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Correspondence

Low molecular weight heparin to prevent postpartum venous thromboembolism: A pilot study to assess the feasibility of a randomized, open-label trial

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Dear Sir,

Pulmonary embolism (PE) is one of the leading causes of maternal mortality in the developed world [1]. Post-partum venous thromboembolism (VTE) is estimated to occur in 3 to 7 per 10,000 deliveries [2]. The heightened clinical risk of VTE rapidly diminishes during the postpartum period [3], returning to antenatal levels of risk by 3 weeks postpartum and then returns to non-pregnant levels after the 12th postpartum week [4–6].

Offering universal post-partum prophylaxis would likely cause more harm from major bleeding than prevent VTE [7]. As such, risk stratification is suggested to identify high risk patients that might benefit from VTE prophylaxis. Guidelines have suggested complex tools that are difficult to implement in practice and these tools are not validated [8,9]. Jacobsen et al. identified independent risk factors for developing postpartum VTE in a well-conducted case control study [4]. When controlling for confounding risk factors postpartum infection, emergency caesarean section, antepartum immobilization, BMI ≥25 kg/m^2, postpartum hemorrhage ≥1000 ml, small for gestational age infant, preeclampsia, and smoking during pregnancy were identified as independent risk factors that significantly increased the risk of postpartum VTE [4]. Beyond the risk factors identified in Jacobsen's case control study it is also well known that hereditary thrombophilias (factor V Leiden, prothrombin gene mutation and deficiencies of protein C, S and antithrombin) are associated with an increased risk of pregnancy and postpartum VTE (3 to 15 fold higher risk) [10–12].

Thromboprophylaxis with low molecular weight heparin (LMWH) is the most commonly prescribed method for preventing VTE after delivery due to its ease of administration and favourable safety profile [13,14]. However, there is a striking paucity of information to guide the use of thromboprophylaxis in the postpartum period. A recently updated (2014) Cochrane Review included RCTs assessing the effectiveness and safety of VTE prophylaxis in pregnancy and the early postpartum period [15]. A total of nine trials assessed thromboprophylaxis post-caesarean section, 5 of which included a LMWH intervention. Only 2 of these trials included a placebo comparator and most of the trials had small sample sizes. There were no trials evaluating LMWH thromboprophylaxis following vaginal delivery. The authors of the review concluded that there is a clear need for rigorously conducted RCTs with sufficiently large samples to evaluate the effects of thromboprophylaxis on VTE outcomes during pregnancy and the post-partum period. They described the ideal future trial as one that compares prophylaxis to a placebo control in a fully blinded fashion but they acknowledged the substantial challenges of completing such a trial.

We recently conducted a placebo-controlled pilot study to determine the feasibility of conducting a full scale multi-centre randomized double-blind trial comparing LMWH to a placebo control in women at high risk of postpartum VTE [16]. Eligible consenting women were randomized equally and blindly to either the treatment group (prophylactic-dose dalteparin 5000 IU) or matching placebo saline, administered subcutaneously once daily for 21 days. The primary endpoint was the number of participants randomized per centre per month, which a priori was targeted at a minimum average of six participants recruited per centre per month. Unfortunately, the total recruitment in 6 centres over 6 months was 25, resulting in a recruitment rate of just 0.7 per centre per month.

In our previous pilot, participants primarily tended to refuse participation due to being uncomfortable with injections (27.2%), not feeling they had the time to participate (15%) and not wanting to receive placebo (2.3%). We asked 171 eligible women, that were refusing to consent to the double-blind RCT pilot, if they would be more likely to participate in the trial if it was open-label and 26 (15%) indicated that they would be more likely to participate if they knew whether or not they were receiving study drug. Of 142 respondents, an additional 15 (10%) women indicated that they would be more likely to participate if they were required to do less injections (1 week vs. 3 weeks of injections). We used this information to design a second pilot to improve the feasibility of a much needed full RCT in this patient population. The second pilot sought to examine the feasibility of conducting a randomized, open-label trial of 10 days of LMWH for postpartum prophylaxis in women at risk of VTE.

We piloted an RCT comparing daily prophylactic dalteparin 5000 IU subcutaneous injections to no treatment for 10 days following delivery. Women at higher VTE risk due to known low-risk thrombophilia or immobilization [4] were eligible, as were those with any 2 of the following: postpartum infection; postpartum hemorrhage; pre-pregnancy body mass index >25 kg/m^2; emergency caesarean birth; smoking >5 cigarettes per day prior to pregnancy; preeclampsia or infant birth weight < 3rd percentile. Women were excluded if they met any of the following criteria at the time of randomization: <6 h or >36 h since delivery; need for anticoagulation; contraindication to heparin; received more than one dose of heparin or LMWH since delivery; below the age of legal majority; prior trial participation; and no informed consent.

Women were recruited in the third trimester of pregnancy, while in labour and delivery, or within 36 h following delivery. Screening and recruitment were conducted at 6 Canadian teaching hospitals and 2 teaching hospitals in the United States. Randomization was in permuted blocks of eight, prepared by the trial statistician using random number tables and stratified by centre. Eligible consenting women were randomized via central web randomization by a study coordinator within

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36 h after delivery of the placenta. Participants were equally allocated to 1 of 2 arms: the treatment arm (prophylactic-dose dalteparin 5000 IU administered subcutaneously once daily for 10 days) or the control arm (no treatment).

The primary endpoint of the pilot study was the number of participants randomized per centre per month. Our a priori target was a minimum monthly average recruitment rate of 6 participants per centre. Other indicators of feasibility included: proportion of referred participants who meet eligibility criteria (>20%); proportion of eligible participants who provide consent (>30%); withdrawals/losses to follow-up (<10%); and level of compliance with study drug (>60%). We also measured our primary outcome for the full trial: adjudicated VTE in the early postpartum period, between randomization and the last dose of study drug at 10 days or asymptomatic proximal DVT detected by screening compression ultrasonography of both legs performed within 24 h of the last dose of study drug. Secondary outcomes included late symptomatic VTE (10–90 days post-delivery), death from VTE, major bleeding according to standardized criteria [17], clinically relevant non-major bleeding, and heparin-induced thrombocytopenia. Outcome adjudicators were blinded to the treatment allocation.

The primary analysis was the calculation of an unadjusted mean monthly recruitment rate and the 95% confidence interval of the mean. Sample size was determined based on an assumption that for the full trial we would need to recruit at least 3 women per centre per month in 40 centres; this would then require recruitment over 3 years to complete a 4000 participant trial. The a priori estimate of full trial sample size based on a minimal clinically important difference in primary outcome event rates of 1%, a primary outcome event rate of 3% in the control arm, with 80% power at alpha 0.05. Based on simulation studies, assuming that recruitment rates would follow a Poisson distribution and an observed average recruitment rate of 2.5 per month, with a range from 0.2 to 5.1 in a prior similar study [18], the 4-month pilot would have >80% power to demonstrate that the average monthly recruitment rate was at least 6 women per month.

Following approval by regulatory authorities and institutional research ethics boards, recruitment occurred between November 2012 and November 2013 with trial follow-up concluded by February 2014. Participant flow is illustrated in Fig. 1. In 8 centres, recruiting for a mean of 4.9 months, 2014 women were assessed for eligibility and 1671 were ineligible. A total of 343 were eligible for enrollment (17%), of those 37 (11%) provided consent. A total of 37 participants were randomized over 4.9 months giving a recruitment rate of 0.9 per centre per month.

Of the 306 participants that were eligible, but refused consent: 98 (32.0%) were too overwhelmed or preoccupied in the postpartum period to consider research; 87 (28.4%) declined because they wanted to avoid study injections; 43 women (14.1%) felt the time commitment to participate was too much and 25 (8.2%) did not want to receive study drug. There were 53 women (17.3%) who provided other reasons for not wanting participate, such as: wanting to deliver at home, not wanting additional interventions or generally not interested in research. Of the 37 randomized participants, 16 were allocated to dalteparin and 21 to the control arm. Two participants in the control arm were lost to follow-up with one additional control arm participant refusing to complete the 10-day ultrasound. One participant in the treatment arm refused to complete the 10-day ultrasound appointment. The majority of participants in the treatment arm (69%) had a study drug compliance rate >80%.

Three patients (8.1%) had suspected VTE, though none were adjudicated as VTE. All screening compression ultrasounds were normal.

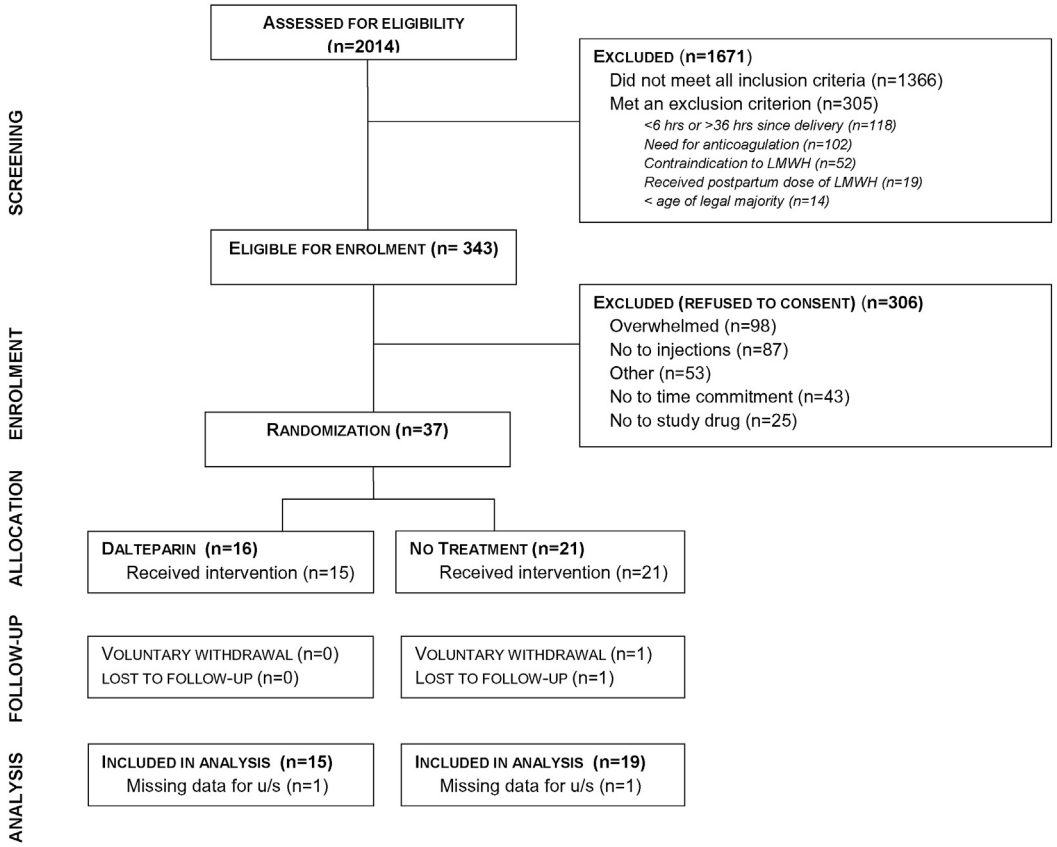

Fig. 1. PROSPER participant flow diagram.