Title of Study: Heparin Prophylaxis Dosing for Antepartum Hospitalizations (HEPDOSE)

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LIST OF ABBREVIATIONS

AE	adverse event
aPTT	activated partial thromboplastin time
CFR	Code of Federal Regulations
CRF	case report form
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act of 1996
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
PI	Principal Investigator
SAE	serious adverse experience
VTE	venous thromboembolism
ACOG	American College of Obstetricians and Gynecologists
NPMS	National Partnership for Maternal Safety

PROTOCOL SYNOPSIS

TITLE	Randomized Control Trial of Unfractionated Heparin Dosing for Thromboprophylaxis of Hospitalized Antepartum Patients
SPONSOR	Rashmi Rao, MD
FUNDING ORGANIZATION	N/A
NUMBER OF SITES	1
RATIONALE	VTE is one of the leading causes of maternal morbidity and mortality, and antepartum hospitalizations place pregnant patients at an even higher risk of developing thromboembolism. As a result, there is an increased emphasis on administering pharmacologic thromboprophylaxis for antepartum patients with prolonged hospitalizations. Previously, standard dosing of unfractionated heparin was widely adopted for thromboprophylaxis in the pregnant population. However, due to a suspected altered metabolism of unfractionated heparin in pregnancy resulting in a decrease response, the American College of Obstetricians and Gynecologists (ACOG) and National Partnership for Maternal Safety (NPMS) currently recommends considering gestational age-based dosing for unfractionated heparin for thromboprophylaxis in pregnancy with standard dosing as an alternative option. The data supporting altered dosing is very limited. In addition, increased dosing of heparin may result in challenges in anesthetic management, potentially limiting the receipt of neuraxial anesthesia resulting in increased need for general anesthesia associated with both increased maternal and fetal risks. The potential effects of higher prophylactic unfractionated heparin dosing in pregnant patients need to be further explored before being widely adopted for inpatient antepartum thromboprophylaxis. We propose this study to provide a direct comparison of gestational age-based unfractionated heparin dosing to standard dosing of unfractionated heparin for pharmacologic thromboprophylaxis of hospitalized antepartum patients.
STUDY DESIGN	This is a single center, open label, randomized control trial.
PRIMARY OBJECTIVE	Compare gestational age-based dosing to standard dosing of unfractionated heparin for thromboprophylaxis of pregnant patients with prolonged hospitalizations and determine its effect on receipt of neuraxial anesthesia and pregnancy outcomes.
SECONDARY OBJECTIVES	Evaluate pharmacokinetics and pharmacodynamics of unfractionated heparin in pregnancy.

	a) Determine the frequency of adjusted unfractionated heparin dosing based on elevated activated partial thromboplastin time (aPTT) values and assess maternal characteristics associated with elevated aPTT values. b) Determine the appropriate dosing of unfractionated heparin for pharmacologic thromboprophylaxis of hospitalized antepartum patients.
NUMBER OF SUBJECTS	46
SUBJECT SELECTION CRITERIA	Inclusion Criteria: • At least 18 years of age • Speak English or Spanish • Antepartum admission for at least 72 hours at Ronald Reagan UCLA Medical Center • Provides informed consent for study participation Exclusion Criteria: • Active or threatened antenatal bleeding • Disseminated intravascular coagulation • Risk of imminent delivery (delivery within 12 hours) • Thrombocytopenia (platelet count < 100 x 10^9) • Elevated baseline aPTT (> 36.2 seconds) • Concern for hemolysis, elevated liver enzymes, low platelet count (HELLP) syndrome • Congenital bleeding disorders (hemophilias) • Receiving therapeutic or prophylactic anticoagulation (unfractionated heparin, low molecular weight heparin, oral anticoagulants) for alternative indication (e.g., acquired or inherited thrombophilia, history of VTE) • History of heparin-induced thrombocytopenia (HIT) • SARS-CoV-2 positive • Cognitive impairment, psychiatric instability, or language barriers that limit their ability to provide informed consent • Presence of a condition or abnormality that in the opinion of the Investigator would compromise the safety of the patient or the quality of the data.
TEST PRODUCT, DOSE, AND ROUTE OF ADMINISTRATION	Gestational age-based unfractionated heparin dosing: First trimester (≤ 13w6d): 5,000 units subcutaneous unfractionated heparin every 12 hours

	Second trimester (14w0d – 27w6d): 7,500 units subcutaneous unfractionated heparin every 12 hours Third trimester (≥ 28w0d): 10,000 units subcutaneous unfractionated heparin every 12 hours Duration: throughout hospitalization (until discharge or delivery)
CONTROL PRODUCT, DOSE AND ROUTE OF ADMINISTRATION	Standard unfractionated heparin dosing (comparator): 5,000 units subcutaneous unfractionated heparin every 12 hours Duration: throughout hospitalization (until discharge or delivery)
DURATION OF SUBJECT PARTICIPATION AND DURATION OF STUDY	Subjects will be on study for the duration of their inpatient admission. The total duration of the study is expected to be approximately 18 months (16 months for subject recruitment and 2 months for final subject follow-up).
CONCOMMITANT MEDICATIONS	Allowed: All except for prohibited medications (listed below) Prohibited: low molecular weight heparin, warfarin, oral anticoagulants
PRIMARY ENDPOINT	Elevated serum aPTT value above the normal range (> 36.2 seconds)
SECONDARY ENDPOINTS	• Diagnosis of venous thromboembolism (pulmonary embolism and/or deep venous thromboembolism) • Nonreceipt or delay of neuraxial anesthesia due to unfractionated heparin defined as inability to receive neuraxial anesthesia due to an elevated aPTT value or because the subject received heparin • Receipt of general anesthesia due to unfractionated heparin • Delay in timing of delivery due to unfractionated heparin defined as presence of an indication to proceed with delivery via cesarean delivery or induction of labor but this does not immediately occur due to an elevated aPTT value or because the subject received heparin • Mode of delivery • Estimated blood loss at time of delivery • Receipt of blood transfusion • CBC for hemoglobin and platelet count (to be assessed weekly while receiving unfractionated heparin) • Anti-Xa levels (to be assessed with aPTTs while receiving unfractionated heparin) • Goal anti-Xa level achieved (0.2-0.5 IU/mL) • Number of times adjustment in dose made • Development of side effects from heparin administration (e.g bruising, epistaxis) • Neonatal outcomes

	○ Gestational age at delivery ○ Birthweight ○ 1 minute and 5 minute APGAR scores ○ Cord blood gas values: umbilical artery pH, umbilical artery CO2, umbilical artery base excess ○ NICU admission ○ Neonatal death
SAFETY EVALUATIONS	• Incidence of adverse events
STATISTICS **Primary Analysis Plan**	Analysis of the primary endpoint of whether or not there was an elevation in aPTT in each dosing group will be performed with a Chi-squared test. Multivariate logistic regression analysis will be performed to determine which factors were associated with an elevated aPTT value. Comparison of maternal demographics, baseline characteristics, additional maternal outcomes, and neonatal outcomes between the two groups will be analyzed using Student's t-test for parametric data, Wilcoxon signed-rank test for nonparametric data, and Chi-squared or Fisher's exact test for comparison of proportions. Descriptive statistics will be performed to summarize which dose resulted in a normal aPTT value and anti-Xa within goal range. Statistical significance will be set at a p-value of < 0.05 or 95% confidence interval not overlapping.
Rationale for Number of Subjects	Assuming 40% of patients receiving gestational age-based dosing and 3% receiving standard dosing have an elevated aPTT value, a sample size of 36 women (18 in each arm) would have 80% power to demonstrate a significant difference between the proportion of women with elevated aPTT values after administration. We plan to recruit 46 (23 in each arm) to account for post-randomization drop out and lab sampling errors.

1 BACKGROUND

1.1 Overview of Non-Clinical and Clinical Studies

Venous thromboembolism (VTE) is one of the leading causes of maternal morbidity and mortality, accounting for 14.9% of maternal deaths in developed countries and 9.3% of maternal deaths in the United States according to the World Health Organization's systematic review of maternal mortality.[1] Antepartum hospitalizations may place pregnant patients at an even higher risk of developing a thromboembolism. A study in England found that the risk of VTE was 17.5-fold higher when patients were hospitalized compared with outpatient with the risk significantly higher for patients hospitalized 3 days or longer.[2] As a result, there has been an increased emphasis on considering pharmacologic thromboprophylaxis for antepartum patients with prolonged hospitalizations.

However, the recommendations on administration of pharmacologic prophylaxis in pregnancy from different societies vary.[3-7] Administration of routine pharmacologic prophylaxis has demonstrated a significant decrease in maternal mortality in the United Kingdom attributed to VTE.[8] The National Partnership for Maternal Safety (NPMS) compiled recommendations from societies and reviewed the available evidence to develop a thromboembolism safety bundle with the aims of decreasing VTE in pregnancy and improving maternal outcomes. One of these recommendations is that pharmacologic thromboprophylaxis should be given to all antepartum patients hospitalized for at least 72 hours and not at high risk for bleeding or imminent childbirth.[9]

The American College of Obstetricians and Gynecologists (ACOG) states that the preferred anticoagulant for pregnancy are heparin compounds, including unfractionated heparin and low molecular weight heparin.[6] Heparin compounds do not cross the placenta and are considered safe in pregnancy.[10-12] It is agreed upon that heparin compounds are considered first line therapy for anticoagulation in pregnancy. However, multiple physiological changes of pregnancy, including expansion of maternal blood volume, higher renal excretion of heparin, and increased non-specific binding proteins, alter the metabolism of unfractionated heparin in pregnant patients compared to nonpregnant patients.[13,14] There is limited data on heparin dosing in pregnancy for thromboembolic prophylaxis. A single study of fourteen pregnant patients on heparin prophylaxis for a history of thromboembolism demonstrated that the standard heparin dose of 5,000 units administered subcutaneously (SC) twice daily was inadequate to achieve the desired anti-Xa level range in all patients.[15] Although data is limited, responses to heparin in pregnant patients are highly variable and there is a suspected need for higher dosing with increasing gestational age.

Standard dosing of unfractionated heparin of 10,000-15,000 units daily (5,000 units SC every 8-12 hours) has been demonstrated to be effective for thromboprophylaxis in the surgical population.[16] This dosing is recommended by the American College of Chest Physicians and widely accepted in the nonpregnant population.[17] Previously, standard dosing of unfractionated heparin was also adopted for use in the pregnant population. However, ACOG and the NPMS now recommends considering gestational age-based dosing for unfractionated heparin for thromboprophylaxis in pregnancy (5,000-7,500 units SC every 12 hours in the first trimester, 7,500-10,000 units SC every 12 hours in the second trimester, and 10,000 units SC every 12

hours in the third trimester) with standard dosing of 5,000 units SC every 12 hours as an alternative option for hospitalized patients that may require delivery to facilitate receipt of neuraxial anesthesia.[6, 18]

Increasing dosing of heparin for thromboprophylaxis presents challenges in anesthetic management. Various anesthesia professional organizations have provided recommendations on when to proceed with neuraxial anesthesia for a patient on pharmacologic thromboprophylaxis, based on dose and time of administration and pertinent laboratory values such as activated partial thromboplastin time (aPTT).[19-22] At our institution, neuraxial anesthesia can be offered at anytime if a patient is receiving 5,000 units SC every 12 hours, but if the patient is receiving 7,500 units-10,000 units SC every 12 hours then the anesthesiologists require at least a 6-12 hour interval with an aPTT value in the normal range ($\leq$ 36.2 seconds) to consider neuraxial anesthesia.

In an effort to decrease incidence of VTE and associated maternal morbidity and mortality, our institution has adopted the recommendations for pharmacologic thromboprophylaxis for all inpatient antepartum admissions over 72 hours and utilized ACOG's gestational age-based dosing for unfractionated heparin. An informal/pilot review of 30 antepartum admissions receiving trimester based dosing of unfractionated heparin for VTE prophylaxis demonstrated that 40% of the patients had an abnormally elevated aPTT value with two patients being in the therapeutic range. One patient was unable to receive an epidural in active labor and one patient had a delay in her cesarean delivery due to receiving heparin prophylaxis within the 6 hour interval. Although increased administration pharmacologic prophylaxis is associated with a decreased risk of VTE, our preliminary data demonstrates that the trimester based dosing of unfractionated heparin may lead to elevated aPTT values, potentially limiting the receipt of neuraxial anesthesia. This may then lead to an increased need for general anesthesia associated with both increased maternal and fetal risks.

To the best of our knowledge, there have been no prior studies comparing standard dosing with gestational age-based dosing of unfractionated heparin for VTE prophylaxis. The potential effects of higher prophylactic unfractionated heparin dosing need to be further explored before being widely adopted for inpatient antepartum thromboprophylaxis.

2 STUDY RATIONALE

VTE is one of the leading causes of maternal morbidity and mortality. In efforts to decrease rates of VTE, there is an increased emphasis on administering pharmacologic thromboprophylaxis for antepartum patients with prolonged hospitalizations. Due to physiological changes of pregnancy that may alter the metabolism of unfractionated heparin, it is suspected that dosing of pharmacologic thromboprophylaxis may need to be altered. ACOG's current recommendation is to consider gestational age-based dosing of unfractionated heparin for hospitalized pregnant patients rather than standard dosing. However, there are no prior studies assessing the potential effects of higher dosing. Potential effects of higher dosing include limited receipt of neuraxial anesthesia, increased administration of general anesthesia, delayed time to delivery, and increased bleeding risk. We propose this study to provide a direct comparison of gestational age-based unfractionated heparin dosing to standard dosing of unfractionated heparin for pharmacologic thromboprophylaxis of hospitalized antepartum patients.

For our primary objective, we hypothesize that compared to standard dosing, gestational age-based dosing for VTE prophylaxis is associated with higher rates of elevated aPTT values, a surrogate marker of ineligibility for neuraxial anesthesia. For our additional exploratory objectives, we hypothesize that there will be no significant difference in achieving goal anti-Xa levels (0.2-0.5 IU/mL) between standard dosing and gestational age-based dosing and that particular characteristics (e.g., increased eGFR and higher BMI) are associated with elevated aPTT values with unfractionated heparin administration.

ACOG Practice Bulletin No.123. Thromboembolism in Pregnancy. Obstet Gynecol 2011;118:718-729.

Table 2. Anticoagulation Regimen Definitions

Anticoagulation Regimen	Anticoagulation Dosage
Prophylactic LMWH*	Enoxaparin, 40 mg SC once daily
	Dalteparin, 5,000 units SC once daily
	Tinzaparin, 4,500 units SC once daily
	Nadroparin, 2,850 units SC once daily
Intermediate-dose LMWH	Enoxaparin, 40 mg SC every 12 hours
	Dalteparin, 5,000 units SC every 12 hours
Adjusted-dose (therapeutic) LMWH†	Enoxaparin, 1 mg/kg every 12 hours
	Dalteparin, 200 units/kg once daily
	Tinzaparin, 175 units/kg once daily
	Dalteparin, 100 units/kg every 12 hours
	Target an anti-Xa level in the therapeutic range of 0.6–1.0 units/mL 4 hours after last injection for twice-daily regimen; slightly higher doses may be needed for a once-daily regimen.
Prophylactic UFH	UFH, 5,000–7,500 units SC every 12 hours in first trimester
	UFH, 7,500–10,000 units SC every 12 hours in the second trimester
	UFH, 10,000 units SC every 12 hours in the third trimester, unless the aPTT is elevated
Adjusted-dose (therapeutic) UFH†	UFH, 10,000 units or more SC every 12 hours in doses adjusted to target aPTT in the therapeutic range (1.5–2.5 × control) 6 hours after injection
Postpartum anticoagulation	Prophylactic, intermediate, or adjusted dose LMWH for 6–8 weeks as indicated. Oral anticoagulants may be considered postpartum based upon planned duration of therapy, lactation, and patient preference.
Surveillance	Clinical vigilance and appropriate objective investigation of women with symptoms suspicious of deep vein thrombosis or pulmonary embolism. VTE risk assessment should be performed prepregnancy or early in pregnancy and repeated if complications develop, particularly those necessitating hospitalization or prolonged immobility.

Abbreviations: aPTT, activated partial thromboplastin time; INR, international normalized ratio; LMWH, low-molecular-weight heparin; SC, subcutaneously; UFH, unfractionated heparin; VTE, venous thromboembolism.

*Although at extremes of body weight, modification of dose may be required.

†Also referred to as weight adjusted, full treatment dose.

Friedman AM, D'Alton ME. Venous thromboembolism bundle: Risk assessment and prophylaxis for obstetric patients. Semin Perinatol 2016; 40: 87-92.

Prophylactic Dosing

Agent	Enoxaparin	Dalteparin	Tinzaparin	Unfractionated heparin	
Weight based				*Gestational age-based*	
<50kg	*20mg daily*	*2500 units daily*	*3500 units daily*	*First trimester*	*5000-7500 units twice daily*
50-90kg	*40mg daily*	*5000 units daily*	*4500 units daily*	*Second trimester*	*7500-10000 units twice daily*
91-130kg	*60mg daily**	*7500 units daily**	*7000 units daily**	*Third trimester*	*10000 units twice daily*
131-170kg	*80mg daily**	*10000 units daily**	*9000 units daily*	*Postpartum*	*5000 units twice daily*
>170kg	*0.6mg/kg/day**	*75 units/kg/day*	*75 units/kg/day*		

Hospitalized antepartum patients may receive 5000 units UFH twice daily for prophylaxis to facilitate regional anesthesia

* May be administered in divided doses

2.1 Risk / Benefit Assessment

Like all medications, unfractionated heparin has the potential to cause side effects. The most common side effects are bleeding or bruising and redness and swelling around the puncture site. Rare side effects include hypersensitivity to the medication (hives, fever, swelling of throat, difficulty breathing) and thrombocytopenia. If significant side effects occur, the medication will be discontinued. Unfractionated heparin does not cross the placenta and is considered safe in pregnancy without any increased risk of fetal malformations. Subjects would receive unfractionated heparin outside of a research context as part of standard hospital protocol for pharmacologic thromboprophylaxis. As a result, participation in this study does not pose increased risk in exposure to unfractionated heparin.

Currently, ACOG and NPMS recommend both gestational age-based or standard unfractionated heparin dosing to be considered as standard of care for pharmacologic thromboprophylaxis of hospitalized antepartum patients. Because standard dosing is lower than gestational age-based dosing, there is a theoretical risk that this lower dose may not provide adequate prophylaxis against thrombosis/thromboembolism. However, the absolute risk of venous thrombembolism development in hospitalized pregnant patients is low (less than 2%) and standard unfractionated heparin dosing has demonstrated efficacy and safety in the general, urologic, and orthopedic surgery. Higher gestational age-based dosing may lead to restrictions in receipt of neuraxial anesthesia. However, we will be monitoring closely with serial aPTTs and alternating dosing in response to these results in order to mitigate this risk for subjects randomized to this dosing arm. If not within the study, eligible subjects will receive higher gestational age-based dosing per current standard hospital protocol, so subjects randomized to gestational age-based dosing will not be at increased risk.

Blood draws are associated with side effects, including temporary discomfort from the needle stick, bruising, and rarely, infection and fainting. All antepartum patients who receive unfractionated heparin will undergo serial lab draws as part of standard of care at our institution to ensure safety of the medication. Therefore, the risks of blood draw are not significantly increased by participation within the study.

Because the subjects will be randomized into a study arm, there are risks associated with randomization. The subject will be assigned to a study group by chance (like a coin flip) rather

than a medical decision made by the researchers. The study group the subject is assigned to might not be the group they would prefer to be in. It might also prove to be less effective or have more side effects than the other study group, or standard treatments available for the condition.

Because information will be collected from each subject's medical record, there is a possibility of a breach of confidentiality. However, all precautionary measures will be taken to ensure that confidentiality and privacy are maintained, and that data is stored securely. All conversations with subjects will occur in a private setting. All data will be de-identified and coded. A code will be kept, but it will be kept on a password protected file separate from the data. All clinical data will be entered in REDCap, a secure web-based data management system provided by the Clinical Translational Science Institute at UCLA that only the research team will have access to. Analysis will be carried out utilizing only the study code numbers. Analyzed information will be stored on a password-protected computer with encrypted storage media. All informed consents/assents will be stored in PI's office, which is only accessible with a key by the study team, in a locked cabinet in accordance with local IRB guidelines.

As for benefits, subjects randomized to the gestational-age based dosing arm may not directly benefit from participating in this study. However, information from this study will improve the understanding of dosing of unfractionated heparin for pharmacologic VTE prophylaxis. This would benefit future pregnant patients. For subjects randomized to the standard dosing arm, there is potential that the standard dose demonstrates adequate thromboprophylaxis without an increased risk of bleeding or restrictions on neuraxial anesthesia. Subjects randomized to this standard dosing arm would receive direct benefit in receiving this dose.

The risks involved with participation, specifically exposure to unfractionated heparin and blood draws, are not significantly higher than antepartum patients that elect to not participate in the study because antepartum patients receive gestational age-based dosing of unfractionated heparin with serial lab measurements as part of standard of care at our institution. Subjects randomized to the standard dosing arm encounter the theoretical risk of the lower dose providing inadequate prophylaxis against thrombosis/thromboembolism. However, this absolute risk is low (less than 2%), and subjects randomized to the standard dosing arm may receive direct benefit from the study if the lower dose demonstrate adequate efficacy with an improved safety profile. Overall, the risks of participation are limited, some subjects may receive direct benefit, and this study would provide valuable information to improve the understanding of dosing of unfractionated heparin for pharmacologic VTE prophylaxis. As a result, the risk/benefit ratio is favorable.

3 STUDY OBJECTIVES

3.1 Primary Objective

The primary objective is to compare gestational age-based dosing to standard dosing of unfractionated heparin for thromboprophylaxis of pregnant patients with prolonged hospitalizations and determine its effect on receipt of neuraxial anesthesia and pregnancy outcomes.

3.2 Secondary Objectives

The secondary objective of this study is to evaluate pharmacokinetics and pharmacodynamics of unfractionated heparin in pregnancy.

a) Determine the frequency of adjusted unfractionated heparin dosing based on elevated aPTT values and assess maternal characteristics associated with elevated aPTT values.
b) Determine the appropriate dosing of unfractionated heparin for pharmacologic thromboprophylaxis of hospitalized antepartum patients (anti-Xa levels within prophylactic goal grange, normal aPTT).

4 STUDY DESIGN

4.1 Study Overview

This is a single center, open-label, non-placebo-controlled, randomized trial of gestational age-based dosing and standard dosing of unfractionated heparin for pharmacologic thromboprophylaxis of antepartum patients hospitalized for at least 72 hours. 46 (23 in arm 1 and 23 in arm 2) subjects are planned.

Screening data will be reviewed to determine subject eligibility. Subjects who meet all inclusion criteria and none of the exclusion criteria will be recruited for the study. Each subject will be assigned to receive one of two dosing of unfractionated heparin. Subjects will be assigned to the doses in random order.
The following treatment regimens will be used:

- ARM 1 (Control Arm)
    - Standard dosing: 5,000 units subcutaneous unfractionated heparin every 12 hours
- ARM 2
    - Gestational age-based dosing:
        - 1st trimester (< 14 weeks of gestation): 5,000 units subcutaneous unfractionated heparin every 12 hours
        - 2nd trimester (14-28 weeks of gestation): 7,500 units subcutaneous unfractionated heparin every 12 hours
        - 3rd trimester (≥ 28 weeks of gestation): 10,000 units subcutaneous unfractionated heparin every 12 hours

Patients will receive serial lab measurements after 2nd dose, 4th dose, 10th dose, and then weekly to monitor. Dosing will be adjusted based on aPTT values (APPENDIX 1).

Total duration of subject participation will be throughout the patient's inpatient hospitalization until they undergo delivery or discharge. Total duration of the study is anticipated to be approximately 18 months.

5 CRITERIA FOR EVALUATION

5.1 Primary Efficacy Endpoint

- Elevated serum aPTT value above the normal range (> 36.2 seconds). Prophylactic dosing of anticoagulation should not cause elevations in coagulation parameters.
    - To be assessed after 2nd dose, 4th dose, and then weekly while receiving unfractionated heparin
    - Surrogate marker for whether or not the patient would be eligible for neuraxial anesthesia based on guidelines for neuraxial anesthesia in pregnant women receiving VTE prophylaxis

- American Society for Regional Anesthesia (ASRA)
    - 5,000 units every 12 hours – normal aPTT value or 4 hours since last dose
    - 7,500 – 10,000 units every 12 hours – normal aPTT value and 12 ours since last dose
- Society of Obstetric Anesthesia and Perinatology
    - 5,000 units every 12 hours – always eligible for neuraxial anesthesia
    - 7,500 – 10,000 units every 12 hours – normal aPTT value or 12 hours since last dose

5.2 Secondary Efficacy Endpoints

- Diagnosis of venous thromboembolism (pulmonary embolism and/or deep venous thromboembolism)
- Nonreceipt or delay of neuraxial anesthesia due to unfractionated heparin defined as inability to receive neuraxial anesthesia due to an elevated aPTT value or because the subject received heparin
- Receipt of general anesthesia due to unfractionated heparin
- Delay in timing of delivery due to unfractionated heparin defined as presence of an indication to proceed with delivery via cesarean delivery or induction of labor but this does not immediately occur due to an elevated aPTT value or because the subject received heparin
- Mode of delivery
- Estimated blood loss at time of delivery
- Receipt of blood transfusion
- CBC for hemoglobin and platelet count (to be assessed weekly while receiving unfractionated heparin)
- Anti-Xa levels (to be assessed with aPTTs while receiving unfractionated heparin)
- Goal anti-Xa level achieved (0.2-0.5 IU/mL)
- Number of times adjustment in dose made
- Development of side effects from heparin administration (e.g bruising, epistaxis)
- Neonatal outcomes
    - Gestational age at delivery
    - Birthweight
    - 1 minute and 5 minute APGAR scores
    - Cord blood gas values: umbilical artery pH, umbilical artery CO2, umbilical artery base excess
    - NICU admission
    - Neonatal death

6 SUBJECT SELECTION

6.1 Study Population

Subjects that are pregnant and undergoing antepartum admission for at least 72 hours who meet the inclusion and exclusion criteria will be eligible for participation in this study.

6.2 Inclusion Criteria

1. Female ≥ 18 years of age at Visit X.
2. Antepartum admission for at least 72 hours at Ronald Reagan UCLA Medical Center
3. Speaks English or Spanish
4. Written informed consent (and assent when applicable) obtained from subject or subject's legal representative and ability for subject to comply with the requirements of the study.

6.3 Exclusion Criteria

1. Active or threatened antenatal bleeding
2. Risk of imminent delivery (delivery within 12 hours)
3. Disseminated intravascular coagulation
4. Thrombocytopenia (platelet count < 100 x 10^9)
5. Elevated baseline aPTT (> 36.2 seconds)
6. Concern for hemolysis, elevated liver enzymes, low platelet count (HELLP) syndrome
7. Congenital bleeding disorders (e.g., hemophilias)
8. Receiving therapeutic or prophylactic anticoagulation (unfractionated heparin, low molecular weight heparin, oral anticoagulants) for alternative indications (e.g., acquired or inherited thrombophilia, history of VTE)
9. History of heparin-induced thrombocytopenia (HIT)
10. SARS-CoV-2 positive
11. Cognitive impairment, psychiatric instability, or language barriers that limit their ability to provide informed consent
12. Presence of a condition or abnormality that in the opinion of the Investigator would compromise the safety of the patient or the quality of the data.

7 CONCURRENT MEDICATIONS

7.1 Allowed Medications and Treatments

Standard therapy provided in pregnancy is allowed except for treatments noted in the exclusion criteria described above and as noted in the prohibited medications section below.

Prohibited Medications and Treatments

The following medications are prohibited during the study and administration will be considered a protocol violation.

- Low molecular weight heparin
- Oral anticoagulants

8 STUDY TREATMENTS

8.1 Method of Assigning Subjects to Treatment Groups

46 eligible patients will be randomly assigned to standard dosing of unfractionated heparin or gestational age-based dosing of unfractionated heparin in a 1:1 ratio. They will immediately be allocated to their designated arm and this will be documented in their prenatal record. The medical team will be notified of the patient's designated arm and then place the order for unfractionated heparin.

8.2 Blinding

Due to the objectives of the study, the identity of dosing will be known to investigators, medical providers, and patients. This study is non-blinded.

8.3 Formulation of Test and Control Products

The drug product to be studied is unfractionated heparin, which is a previously standardized medication. Formulation will be per UCLA pharmacy.

8.3.1 Formulation of Test Product

The tested product will be two variations in dosing of unfractionated heparin. Formulation and dispensing of medication will be per UCLA pharmacy after the appropriate order with assigned dosing is placed by the medical team.

8.3.2 Formulation of Control Product

No control product will be provided.

8.3.3 Packaging and Labeling

Not applicable.

8.4 Supply of Study Drug at the Site

Unfractionated heparin will be provided by the UCLA pharmacy.

8.4.1 Dosage/Dosage Regimen

ARM 1: Standard dosing

- Dose: 5,000 units unfractionated heparin subcutaneous injection every 12 hours
- Decrease in dosing will be made for elevated aPTT > 36.2 seconds (APPENDIX 1)

ARM 2: Gestational age-based dosing

- Dose:
    - If less than 14 weeks of gestation - 5,000 units unfractionated heparin subcutaneous injection every 12 hours
    - If 14 weeks of gestation to 27 and 6 weeks of gestation – 7,500 units unfractionated heparin subcutaneous injection every 12 hours
    - If greater than or equal to 28 weeks of gestation – 10,000 units unfractionated heparin subcutaneous injection every 12 hours

- Decrease in dosing will be made for elevated aPTT > 36.2 seconds (APPENDIX 1)

8.4.2 Dispensing

The pharmacist will dispense the drug.

8.4.3 Administration Instructions

The assigned inpatient nurse caring for the patient will administer the drug.

8.5 Supply of Study Drug at the Site

Not applicable since this is not a study drug.

8.5.1 Storage

Unfractionated heparin will be stored in the pharmacy per UCLA pharmacy protocol.

8.6 Study Drug Accountability

Not applicable since this is not a study drug.

8.7 Measures of Treatment Compliance

Treatment compliance will be ensured through study staff's evaluation of the patient's medication administration record (MAR) in the medical chart. This provides information on dose provided and time of administration.

9 STUDY PROCEDURES AND GUIDELINES

A Schedule of Events representing the required testing procedures and adjustments in dosing of medications to be performed for the duration of the study is diagrammed in Appendix 1.

Prior to conducting any study-related activities, written informed consent and the Health Insurance Portability and Accountability Act (HIPAA) authorization must be signed and dated by the subject or subject's legal representative. If appropriate, assent must also be obtained prior to conducting any study-related activities.

9.1 Clinical Assessments

9.1.1 Concomitant Medications

All concomitant medication and concurrent therapies will be documented at screening. Dose, route, unit frequency of administration, and indication for administration and dates of medication will be captured.

9.1.2 Demographics

Demographic information (date of birth, gender, race) will be recorded at screening.

9.1.3 Medical History

Relevant medical history, including history of current disease, other pertinent respiratory history, and information regarding underlying diseases will be recorded at screening.

9.1.4 Physical Examination

A complete physical examination will be performed by the medical team, which consists of a physician at UCLA Medical Center, on admission to the hospital. This physical exam will be documented in the medical chart. The medical team (MD, RN) will perform physical exams daily per hospital protocol and monitor for development of side effects (e.g., bruising, rash, epistaxis). New abnormal physical exam findings must be documented and will be followed by a physician once reported.

9.1.5 Vital Signs

Body temperature, blood pressure, pulse and respirations will be performed after resting for 5 minutes at least once daily as part of the patient's hospitalization.

9.1.6 Adverse Events

Information regarding occurrence of adverse events will be captured throughout the study. Duration (start and stop dates and times), outcome, treatment and relation to study drug will be recorded on the case report form (CRF).

9.2 Clinical Laboratory Measurements

9.2.1 Hematology

Blood will be obtained and sent to to the clinical hematology lab for a complete blood count (hemoglobin, hematocrit, red blood cell count, white blood cell count, white blood cell differential, and platelet count), activated partial thromboplastin time (aPTT), and anti-Xa levels.

9.2.2 Blood Chemistry Profile

Blood will be obtained and sent to each clinical chemistry lab for determination of creatinine.

10 EVALUATIONS BY VISIT

REFER TO APPENDIX 2

10.1 Visit 1: Day 1

1. Review the study with the subject (subject's legal representative) and obtain written informed consent and HIPAA authorization and assent, if appropriate.
2. Assign the subject a unique screening number.
3. Record demographics data.
4. Record medical and surgical history
5. Record concomitant medications.
6. Collect blood for clinical laboratory tests (CBC, aPTT, anti-Xa, serum creatinine).
7. Randomize subject
8. Order unfractionated heparin dosing that subject is randomized to (first dose ordered for 21:00 PM the day patient is randomized)

10.2 Visit 2: Day 2

1. Record any Adverse Experiences
2. Record times when patient received unfractionated heparin or noncompliance to medication
3. Collect blood for aPTT and anti-Xa 6 hours after second dose of heparin (~15:00 PM on day 2)
4. Follow-up aPTT
   a. If < 36.2 seconds, continue current dose of heparin
   b. If ≥ 36.2 seconds, adjust heparin dose and repeat aPTT, anti-Xa, and serum creatinine per protocol (APPENDIX 1)

10.3 Visit 3: Day 3

1. Record any Adverse Experiences
2. Record times when patient received unfractionated heparin or had noncompliance to medication
3. Collect aPTT and anti-Xa 2 hours after fourth dose of heparin (~11:00 AM on day 3)
4. Collect aPTT and anti-Xa 6 hours after fourth dose of heparin (~15:00 PM on day 3)
5. Follow-up aPTT
   a. If < 36.2 seconds, continue current dose of heparin
   b. If ≥ 36.2 seconds, adjust heparin dose and repeat aPTT and anti-Xa per protocol (APPENDIX 1)

10.4 Visit 4: Day 6

1. Record any Adverse Experiences or side effects
2. Record times when patient received unfractionated heparin or had noncompliance to medication
3. Collect CBC, aPTT, and anti-Xa 6 hours after tenth dose of heparin (~15:00 PM on day 6)
4. Follow up aPTT
   a. If < 36.2 seconds, continue current dose of heparin
   b. If ≥ 36.2 seconds, adjust heparin dose and repeat aPTT and anti-Xa per protocol (APPENDIX 1)

10.5 Weekly Visits (Day 13, 20, 27, 34+ until delivery or discharge from hospital)

1. Record any Adverse Experiences or side effects
2. Record times when patient received unfractionated heparin or had noncompliance to medication
3. Collect CBC, aPTT, and anti-Xa 6 hours after AM dose of heparin (~15:00 PM)

4. Follow up aPTT

   a. If < 36.2 seconds, continue current dose of heparin
   b. If ≥ 36.2 seconds, hold or decrease heparin dose and repeat aPTT and anti-Xa per protocol (APPENDIX 1)

10.6 Early Withdrawal Visit

1. Record any Adverse Experiences or side effects
2. Record times when patient received unfractionated heparin or had noncompliance to medication
3. Collect aPTT and anti-Xa 6 hours after AM dose of heparin

11 STATISTICAL METHODS AND CONSIDERATIONS

Prior to the analysis of the final study data, a detailed Statistical Analysis Plan (SAP) will be written describing all analyses that will be performed. The SAP will contain any modifications to the analysis plan described below.

11.1 Data Sets Analyzed

All patients randomized into the study that received two doses of unfractionated heparin and had at least one aPTT measurement available for review will be included within the analysis.

11.2 Demographic and Baseline Characteristics

The following demographic variables will be collected at screening: age, height and weight, body mass index, race, ethnicity. The following baseline characteristics will be collected at screening: gestational age at randomization, gravida, parity, maternal comorbidities.

11.3 Analysis of Primary Endpoint

Analysis of the primary endpoint of whether or not there was an elevation in aPTT in each dosing group will be performed with a Chi-squared test. Comparison will be considered statistically significant at a p-value of < 0.05.

11.4 Analysis of Secondary Endpoints

Comparison of maternal demographics, baseline characteristics, additional maternal outcomes, and neonatal outcomes between the two groups will be analyzed using Student's t-test for parametric data, Wilcoxon signed-rank test for nonparametric data, and Chi-squared or Fisher's exact test for comparison of proportions. Descriptive statistics will be performed to summarize which dose resulted in a normal aPTT value and anti-Xa within goal range. Multivariate logistic regression analysis will be performed to determine which factors were associated with an elevated aPTT value. Statistical significance will be set at a p-value of < 0.05 or 95% confidence interval not overlapping.

11.5 Sample Size and Randomization

Based on an informal/pilot review of antepartum admissions at our institution receiving gestational age-based dosing of unfractionated heparin, 40% of patients and an elevated aPTT

value. Assuming 40% of patients receiving gestational age-based dosing and 3% receiving standard dosing had elevated serum aPTT values, a sample size of 18 women in each dosing group would have 80% power (alpha = 0.05) to demonstrate a significant difference in our primary outcome of evaluating the proportion of women with elevated aPTT values after heparin administration. We increased the sample size by 25% to account for post-randomization drop-out or lab sampling errors. We plan to recruit 46 patients.

12 ADVERSE EXPERIENCE REPORTING AND DOCUMENTATION

12.1 Adverse Events

An adverse event (AE) is any untoward medical occurrence in a clinical investigation of a patient administered a pharmaceutical product and that does not necessarily have a causal relationship with the treatment. An AE is therefore any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the administration of an investigational product, whether or not related to that investigational product. An unexpected AE is one of a type not identified in nature, severity, or frequency in the current Investigator's Brochure or of greater severity or frequency than expected based on the information in the Investigator's Brochure.

The Investigator will probe, via discussion with the subject, for the occurrence of AEs during each subject visit and record the information in the site's source documents. Adverse events will be recorded in the patient CRF. Adverse events will be described by duration (start and stop dates and times), severity, outcome, treatment and relation to study drug, or if unrelated, the cause.

AE Severity

The National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0 should be used to assess and grade AE severity, including laboratory abnormalities judged to be clinically significant. The modified criteria can be found in the study manual. If the experience is not covered in the modified criteria, the guidelines shown in Table 1 below should be used to grade severity. It should be pointed out that the term "severe" is a measure of intensity and that a severe AE is not necessarily serious.

Table 1. AE Severity Grading

Severity (Toxicity Grade)	Description
Mild (1)	Transient or mild discomfort; no limitation in activity; no medical intervention or therapy required. The subject may be aware of the sign or symptom but tolerates it reasonably well.
Moderate (2)	Mild to moderate limitation in activity, no or minimal medical intervention/therapy required.
Severe (3)	Marked limitation in activity, medical intervention/therapy required, hospitalizations possible.
Life-threatening (4)	The subject is at risk of death due to the adverse experience as it occurred. This does not refer to an experience that hypothetically might have caused death if it were more severe.

AE Relationship to Study Drug

The relationship of an AE to the study drug should be assessed using the following the guidelines in Table 2.

Table 2. AE Relationship to Study Drug

Relationship to Drug	Comment
Definitely	Previously known toxicity of agent; or an event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to the suspected drug; that is confirmed by stopping or reducing the dosage of the drug; and that is not explained by any other reasonable hypothesis.
Probably	An event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to the suspected drug; that is confirmed by stopping or reducing the dosage of the drug; and that is unlikely to be explained by the known characteristics of the subject's clinical state or by other interventions.
Possibly	An event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to that suspected drug; but that could readily have been produced by a number of other factors.
Unrelated	An event that can be determined with certainty to have no relationship to the study drug.

12.2 Serious Adverse Experiences (SAE)

An SAE is defined as any AE occurring at any dose that results in any of the following outcomes:

- death
- a life-threatening adverse experience
- inpatient hospitalization or prolongation of existing hospitalization
- a persistent or significant disability/incapacity
- a congenital anomaly/birth defect

Other important medical events may also be considered an SAE when, based on appropriate medical judgment, they jeopardize the subject or require intervention to prevent one of the outcomes listed.

12.2.1 Serious Adverse Experience Reporting

Study sites will document all SAEs that occur (whether or not related to study drug) per UCLA OHRPP Guidelines. The collection period for all SAEs will begin after informed consent is obtained and end after procedures for the final study visit have been completed.

In accordance with the standard operating procedures and policies of the local Institutional Review Board (IRB)/Independent Ethics Committee (IEC), the site investigator will report SAEs to the IRB/IEC.

12.3 Medical Monitoring

Thalia Mok should be contacted directly at these numbers to report medical concerns or questions regarding safety.

Phone: (310) 210-2246
Pager: x31460

13 DISCONTINUATION AND REPLACEMENT OF SUBJECTS

13.1 Early Discontinuation of Study Drug

A subject may be discontinued from study treatment at any time if the subject or the investigator feels that it is not in the subject's best interest to continue. The following is a list of possible reasons for study treatment discontinuation:

- Subject withdrawal of consent (or assent)
- Subject is not compliant with study procedures
- Adverse event that in the opinion of the investigator would be in the best interest of the subject to discontinue study treatment
- Protocol violation requiring discontinuation of study treatment
- Lost to follow-up
- Sponsor request for early termination of study

If a subject is withdrawn from treatment due to an adverse event, the subject will be followed and treated by the Investigator until the abnormal parameter or symptom has resolved or stabilized.

All subjects are free to withdraw from participation at any time, for any reason, specified or unspecified, and without prejudice.

Reasonable attempts will be made by the investigator to provide a reason for subject withdrawals. The reason for the subject's withdrawal from the study will be specified in the subject's source documents Refer to Section 10 for early termination procedures.

13.2 Withdrawal of Subjects from the Study

A subject may be withdrawn from the study at any time if the subject or the investigator feels that it is not in the subject's best interest to continue.

All subjects are free to withdraw from participation at any time, for any reason, specified or unspecified, and without prejudice.

Reasonable attempts will be made by the investigator to provide a reason for subject withdrawals. The reason for the subject's withdrawal from the study will be specified in the subject's source documents. Refer to Section 10 for early termination procedures.

13.3 Replacement of Subjects

Subjects who withdraw from the study treatment will not be replaced.

14 PROTOCOL VIOLATIONS

A protocol violation occurs when the subject or investigator fails to adhere to significant protocol requirements affecting the inclusion, exclusion, subject safety and primary endpoint criteria. Protocol violations for this study include, but are not limited to, the following:

- Failure to meet inclusion/exclusion criteria
- Use of a prohibited concomitant medication

Failure to comply with Good Clinical Practice (GCP) guidelines will also result in a protocol violation. The principal investigators will determine if a protocol violation will result in withdrawal of a subject.

When a protocol violation occurs, it will be discussed with the investigator and a Protocol Violation Form detailing the violation will be generated. This form will be signed by a Sponsor representative and the Investigator. A copy of the form will be filed in the site's regulatory binder and in the Sponsor's files.

15 DATA COLLECTION, RETENTION AND MONITORING

15.1 Data Collection Instruments

All clinical data will be entered by the Investigator in REDCap, a secure web-based data management system provided by the Cinical Translational Science Institute at UCLA that only the research team has access to. Each subject will also have a protocol-specific Case Report Form (eCRF) where the investigator will report the following information:

- Date of randomization
- Randomization to ARM 1 (standard dosing) or ARM 2 (gestational-age based dosing)
- Dosing of unfractionated heparin received
- Number of times unfractionated heparin dose was changed
- Side effects
- Adverse events

Subjects will not be identified by name in the study database or on any study documents to be collected by the Sponsor (or designee), but will be identified by a subject number and initials. If a correction is made on a CRF, the investigator will line through the incorrect data, write in the correct data and initial and date the change.

The investigator is responsible for all information collected on subjects enrolled in this study. All data collected during the course of this must be reviewed and verified for completeness and accuracy by the investigator.

15.2 Data Management Procedures

The data will be entered in REDCap, a secure web-based data management system provided by the Clinical Translational Science Institute at UCLA. Only the research team will have access to the data and be responsible for data processing, in accordance with procedural documentations. All procedures for the handling and analysis of data will be conducted using good computing practices meeting FDA guidelines for the handling and analysis of data for clinical trials.

15.3 Archival of Data

The database is safeguarded against unauthorized access by established security procedures; appropriate backup copies of the database and related software files will be maintained. Databases are backed up by the database administrator in conjunction with any updates or changes to the database.

15.4 Availability and Retention of Investigational Records

The Investigator must make study data accessible to the monitor, other authorized representatives of the Sponsor (or designee), IRB/IEC, and Regulatory Agency (e.g., FDA) inspectors upon request. A file for each subject must be maintained that includes the signed Informed Consent, HIPAA Authorization and Assent Form and copies of all source documentation related to that subject. The Investigator must ensure the reliability and availability of source documents from which the information on the CRF was derived.

All study documents (patient files, signed informed consent forms, copies of CRFs, Study File Notebook, etc.) must be kept secured for a period of two years following marketing of the investigational product or for two years after centers have been notified that the IND has been discontinued. There may be other circumstances for which the Sponsor is required to maintain study records and, therefore, the Sponsor should be contacted prior to removing study records for any reason.

15.5 Monitoring

Monitoring visits will be conducted by representatives of the Sponsor according to the U.S. CFR Title 21 Parts 50, 56, and 312 and ICH Guidelines for GCP (E6). By signing this protocol, the Investigator grants permission to the Sponsor (or designee), and appropriate regulatory authorities to conduct on-site monitoring and/or auditing of all appropriate study documentation.

15.6 Subject Confidentiality

In order to maintain subject confidentiality, only a subject number will identify all study subjects on CRFs and other documentation. Additional subject confidentiality issues (if applicable) are covered in the Clinical Study Agreement.

16 DATA AND SAFETY MONITORING PLAN

SEE APPENDIX 3

17 ADMINISTRATIVE, ETHICAL, REGULATORY CONSIDERATIONS

The study will be conducted according to the Declaration of Helsinki, Protection of Human Volunteers (21 CFR 50), Institutional Review Boards (21 CFR 56), and Obligations of Clinical Investigators (21 CFR 312).

To maintain confidentiality, all laboratory specimens, evaluation forms, reports and other records will be identified by a coded number and initials only. All study records will be kept in a locked file cabinet and code sheets linking a patient's name to a patient identification number will be stored separately in another locked file cabinet. Clinical information will not be released without written permission of the subject, except as necessary for monitoring by the FDA. The Investigator must also comply with all applicable privacy regulations (e.g., Health Insurance Portability and Accountability Act of 1996, EU Data Protection Directive 95/46/EC).

17.1 Protocol Amendments

Any amendment to the protocol will be written by the principal investigators. Protocol amendments cannot be implemented without prior written IRB/IEC approval except as necessary to eliminate immediate safety hazards to patients. A protocol amendment intended to eliminate

an apparent immediate hazard to patients may be implemented immediately, provided the IRBs are notified within five working days.

17.2 Institutional Review Boards and Independent Ethics Committees

The protocol and consent form will be reviewed and approved by the IRB/IEC of each participating center prior to study initiation. Serious adverse experiences regardless of causality will be reported to the IRB/IEC in accordance with the standard operating procedures and policies of the IRB/IEC, and the Investigator will keep the IRB/IEC informed as to the progress of the study. The Investigator will obtain assurance of IRB/IEC compliance with regulations.

Any documents that the IRB/IEC may need to fulfill its responsibilities (such as protocol, protocol amendments, Investigator's Brochure, consent forms, information concerning patient recruitment, payment or compensation procedures, or other pertinent information) will be submitted to the IRB/IEC. The IRB/IECs written unconditional approval of the study protocol and the informed consent form will be in the possession of the Investigator before the study is initiated. This approval must refer to the study by exact protocol title and number and should identify the documents reviewed and the date of review.

Protocol and/or informed consent modifications or changes may not be initiated without prior written IRB/IEC approval except when necessary to eliminate immediate hazards to the patients or when the change(s) involves only logistical or administrative aspects of the study. Such modifications will be submitted to the IRB/IEC and written verification that the modification was submitted and subsequently approved should be obtained.

The IRB/IEC must be informed of revisions to other documents originally submitted for review; serious and/or unexpected adverse experiences occurring during the study in accordance with the standard operating procedures and policies of the IRB; new information that may affect adversely the safety of the patients of the conduct of the study; an annual update and/or request for re-approval; and when the study has been completed.

17.3 Informed Consent Form

Informed consent will be obtained in accordance with the Declaration of Helsinki, ICH GCP, US Code of Federal Regulations for Protection of Human Subjects (21 CFR 50.25[a,b], CFR 50.27, and CFR Part 56, Subpart A), the Health Insurance Portability and Accountability Act (HIPAA, if applicable), and local regulations.

The Investigator will prepare the informed consent form, assent and HIPAA authorization and provide the documents to the Sponsor or designee for approval prior to submission to the IRB/IEC. The consent form generated by the Investigator must be acceptable to the Sponsor and be approved by the IRB/IEC. The written consent document will embody the elements of informed consent as described in the International Conference on Harmonisation and will also comply with local regulations. The Investigator will send an IRB/IEC-approved copy of the Informed Consent Form to the Sponsor (or designee) for the study file.

A properly executed, written, informed consent will be obtained from each subject prior to entering the subject into the trial. Information should be given in both oral and written form and subjects (or their legal representatives) must be given ample opportunity to inquire about details of the study. If appropriate and required by the local IRB/IEC, assent from the subject will also be obtained. If a subject is unable to sign the informed consent form (ICF) and the HIPAA

authorization, a legal representative may sign for the subject. A copy of the signed consent form (and assent) will be given to the subject or legal representative of the subject and the original will be maintained with the subject's records.

17.4 Publications

The preparation and submittal for publication of manuscripts containing the study results shall be in accordance with a process determined by mutual written agreement among the study Sponsor and participating institutions. The publication or presentation of any study results shall comply with all applicable privacy laws, including, but not limited to, the Health Insurance Portability and Accountability Act of 1996.

17.5 Investigator Responsibilities

By signing the Agreement of Investigator form, the Investigator agrees to:

1. Conduct the study in accordance with the protocol and only make changes after notifying the Sponsor (or designee), except when to protect the safety, rights or welfare of subjects.
2. Personally conduct or supervise the study (or investigation).
3. Ensure that the requirements relating to obtaining informed consent and IRB review and approval meet federal guidelines, as stated in § 21 CFR, parts 50 and 56.
4. Report to the Sponsor or designee any AEs that occur in the course of the study, in accordance with §21 CFR 312.64.
5. Ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations in meeting the above commitments.
6. Maintain adequate and accurate records in accordance with §21 CFR 312.62 and to make those records available for inspection with the Sponsor (or designee).
7. Ensure that an IRB that complies with the requirements of §21 CFR part 56 will be responsible for initial and continuing review and approval of the clinical study.
8. Promptly report to the IRB and the Sponsor (or designee) all changes in the research activity and all unanticipated problems involving risks to subjects or others (to include amendments and IND safety reports).
9. Seek IRB approval before any changes are made in the research study, except when necessary to eliminate hazards to the patients/subjects.
10. Comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements listed in § 21 CFR part 312.

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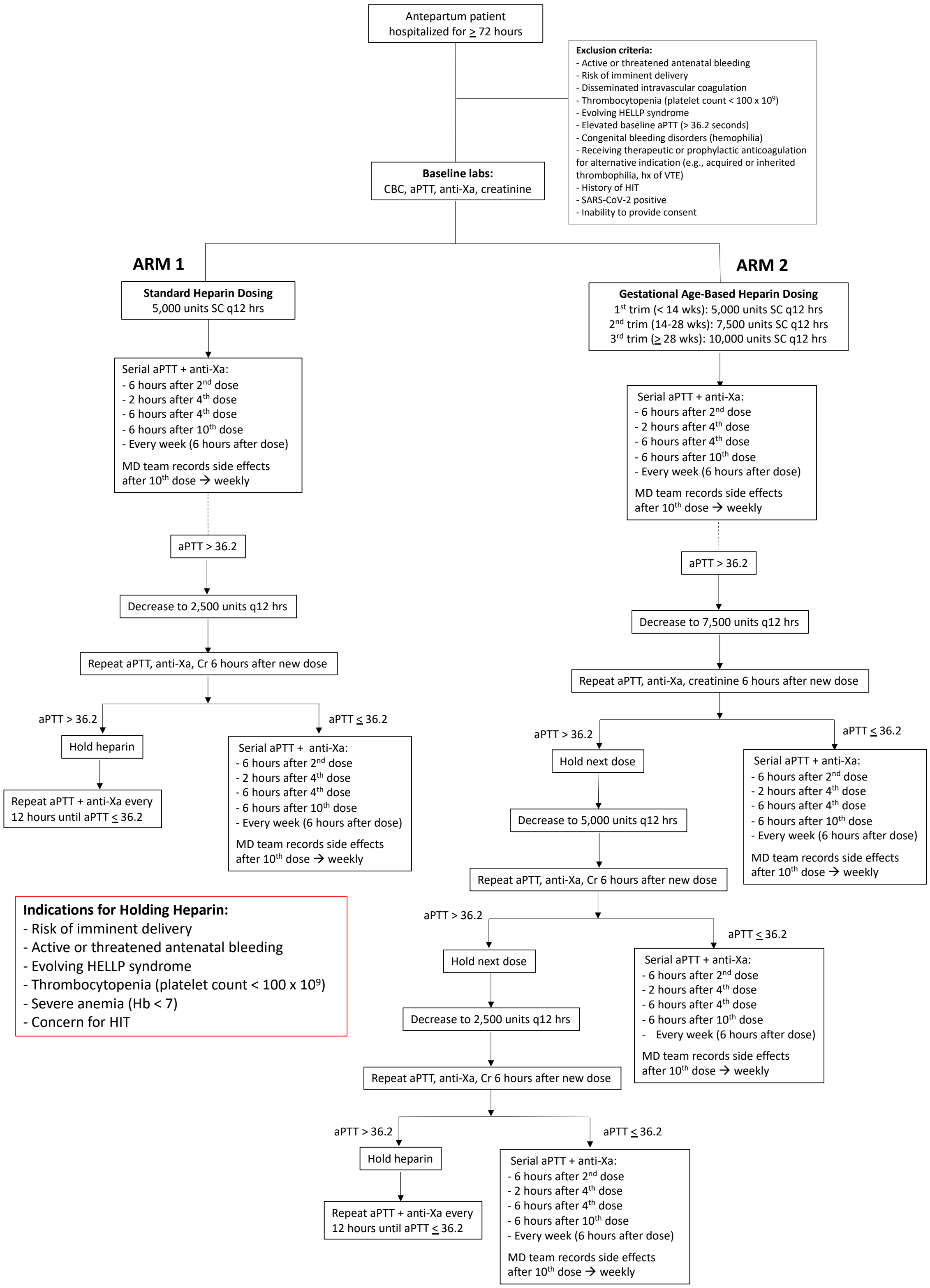
APPENDIX 1. Study Dosing Protocol

Antepartum HEPARIN Dosing RCT Protocol



APPENDIX 2. Schedule of Events

ARM 1: Standard dose of unfractionated heparin

	VISIT (Day 1 – Baseline)	VISIT 2 (Day 2)	VISIT 3 (Day 3)	VISIT 4 (Day 6)	WEEKLY VISITS (Day 13, 20, 27+ until delivery or discharge)
Informed Consent	**X**				
Medical History	**X**				
Complete Physical Exam	**X**				
Abbreviated Physical Exam		**X**	**X**	**X**	**X**
Height	**X**				
Weight	**X**				
Demographics	**X**				
Medical/surgical history	**X**				
Concomitant medications	**X**				
Randomization	**X**				
Unfractionated heparin given	**X**	**X**	**X**	**X**	**X**
CBC	**X**			**X**	**X**
Trough aPTT	**X**	**X** 6 hours after heparin at ~15:00 PM	**X** 6 hours after heparin at ~15:00 PM	**X** 6 hours after heparin at ~15:00 PM	**X** 6 hours after heparin at ~15:00 PM
Trough Anti-Xa	**X**	**X** 6 hours after heparin at ~15:00 PM	**X** 6 hours after heparin at ~15:00 PM	**X** 6 hours after heparin at ~15:00 PM	**X** 6 hours after heparin at ~15:00 PM
Serum creatinine	**X**				
Peak aPTT			**X** 2 hours after heparin at ~11:00 AM		
Peak Anti-Xa			**X** 2 hours after heparin at ~11:00 AM		
Adverse Experiences		**X**	**X**	**X**	**X**
Follow-up trough aPTT (adjust or keep dose per APPENDIX 1)		**X**	**X**	**X**	**X**
Assess side effects				**X**	**X**

ARM 2 : Gestational-age based dose of unfractionated heparin

	VISIT (Day 1 – Baseline)	**VISIT 2 (Day 2)**	**VISIT 3 (Day 3)**	**VISIT 4 (Day 6)**	**WEEKLY VISITS (Day 13, 20, 27+ until delivery or discharge)**
Informed Consent	**X**				
Medical History	**X**				
Complete Physical Exam	**X**				
Abbreviated Physical Exam		**X**	**X**	**X**	**X**
Height	**X**				
Weight	**X**				
Demographics	**X**				
Medical/surgical history	**X**				
Concomitant medications	**X**				
Randomization	**X**				
Unfractionated heparin given	**X**	**X**	**X**	**X**	**X**
CBC	**X**			**X**	**X**
Trough aPTT	**X**	**X** 6 hours after heparin at ~15:00 PM	**X** 6 hours after heparin at ~15:00 PM	**X** 6 hours after heparin at ~15:00 PM	**X** 6 hours after heparin at ~15:00 PM
Trough Anti-Xa	**X**	**X** 6 hours after heparin at ~15:00 PM	**X** 6 hours after heparin at ~15:00 PM	**X** 6 hours after heparin at ~15:00 PM	**X** 6 hours after heparin at ~15:00 PM
Serum creatinine	**X**				
Peak aPTT			**X** 2 hours after heparin at ~11:00 AM		
Peak Anti-Xa			**X** 2 hours after heparin at ~11:00 AM		
Adverse Experiences		**X**	**X**	**X**	**X**
Follow-up trough aPTT (adjust or keep dose per APPENDIX 1)		**X**	**X**	**X**	**X**
Assess side effects				**X**	**X**

APPENDIX 3. Data and Safety Monitoring Plan

Study Title: Randomized Control Trial of Unfractionated Heparin Dosing for Thromboprophylaxis of Hospitalized Antepartum Patients

Principal Investigator: Thalia Mok, MD and Rashmi Rao, MD

I. Study Overview

A. Purpose of the study

Venous thromboembolism (VTE) is one of the leading causes of maternal morbidity and mortality, and antepartum hospitalizations place pregnant patients at an even higher risk of developing thromboembolism. As a result, there is an increased emphasis on administering pharmacologic thromboprophylaxis for antepartum patients with prolonged hospitalizations.

Previously, standard dosing of unfractionated heparin was widely adopted for thromboprophylaxis in the pregnant population. However, due to a suspected altered metabolism of unfractionated heparin in pregnancy resulting in a decrease response, the American College of Obstetricians and Gynecologists (ACOG) and National Partnership for Maternal Safety (NPMS) currently recommends considering gestational age based dosing for unfractionated heparin for thromboprophylaxis in pregnancy with standard dosing as an alternative option. The data supporting altered dosing is very limited. In addition, increased dosing of heparin may result in challenges in anesthetic management, potentially limiting the receipt of neuraxial anesthesia resulting in increased need for general anesthesia associated with both increased maternal and fetal risks. The potential effects of higher prophylactic unfractionated heparin dosing in pregnant patients need to be further explored before being widely adopted for inpatient antepartum thromboprophylaxis. We propose this study to provide a direct comparison of gestational age based unfractionated heparin dosing to standard dosing of unfractionated heparin for pharmacologic thromboprophylaxis of hospitalized antepartum patients.

B. Adherence statement

The Data and Safety Monitoring Plan (SMP) outlined below will adhere to the protocol approved by the University of California, Los Angeles IRB.

II. Adverse events

A. Adverse event assessment

The risks that may occur as part of participation in this study are detailed in section 2.1 of the study protocol. They include side effects from unfractionated heparin, discomfort of blood draws, and limitations in receipt of neuraxial anesthesia if resulting activated partial thromboplastin time (aPTT) is above the normal range. In order to mitigate risks to subject participants, the study protocol closely monitors lab values (aPTT and CBC) and provides subsequent decreases in dosing of unfractionated heparin. Because this study only includes hospitalized patients, subjects will be continuously assessed for side effects of unfractionated

heparin and adverse events by the medical team caring for her during the hospitalization. In addition, a formal assessment of side effects and adverse events will be performed by the investigator on weekly, while the subject is enrolled in the study.

B. Adverse event reporting

Every adverse event that is reported to the principal investigator or research team by the subject or medical staff caring for the subject and meets criteria will be documented. An adverse event report will be generated for each event and the report will include a description of the event, when it was reported, by whom it was reported, along with any official chart records or documentation to corroborate the event. The report will be provided to the IRB.

III. Safety Review Plan and Monitoring

A. Justification of sample size

Based on an informal/pilot review of antepartum admissions at our institution receiving gestational age-based dosing of unfractionated heparin, 40% of patients and an elevated aPTT value. Assuming 40% of patients receiving gestational age-based dosing and 3% receiving standard dosing had elevated serum aPTT values, a sample size of 18 women in each dosing group would have 80% power (alpha = 0.05) to demonstrate a significant difference in our primary outcome of evaluating the proportion of women with elevated aPTT values after heparin administration. We increased the sample size by 25% to account for post-randomization drop-out or lab sampling errors. We plan to recruit 46 patients with 23 patients in each arm.

B. Safety and study progress reviews

Study progress and safety will be reviewed monthly and more frequently if needed by the principle investigator. Review of subject accrual and compliance with inclusion/exclusion criteria will be performed to ensure that there are sufficient number of participants being enrolled and that they meet eligibility criteria. Adherence to treatment protocol and subject retention will be reviewed. Adverse events and side effects will also be reviewed by the principal investigator and reported per above. An interim analysis will be performed when 50% of the target sample size (23 subjects) have completed the study. A report will then be provided and contain a list and summary of adverse events, summary of recruitment and retention and reason for dropouts, and whether or not the study is on track to be completed and accomplish the stated aims.

C. Stopping rules

This study will be stopped prior to its completion if:

1. Gestational age-based dosing is associated with a significantly higher rate (defined as 50% of the study arm) of administration of general anesthesia despite dosing adjustments based on aPTT levels.
2. National guidelines from ACOG change during the trial and state that gestational age-based dosing should not be given for our study population.

3. Maternal or neonatal death occur secondarily to administration of unfractionated heparin.

IV. Informed Consent

Informed consent will be obtained from each subject before enrollment and per local institutional review board guidelines. Consent will be obtained in an ethical manner. The process of consenting will be obtained in the subject's primary language. Subjects will be provided with written material and will be given ample time to review the material and ask questions.

V. Data Quality and Management

Data on treatment protocol and lab values will be evaluated at least weekly by the research team and entered into the REDCap database, which is a secure web-based data management system provided by the Clinical Translational Science Institute at UCLA. The principal investigator will review all data collection forms for data completeness and accuracy. The collected data will be verified based on original source documents available in the electronic medical records. Only the research team will have access to the database.

VI. Confidentiality

All precautionary measures will be taken to ensure that confidentiality and privacy is maintained. All conversations with subjects and consents will be performed in a private setting. All data will be stored securely and only accessible to the research staff. Only a subject ID number will be associated with data to maintain subject confidentiality. A code sheet linking subject information to subject ID will be maintained but kept on a password protected computer and in a password protected file; this will only be accessible to the principle investigators.