OBSTETRICS

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

Katie M. Groom, MBBS, PhD, FRANZCOG, CMFM; Lesley M. McCowan, MB ChB, MD, FRANZCOG, CMFM; Laura K. Mackay, BSc; Arier C. Lee, PhD; Joanne M. Said, MBBS, PhD, FRANZCOG, CMFM; Stefan C. Kane, MBBS, FRANZCOG; Susan P. Walker, MBBS, MD, FRANZCOG, CMFM; Thijs E. van Mens, MD, MBA; Natalie J. Hannan, PhD; Stephen Tong, MBBS, PhD, FRANZCOG; Larry W. Chamley, PhD; Peter R. Stone, MB ChB, MD, FRANZCOG, CMFM; Claire McLintock, MB ChB, FRACP; the Enoxaparin for Prevention of Preeclampsia and Intrauterine Growth Restriction Trial Investigator Group

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