomarker statistical analysis was performed using software (GraphPad Prism 6; GraphPad Software, La Jolla, CA).

Results

From July 26, 2010, through Oct. 28, 2015, a total of 157 women in 160 pregnancies consented and were randomly allocated to standard high-risk care and enoxaparin or standard high-risk care only. Three women were approached in 2 pregnancies and only the first eligible pregnancy was included; a fourth woman was deemed ineligible after randomization and was also excluded (156 participants were included). The outcome analysis included all pregnancies that proceeded >16 weeks (n = 149) (Figure 1).

Baseline characteristics for groups are reported in Table 1. Of participants, 44%

TABLE 1
Maternal and pregnancy characteristics *(continued)*

	Standard high-risk care and enoxaparin, n = 73	Standard high-risk care only, n = 83
≥2 Previous pregnancies affected by preeclampsia and/or SGA	5 (6.9%)	15 (18.1%)
Inclusion criteria for trial entry[b]		
Previous preeclampsia delivered <36^{+0} wk	30 (41.1%)	38 (45.8%)
Previous SGA infant <10th customized birthweight percentile delivered <36^{+0} wk	48 (65.8%)	43 (51.8%)
Previous SGA infant ≤3rd customized birthweight percentile delivered at any gestation	60 (82.2%)	63 (75.9%)
Pregnancy characteristics		
Gestational age at randomization, d	83 (42–111)	84 (42–111)
Aspirin use in pregnancy	71 (97.3%)	80 (96.4%)
Calcium use in pregnancy	43 (58.9%)	40 (48.2%)
Pregnancy multivitamin including folic acid use in pregnancy	72 (98.6%)	77 (92.3%)
Miscarriage <16 wk (excluded from outcome analysis)	1 (1.4%)	6 (7.3%)

Data expressed as median (minimum–maximum values) or number (percentage).

FVL, factor V Leiden; *SGA*, small for gestational age.

[a] Type 1/2 diabetes excluded from trial; [b] Each participant may meet >1 criteria; [c] Eligibility pregnancy was termination of pregnancy <20 wk gestation for severe early-onset intrauterine growth restriction.

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(68/156) had a history of preeclampsia delivered <36^{+0} weeks and 58% (91/156) had a history of delivering a SGA infant <36^{+0} weeks; 79% (123/156) had a history of delivering a severe SGA infant (≤3rd percentile). The large majority of women (151/156, 97%) received aspirin therapy during their pregnancy and 53% (83/156) received calcium therapy.

For women in the standard high-risk care and enoxaparin group the median duration of enoxaparin treatment was 156 days (range 1-209 days). Ten women reported skin reactions or significant bruising with enoxaparin treatment; 1 woman had an allergic reaction and transferred to dalteparin therapy. Twelve women elected to discontinue treatment <36^{+0} weeks' gestation (6 due to concerns with injections, 6 due to maternal request for other reasons). No women had thrombocytopenia while on enoxaparin therapy.

Overall, 35 women (23.5%) experienced the primary outcome of preeclampsia and/or SGA <5th percentile. There was no significant difference in the rates of the primary outcome between the 2 groups: 25% (18/72) in standard high-risk care and enoxaparin group compared with 22.1% (17/77) in standard high-risk care only group (adjusted odds ratio, 1.19; 95% CI, 0.53–2.64) (Table 2). There was also no significant difference in any secondary pregnancy, delivery, or neonatal outcomes (Tables 2-4). In subgroup analyses the use of enoxaparin had no effect on the rates of the primary outcome for women with a history of preeclampsia, SGA <3rd percentile, or SGA <10th percentile (Table 5).

Levels of sFlt-1, sEng, PlGF, sVCAM-1, and ET-1 in serum collected from women at recruitment, 20 weeks, and 30 weeks (samples from 127 participants) showed no significant difference with enoxaparin treatment when compared to those receiving standard high-risk care only (Figure 2). Importantly, we identified a significant increase in sFlt-1, sEng, and sVCAM-1 levels in the 30-week time-point serum of women who developed preeclampsia, compared to those who did not (Figure 3). Levels of ET-1 were significantly increased in women who developed preeclampsia at all time points assessed (Figure 3). Among only those women who subsequently developed preeclampsia, no significant difference was observed in analytes in those treated with enoxaparin vs those receiving standard high-risk care only (Supplementary Figure 1).

Analysis of serum from women with pregnancies that subsequently developed SGA <5th percentile demonstrated no significant difference in sFlt-1, sEng, PlGF, or sVCAM-1 (Supplementary Figure 2, A-D). Like for those who developed preeclampsia, there was a significant increase in ET-1 levels at recruitment in the serum from women who later developed SGA pregnancy (Supplementary Figure 2, E).

Comment

The EPPI trial has not shown any beneficial effect of enoxaparin use in pregnancy to reduce the risk of recurrence of preeclampsia and SGA. There may be several reasons for this real or apparent lack of effect.

Many of the previous trials of LMWH have had very broad inclusion criteria for the prevention of placenta-mediated pregnancy complications including recurrent miscarriage,[27,28] second-trimester loss,[22,25] placental abruption,[42] and unexplained stillbirth and nonpregnancy-related conditions (venous thromboembolism, phlebitis, and family history of thromboembolism).[24] If LMWH was effective in one subgroup but not others the significance of this effect may be lost within the pooled results. For this reason our trial aimed to be more specific to preeclampsia and SGA using clearly defined inclusion criteria and a limited

TABLE 2
Pregnancy outcomes

	Standard high-risk care and enoxaparin, n = 72	Standard high-risk care only, n = 77	Adjusted odds ratio[a] (95% CI)
Primary outcome (preeclampsia and/or SGA infant <5th percentile)	18 (25.0%)	17 (22.1%)	1.19 (0.53–2.64)
Preeclampsia	6 (8.3%)	5 (6.5%)	1.24 (0.33–4.64)
Severe preeclampsia	2 (2.8%)	1 (1.3%)	[b]
Preeclampsia with delivery $\leq 33^{+6}$ wk	2 (2.8%)	1 (1.3%)	[b]
Preeclampsia with delivery $\leq 36^{+6}$ wk	4 (5.6%)	2 (2.6%)	[b]
SGA infant <10th percentile	23 (31.9%)	23 (29.9%)	1.17 (0.56–2.47)
SGA infant <5th percentile	15 (20.8%)	13 (16.9%)	1.48 (0.61–3.62)
SGA infant <3rd percentile	9 (12.5%)	10 (13.0%)	1.19 (0.40–3.52)
HELLP syndrome	1 (1.4%)	2 (2.6%)	[b]
Eclampsia	0	0	NA
Gestational hypertension	10 (14.9%)	16 (20.1%)	0.65 (0.25–1.64)
Gestational diabetes	8 (11.1%)	10 (13.0%)	1.01 (0.34–2.99)
Antepartum hemorrhage/abruption	7 (9.7%)	7 (9.1%)	0.92 (0.28–3.0)

Data expressed as number (percentage) unless otherwise indicated.

CI, confidence interval; *NA*, not applicable; *SGA*, small for gestational age; *HELLP*, haemolysis, elevated liver enzymes, low platelets.

[a] Multiple logistic regression adjusted for inclusion criteria, recruitment center, final thrombophilia status, and number of previous preeclampsia/SGA events (1 vs ≥2 events); [b] Event rate too low for formal testing.

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TABLE 3
Delivery outcomes

	Standard high-risk care and enoxaparin, n = 72	Standard high-risk care only, n = 77	Adjusted odds ratio[a] (95% CI) or *P* value
Preterm birth $\leq 36^{+6}$ wk	16 (22.2%)	19 (24.7%)	0.76 (0.33–1.73)
Preterm birth $\leq 33^{+6}$ wk	7 (9.7%)	10 (13.0%)	0.55 (0.17–1.75)
Induction of labor	15 (20.8%)	17 (22.1%)	0.76 (0.33–1.73)
Cesarean delivery	39 (54.1%)	40 (52.0%)	1.35 (0.68–2.71)
Prelabor cesarean delivery	31 (43.1%)	32 (41.6%)	1.34 (0.66–2.72)
Major postpartum hemorrhage >1000 mL	4 (5.6%)	7 (9.1%)	[b]
Postpartum hemorrhage ≥500 mL	27 (37.5%)	30 (39.0%)	0.79 (0.38–1.63)
Fetal loss >16 wk	2 (2.8%)[c]	3 (3.9%)[d]	[b]
Gestational age at delivery, d	268 (118–292)	269 (147–292)	.68
Birthweight, g	2920 (22–4582)	3150 (385–4120)	.70
Birthweight percentile	17.1 (0–99)	22.9 (0–94)	.93

Data expressed as median (minimum–maximum values) or number (percentage) unless otherwise indicated.

CI, confidence interval.

[a] Multiple logistic regression adjusted for inclusion criteria, recruitment center, final thrombophilia status, and number of previous preeclampsia/small-for-gestational-age events (1 vs ≥2 events); [b] Event rate too low for formal testing; [c] Includes termination of pregnancy at 17 wk gestation for severe early-onset intrauterine growth restriction and stillbirth at 25^{+3} wk with severe early-onset intrauterine growth restriction; [d] Includes stillbirth at 24^{+3} wk with abruption, stillbirth at 20^{+5} wk after extreme preterm birth, and stillbirth at 38^{+1} wk with severe preeclampsia, small-for-gestational-age <10th percentile, and abruption.

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TABLE 4
Neonatal outcomes (for live-born only)

	Standard high-risk care and enoxaparin, n = 70	Standard high-risk care only, n = 74	Adjusted odds ratio[a] (95% CI) or *P* value
Neonatal death	0	0	NA
NICU admission	14 (20%)	14 (18.9%)	0.93 (0.37–2.37)
Duration of NICU admission, d	13.5 (1–116)	23.5 (5–126)	.37
Composite outcome severe neonatal morbidity	2 (2.9%)	4 (5.4%)	[b]

Data expressed as median (minimum–maximum values) or number (percentage) unless otherwise indicated.

CI, confidence interval; *NA*, not applicable; *NICU*, neonatal intensive care unit.

[a] Multiple logistic regression adjusted for inclusion criteria, recruitment center, final thrombophilia status, and number of previous PET/small-for-gestational-age events (1 vs ≥2 events); [b] Event rate too low for formal testing.

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composite primary outcome. Our inclusion criteria resulted in a higher proportion of participants with a history of a SGA compared to other trials. This is likely to explain the relatively low rates of recurrence of preeclampsia compared to SGA. Subgroup analyses (although not sufficiently powered to this end) did not indicate any effect of LMWH is limited to preeclampsia and not SGA.

The result of our biomarker studies further supports the premise that LMWH does not have a therapeutic effect for preeclampsia only. An important marker of preeclampsia is the elevated placental release of the antiangiogenic factors sFlt-1 and sEng. They spread throughout the maternal circulation and cause widespread endothelial dysfunction, and blood vessel damage causing hypertension and multiorgan injury. We have shown there were no changes in serum sFlt-1 and sEng concentrations among women treated with enoxaparin, compared to standard high-risk care only. Importantly, we did observe an expected rise in sFlt-1 and sEng among those who subsequently developed preeclampsia, which was not mitigated by the use of enoxaparin. We also found enoxaparin was unable to decrease circulating levels of ET-1 (a potent endothelial-derived vasoconstrictor known to be increased in preeclampsia) among those who subsequently developed preeclampsia (and SGA).

It may be argued that the estimation of the size of effect of LMWH used in our sample size calculation was unrealistic. However, the estimated recurrence rate for the standard high-risk care only group (25%) was very similar to the overall recurrence rate (23.5%) and indeed the same as the rate of recurrence for those treated with additional LMWH (25.0%). Our estimate for a reduction in risk of recurrence to 7% was optimistic but based on the most applicable data set published at that time, which reported a similar composite primary outcome of 5.5%.[22] This was an open-label trial with no placebo arm. Participants, clinicians, and investigators were aware of the assigned treatment group. We originally planned a placebo-controlled trial, however, we were unable to commercially source suitable placebo syringes and were unable to secure sterile manufacture and preparation of syringes that would meet international regulatory requirements. No previous trials of LMWH for the prevention of placenta-mediated pregnancy complications used placebo injections as a comparator and, even in nonpregnant trials of LMWH, placebo has only been used in industry-sponsored trials. We therefore elected to proceed with an open-label trial with no placebo injection. Our

TABLE 5
History subgroup analysis of primary outcome

	Standard high-risk care and enoxaparin	Standard high-risk care only	Unadjusted odds ratio[a] (95% CI)
Preeclampsia ± SGA[b] n = 63	8/30 (26.7%)	6/33 (18.2%)	1.64 (0.49–5.43)
SGA infant ≤3rd percentile with no preeclampsia[b] n = 65	9/34 (26.5%)	8/31 (25.8%)	1.04 (0.34–3.13)
SGA infant <10th percentile with no preeclampsia[b] n = 79	9/38 (23.7%)	9/41 (22.0%)	1.10 (0.39–3.16)

Data expressed as number with primary outcome/total (percentage) unless otherwise indicated.

CI, confidence interval; *SGA*, small for gestational age.

[a] Unadjusted crude odds ratio used as numbers too small for appropriate adjustment; [b] In last ongoing pregnancy reaching >12 wk.

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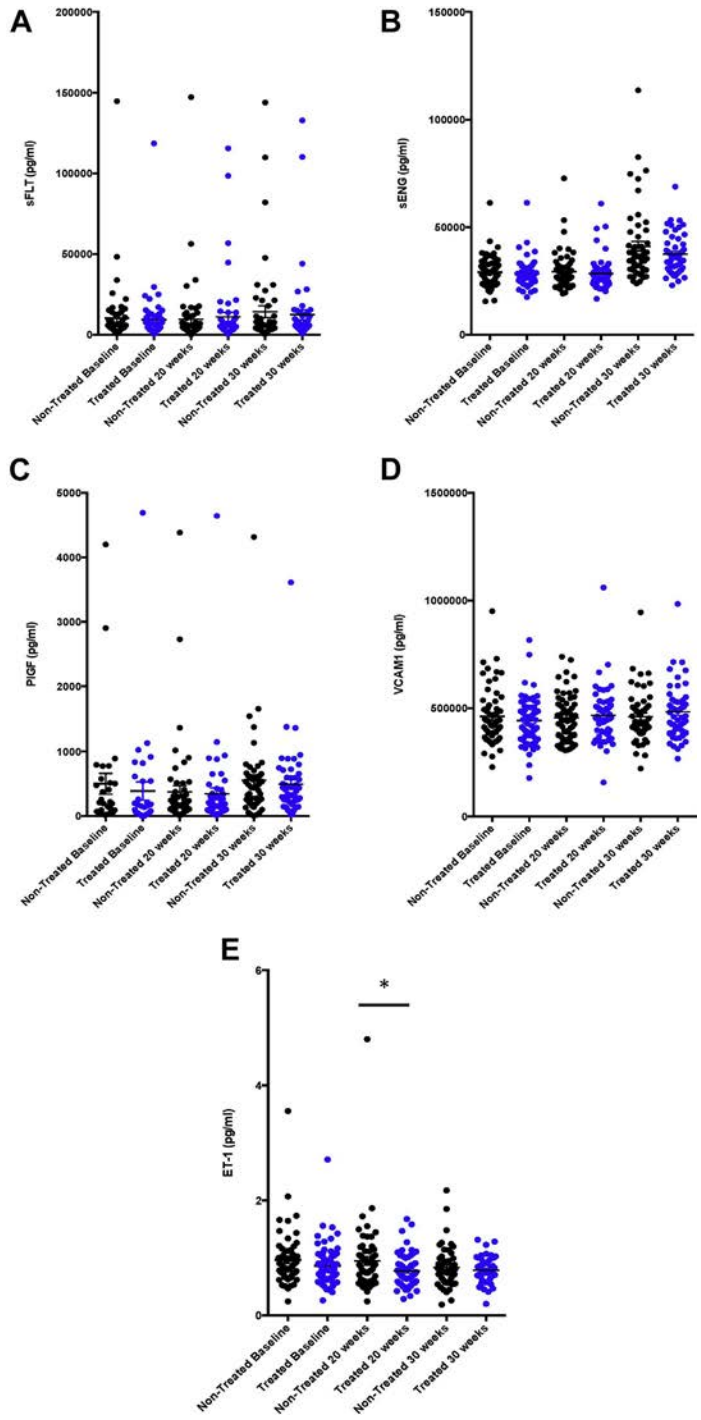
FIGURE 2
Serum biomarker levels in women treated with enoxaparin or standard high-risk care only taken at baseline (recruitment), 20 weeks, and 30 weeks



Serum levels of **A**, soluble fms-like tyrosine kinase (sFlt)-1; **B**, soluble endoglin (sEng); **C**, placental growth factor (PlGF); **D**, soluble vascular cell adhesion molecule (VCAM)-1; and **E**, endothelin (ET)-1 taken at baseline (recruitment), 20 weeks, and 30 weeks were similar for those receiving enoxaparin (treated) and those receiving standard high-risk care only (nontreated). Serum biomarker levels according to treatment group. *$P<0.05$; black closed circles indicate standard high risk care only; blue closed circles indicate enoxaparin treatment.

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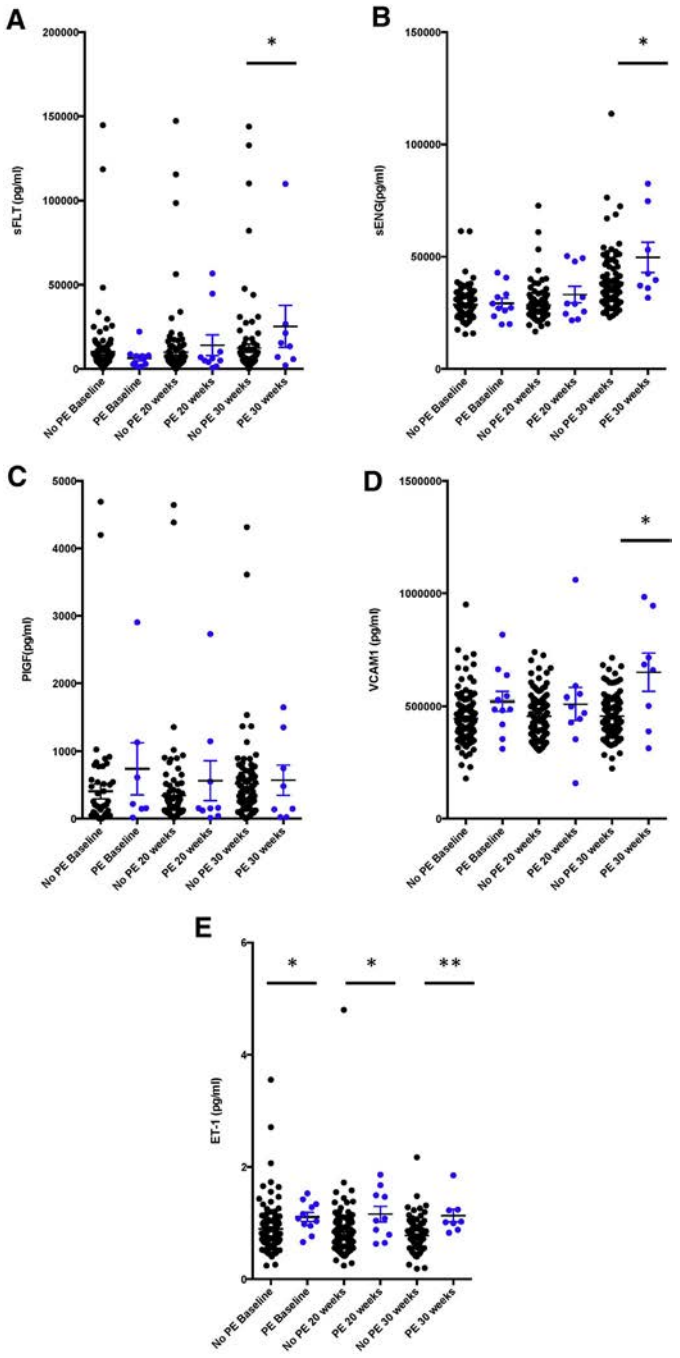
trial had similar issues to other trials with a prolonged recruitment phase. Following a feasibility assessment at the lead trial site it was estimated that with a 30% recruitment rate we would complete recruitment within 2 years. However, a large number of women were not referred until $>16^{+0}$ weeks' gestation and so were not eligible for the trial. Trial duration was extended and additional recruiting sites were identified to ensure the trial was completed to the planned sample size.

Our results conflict with those seen in a published pooled summary-based, study-level meta-analysis including 6 trials and 848 pregnant women. A relative risk reduction of 0.52 (95% CI, 0.32−0.86; 18.7% vs 42.9%) was demonstrated for a primary composite outcome (preeclampsia, SGA <10th percentile, placental abruption, or pregnancy loss >20 weeks) with similar risk reductions for a number of secondary outcomes including preeclampsia, SGA, and preterm birth.[29] However, this meta-analysis showed high heterogeneity (I^2 69%) and the included trials of higher quality suggested no treatment effect. Individual patient data analysis including these same trials and 3 additional trials showed significant heterogeneity between single-center and multicenter trials with no effect seen on a primary composite outcome (early-onset or severe preeclampsia, SGA <5th percentile, placental abruption, or pregnancy loss >20 weeks) for multicenter trials (18% LMWH treatment vs 18% no LMWH treatment) but a significant reduction in single-center trials (8% vs 27% respectively, absolute difference −18.7%; 95% CI, −21.6 to −15.7; $P < .0001$).[30]

The multicenter EPPI trial was designed to be as specific to preeclampsia and SGA as possible. Thrombophilia status was accounted for but did not limit the trial population. Women in both groups consistently received standard high-risk obstetric care. Our trial findings are consistent with the 2 most recently published multicenter trials of LMWH. Both the HAPPY[25] and HEPEPE[26] trials included women at high risk of placental-mediated

FIGURE 3
Serum biomarker levels in women who developed preeclampsia (PE) compared to those who did not taken at baseline (recruitment), 20 weeks, and 30 weeks



There was significant increase in levels of **A**, soluble fms-like tyrosine kinase (sFlt)-1; **B**, soluble endoglin (sEng); **C**, placental growth factor (PlGF); and **D**, soluble vascular cell adhesion molecule (VCAM)-1 at 30 weeks' gestation observed in women who developed PE compared to those who did not. **E**, Significant increase in endothelin (ET)-1 levels was observed in women who developed PE across all time points examined at baseline (recruitment) and at 20 and 30 weeks' gestation. Serum biomarker levels according to preeclampsia status. *$P<0.05$; **$P<0.01$; black closed circles indicate no preeclampsia; blue closed circles indicate developed preeclampsia.

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pregnancy complications, with or without thrombophilia, and reported no difference in rates of preeclampsia or SGA associated with LMWH use. It seems likely these 3 trials are more representative of a general at-risk population. Data from the EPPI trial will make a significant contribution to future meta-analyses. ■

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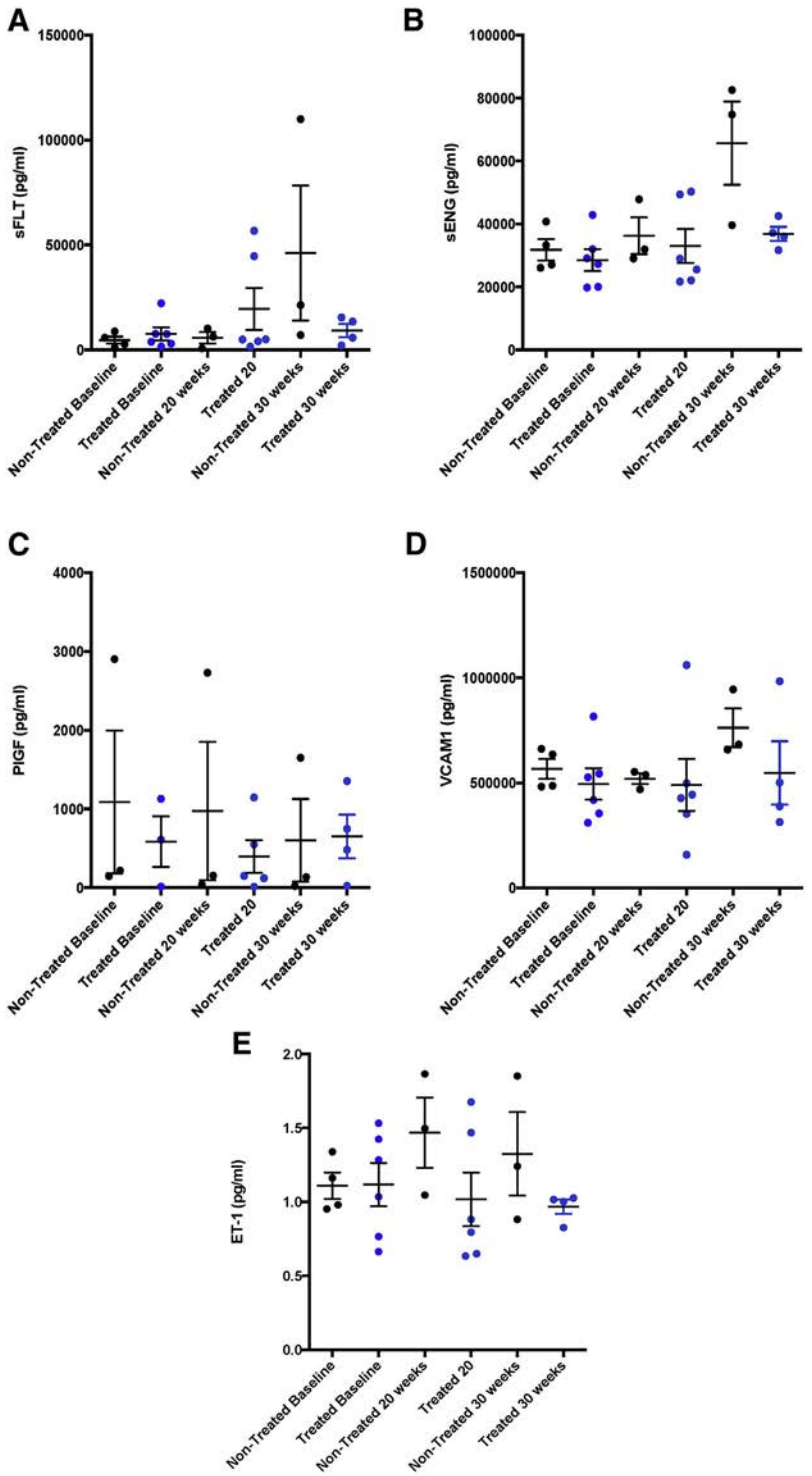
SUPPLEMENTARY FIGURE 1

Serum biomarker levels in women who developed preeclampsia taken at baseline (recruitment), 20 weeks, and 30 weeks treated with enoxaparin or standard high-risk care only



Levels of **A**, soluble fms-like tyrosine kinase (sFlt)-1; **B**, soluble endoglin (sEng); **C**, placental growth factor (PlGF); **D**, soluble vascular cell adhesion molecule (VCAM)-1; and **E**, endothelin (ET)-1 were not significantly changed by treatment with enoxaparin (treated) among women who developed preeclampsia compared to those receiving standard high-risk care only (nontreated). Black closed circles indicate standard high-risk care; blue closed circles indicate enoxaparin.

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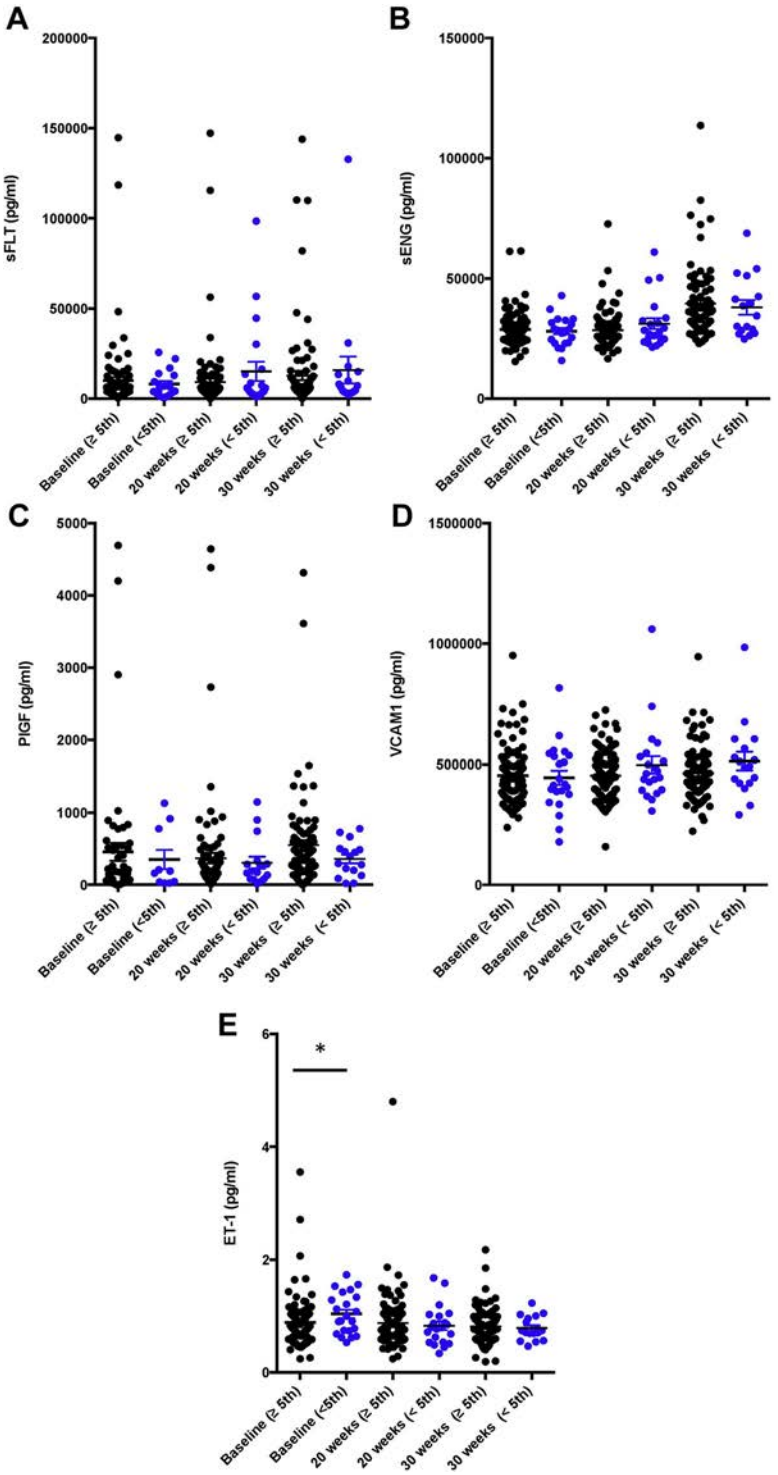
SUPPLEMENTARY FIGURE 2

Serum biomarker levels in women who developed small for gestational age (SGA) <5th percentile compared to those with infants with birthweight ≥5th percentile taken at baseline (recruitment), 20 weeks, and 30 weeks



Levels of **A**, soluble fms-like tyrosine kinase (sFlt)-1; **B**, soluble endoglin (sEng); **C**, placental growth factor (PIGF); and **D**, soluble vascular cell adhesion molecule (VCAM)-1 were similar for those with SGA <5th percentile and those with infant birthweight ≥5th percentile at all time points. **E**, There was significant increase in endothelin (ET)-1 levels at baseline in serum from women who later developed SGA pregnancy. *$P<0.05$; black closed circles indicate non-small for gestational age; blue closed circles indicate small for gestational age.

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