A pilot randomized controlled trial of low molecular weight heparin or no treatment following cesarean delivery

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BACKGROUND

Venous thromboembolism (VTE) contributes to 9% of maternal deaths but we are lacking in evidence-based preventative interventions. Maternal mortality rates in the U.S. exceed those of other developed countries, and excessive national rates have demanded attention from both the academic community and lay public. As a leading contributor, VTE is a prime target for practice changes. The postpartum epoch is the highest risk period for VTE, and national guidelines have called for institutional protocols to categorize risk in postpartum individuals and implement corresponding pharmacologic thromboprophylaxis in an effort to reduce the incidence of postpartum VTE.

Pharmacologic prophylaxis with low molecular weight heparin (LMWH) is effective in reducing VTE peri-operatively in non-obstetric surgical fields. Guidelines recommending the use of LMWH for postpartum populations are based on expert opinion and extrapolate from other surgical fields. The efficacy of LMWH to prevent VTE in obstetrics remains unproven and introduces risk of harm in the form of bleeding and wound complications. While use of LMWH postoperatively is standard of care for most surgical fields, we are uncertain if the same benefits are present for obstetric patients who are generally younger, healthier, and potentially more mobile post-operatively. Experts are split with some calling for more rapid and widespread uptake of prophylaxis in the U.S. while others recommend against widespread uptake of LMWH prophylaxis. The result has been highly variable practice in the U.S. with rates of pharmacologic prophylaxis ranging from 1 to 85%. It is **imperative** that prospective research be performed to understand the efficacy of LMWH prophylaxis for reduction of VTE in postpartum individuals.

Before a large-scale, multicenter, rigorous clinical trial addressing efficacy of postpartum LMWH to prevent VTE can be completed, we must first address ***critical knowledge gaps*** including the feasibility of such a trial and understanding patient perspectives and information needs on the risk-benefit tradeoffs of LMWH prophylaxis versus risk of VTE. A randomized controlled trial (RCT) of postpartum patients at the individual patient level will require thousands of patients to achieve statistical power to detect a difference in rates of VTE by receipt of LMWH prophylaxis versus placebo. There is an **urgent** need to determine whether patients are willing to be randomized to LMWH prophylaxis or placebo, complete the therapy and follow-up. A future trial should also consider patient-centered outcomes. For instance, one patient may only perceive benefit from LMWH prophylaxis if the underlying risk for VTE is greater than 3%, while another patient may favor the potential risks of LMWH prophylaxis even for a VTE risk as low as <1%. Understanding patients' priorities in care and how best to educate patients to enable them to make decisions surrounding VTE prophylaxis is instrumental for future work.

OBJECTIVE / STUDY AIMS

Aim 1. Evaluate the feasibility of randomizing patients to LMWH versus placebo following cesarean delivery. Working hypothesis: Among eligible individuals, at least 35% will enroll, undergo randomization, and complete their allocated treatment.

Aim 2. **Determine information needs, values, and outcome priorities influencing postpartum VTE risk communication**. Working hypothesis: The majority of patients will consider risks of LMWH prophylaxis acceptable if reduction in VTE can be achieved.

METHODS

Specific Aim 1. Evaluate the feasibility of randomizing patients to LMWH versus placebo following cesarean delivery.

Study Design. The proposed research design is a pilot trial of postpartum patients randomized to weight-based LMWH prophylaxis or placebo for VTE prevention. This pilot will test the feasibility of a future large, multicenter RCT.

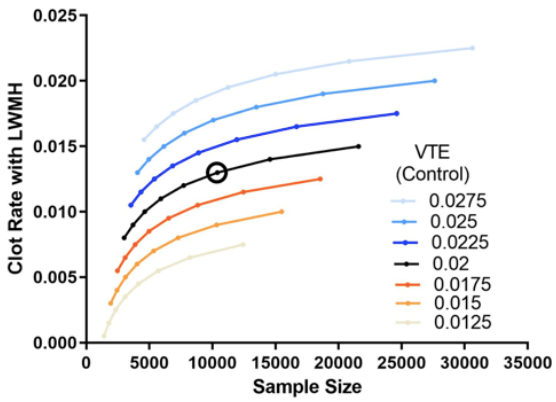
Study Population and Setting. Individuals aged 18 years or older undergoing cesarean delivery at the University of Utah Health will be considered eligible. Exclusion criteria include: contraindication to anticoagulation, plan for therapeutic anticoagulation, renal dysfunction (creatinine clearance <30mL/minute), history of VTE, high risk thrombophilia, or receipt of antepartum anticoagulation (for >2 weeks). Eligible individuals will be approached prior to delivery or within 12 hours postpartum. Informed, written consent will be obtained.

Procedures & Data Collection. Individuals will be randomized to receive either (1) weight-based dosing of LMWH or (2) no therapy after cesarean delivery. Weight-based dosing of LMWH will be 0.5mg/kg rounded to the nearest 10mg every 12 hours based on admission weight. No therapy will be no pharmacologic prophylaxis. Individuals will be randomized in a 1:1 ratio utilizing a permuted block method of randomization with a block size of 6 using REDCap. Participants and clinicians will be unblinded to randomization arm. The intervention, LMWH, will be initiated at 12 hours post-delivery consistent with obstetric anesthesia guidelines. Individuals will receive therapy inpatient and for 14 days following hospital discharge.

The remainder of postpartum care will be per standard institutional practice. Deferral of a dose or discontinuation of therapy early is at the discretion of the clinical care team. All individuals will receive mechanical prophylaxis with sequential compression devices (SCDs) intraoperatively and postoperatively until ambulatory per institutional protocol.

Detailed medical record abstraction will be completed for demographics, medical and obstetric history, delivery outcomes, and postpartum course. Final follow-up and outcomes will be ascertained at 6 weeks postpartum.

Figure 1. Sample size considerations for future multicenter RCT



Outcomes. The primary outcome is feasibility, as defined by ≥35% enrollment of eligible individuals and retention ≥85% of enrolled individuals through all study procedures.[1, 2] Secondary feasibility outcomes will include number of eligible patients per month, enrollment rate (proportion of eligible patients enrolled), and dropout rate. Reasons for enrollment refusal and withdrawal from the study will be elicited and tracked. By design, this pilot trial will not address efficacy or safety outcomes between intervention arms. However, these additional secondary outcomes will be tracked: objectively diagnosed VTE, wound hematoma, or bleeding complication (including readmission or return to the operating room) within 6 weeks postpartum.

Sample Size. The sample size for this pilot was calculated considering available data at UUH with 4,500 deliveries annually with a cesarean delivery rate of 22%. This provides approximately 990 patients anticipated to be eligible over the course of 12 months for the proposed pilot RCT. The sample size also uses statistical power considerations for a future multicenter RCT comparing LMWH to no therapy. Using preliminary data from our institution, an asymptomatic postpartum deep vein thrombosis (DVT) rate is estimated at ~2%. Considering a range of assumptions, 5,195 participants per group for an individual patient RCT would be necessary to detect a 35% reduction in rates of asymptomatic DVT. Modeled across a range of available centers, this trial could be completed in 1-2 years depending on annual enrollment (Figure 1).

To test these assumptions at UUH, an institution anticipated to be enrolling in a future multicenter trial, we determined a sample size of 22 individuals per month enrolled and retained using parameters of 35%

enrollment of eligible individuals and 85% retention through the study procedures would be feasible. We plan for a one-month ramp up and three months of enrollment to assess feasibility.

Statistical Analysis Plan. For all outcomes, the proportion meeting the outcome with 95% confidence interval will be reported. A descriptive summary of reasons for patient refusal to participate or withdrawal will also be reported.

Potential Problems & Alternative Strategies. Some individuals may not want to participate in an RCT of LMWH versus no therapy, or may have stated preferences for one study arm. These perspectives are valuable to inform future trial modifications and determine enrollment feasibility. There are approximately 4,500 deliveries annually at UUH with an institutional cesarean rate of approximately 22%. This will provide ample sample size to complete the feasibility pilot.

Safety Monitoring. There is equipoise for a comparative trial between LMWH prophylaxis and no therapy. However, safety concerns may arise during the course of this pilot trial. Adverse events (AEs) and serious adverse events (SAEs) will be submitted to the institutional review board (IRB) and monitored through a data safety monitoring board (DSMB).

Specific Aim 2. Determine information needs, values, and outcome priorities influencing postpartum VTE risk communication.

Study Design. We will complete semi-structured interviews of patients to collect data on patient information needs and values about VTE risk communication, preventative interventions such as LMWH, and patient priorities related to risks of VTE versus preventative interventions. Interviews of obstetric providers will explore barriers to counseling on VTE risk and interventions.

Study Population and Setting. Patients meeting inclusion/exclusion criteria for the pilot trial (*see Specific Aim 1*) will be eligible for participation. Recruitment will be inpatient after delivery or from the UUH outpatient obstetric clinics at the time of postpartum clinic visit. Obstetric providers, including physicians and advanced practice clinicians (e.g., nurse midwives, nurse practitioners), at UUH will be asked to participate via departmental meetings and e-mail.

Procedures & Data Collection. All interviews will be conducted, in-person or virtual, by trained personnel. Written informed consent will be obtained prior to interviews. Patients will be interviewed 6-12 weeks after delivery. Obstetric providers will be interviewed over the course of the grant period. These facilitated interviews will last 60 minutes. Interviews will assess perspectives on: (1) patient information needs on VTE risk; (2) values around interventions; (3) outcome priorities for decision-making around risks of VTE versus risks of preventative interventions such as LMWH. These will also assess barriers and facilitators to communication that may be incorporated into future decision-aids or clinical practice. Interviews will be audio recorded and transcribed.

Detailed medical record abstraction will be completed for demographics, medical and obstetric history, delivery outcomes, and postpartum course for included patients. Measured characteristics of obstetric providers will include self-reported age, race, ethnicity, gender identity, years in practice, provider type, and provider services.

Outcomes. The outcome of this aim will be qualitative data that will inform future development of patient and provider education tools to aid in decision-making around VTE prevention.

Sample Size. We anticipate completing 15 semi-structured patient interviews and 10 semi-structured obstetric provider interviews. This sample size was selected based on available literature informing anticipated thematic saturation.

Statistical Analysis Plan. The transcribed interviews will be imported into a qualitative analytics software program. Qualitative data analysis will be completed following a standardized coding framework to identify common themes, as previously used by Dr. Rothwell's group.[3-5] In brief, an initial coding template will be defined, each transcript will be coded to identify recurrent and new themes, and coding frequency will be summarized.

Potential Problems & Alternative Strategies. There may be inadequate patient recruitment for interviews. However, based on the estimated population sample available for enrollment (*see Specific Aim 1*), relatively small sample size needed, and UUH record of high recruitment and retention, we anticipate adequate sample size will be achieved. Patient incentivization with gift cards may be added if recruitment is lower than expected.

There are over 75 obstetric providers eligible for recruitment through UUH. Using direct solicitation, which has been found to be an effective method for clinician recruitment, we anticipate achieving the necessary provider sample size.