Increased unfractionated heparin requirements with decreasing body mass index in pregnancy

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Abstract

Background: Pregnant women receiving low-molecular-weight heparin for therapeutic anticoagulation are often converted to unfractionated heparin in anticipation of labor. We aim to characterize the impact of maternal body mass index on attainment of target anticoagulation during the conversion process.

Methods: We conducted a five-year retrospective study of a pregnancy cohort converted from low-molecular-weight heparin to unfractionated heparin in the third trimester. Patient demographics, anticoagulation regimens, and clinical outcomes were extracted from the medical record. Nonparametric statistical methods were used for analysis by body mass index (<30, 30–35, and >35).

Results: Thirty-one subjects were evenly distributed by body mass index ($p = 0.97$). Linear regression revealed an inverse correlation between patient body mass index and unfractionated heparin dose needed to achieve therapeutic anticoagulation ($p = 0.04$). Subjects with body mass index > 35 attained therapeutic activated partial thromboplastin time levels at 18 U (Units)/kg/h, while subjects with body mass index < 30 required 25 U/kg/h ($p = 0.02$).

Conclusion: Higher doses of unfractionated heparin are needed to achieve anticoagulation in patients with body mass index < 30 during pregnancy. This paradoxical relationship may be explained by physiologic characteristics that increase unfractionated heparin elimination, including diminished adiposity and increased renal clearance.

Keywords

Unfractionated heparin, pregnancy, dosage, anticoagulation

Date received: 22 February 2016; accepted: 14 June 2016

Background

Venous thromboembolism (VTE) is the leading cause of death in pregnancy for the United Kingdom and North America. Approximately 11% of pregnancy-related deaths in the United States are caused by VTE, whereas in the United Kingdom two women will die from a pulmonary embolus for every 100,000 births.¹ Women are four times more likely to suffer from a VTE during pregnancy than in the non-pregnant state.² Additionally, estimates of the rate of antenatal deep vein thrombosis may not reflect the true incidence during pregnancy due to underreporting.³

Women with a thromboembolic event during the antepartum period require therapeutic anticoagulation. Low-molecular-weight heparin (LMWH) has been considered the preferred agent for therapeutic anticoagulation in pregnancy due to favorable pharmacokinetic characteristics: a long plasma half-life, increased and consistent bio-availability, weak interactions with platelets, and reduced inhibition of bone formation compared to unfractionated heparin (UFH).⁴ However, LMWH is often converted to UFH in the late third trimester to take advantage of the shorter half-life and measurable anticoagulant effect which decreases the risk of peripartum hemorrhage and increases opportunities for safe neuraxial blockade.

No standardized method of conversion from LMWH to UFH is currently recommended. Two approaches are commonly utilized: use of intravenous UFH followed by subcutaneous UFH or use of subcutaneous UFH alone during the conversion process. Intravenous infusion of heparin results in immediate anticoagulation, whereas subcutaneous administration has been shown to have a 1- to 2-h delay in anticoagulant activity.⁵ A study by Branciazio et al.⁶ found that the pharmacokinetics and pharmacodynamics of subcutaneous administered UFH are altered in pregnant women, partially due to a decreased responsiveness to UFH. These changes include a shorter time to peak heparin effect and a lower peak effect compared with non-pregnant

patients. Additionally, Kroon et al.⁷ have observed inter-individual variation in anticoagulant response to subcutaneous UFH. These factors contribute to a ‘best guess’ approach to titration of UFH dose until therapeutic anticoagulation targets have been reached.⁶

Rapid heparinization is part of the optimal management of the conversion from LMWH to UFH. Weight-based dosing nomograms have been suggested as an alternative to empiric dosing of UFH for therapeutic anticoagulation.⁸ This approach is thought to achieve rapid anticoagulation, allowing for finer adjustments to reach goal activated partial thromboplastin time (aPTT) values.⁹ However, no studies have taken into account the impact of changes in maternal body mass index (BMI) on weight-based dosing of UFH for therapeutic anticoagulation in pregnancy. We sought to determine the relationship between a patient’s BMI at the time of conversion to UFH and the end dose of UFH required to achieve a therapeutic aPTT.

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Methods

Approval was obtained from the University of Tennessee Health Science Center and Regional Medical Center Institutional Review Boards (IRBs) for a retrospective chart review. Due to the retrospective study design, the requirement for informed consent was waived by the IRB. A pharmacy-generated report was used to screen all antenatal patients receiving UFH at the Regional Medical Center at Memphis from June 2003 to June 2008. Patients were selected for inclusion if, in the current pregnancy, they underwent conversion from a maintenance anticoagulant (LMWH or coumadin) to UFH for a history of a thromboembolic event. Exclusion criteria included the use of alternate anticoagulants (e.g., direct factor Xa inhibitors) or prophylactic dosing for any indication. All patients were admitted to the hospital for conversion in accordance with our group practice. During the five-year study period, physicians chose to convert from subcutaneous LMWH to subcutaneous UFH directly, or through the use of intravenous UFH as an intermediate step. Per established dosing guidelines, a bolus of 80 U/kg UFH is given to the patient, followed by the administration of UFH at 18 U/kg/h and subsequent titration until therapeutic aPTTs are obtained. Data collected from the chart review included patient demographics, method of maintenance anticoagulation prior to conversion, method of conversion to UFH, initial heparin dose and dose at discharge, and relevant aPTT values. Patients were considered to be therapeutic once three consecutive aPTT values were within goal range. Primary data can be obtained by request from the authors. Data were analyzed with the nonparametric statistical methods (Chi square test) and regression analysis using JMP and SAS statistical software (SAS, Cary, NC).

Results

Thirty-one gravidas were identified that met the inclusion criteria. Review of the subjects' demographics revealed a mean age of 26.4 years, weight of 93.8 kg, and height of 65.3 inches. Additionally, the population averaged 163% of their ideal body weight and had a mean BMI of 34.1. The mean gestational age at the time of conversion was 35.7 weeks, and 36.5 weeks at the time of discharge from the hospital. Indications for anticoagulation were venous thromboembolic event (90%) or artificial heart valve (10%). Prior to conversion, maintenance LMWH regimens ranged from 40 mg BID to 180 mg BID, with the majority of patients receiving 70–80 mg BID. The cohort was evenly divided by method of conversion, with 16 subjects converted from LMWH to subcutaneous UFH directly, while the remaining 15 subjects were converted through the use of intravenous UFH as an intermediate step.

Regression analysis revealed a significant correlation between patient BMI and subcutaneous end dose ($R^2=0.132$, $p=0.04$; Figure 1). Kruskal–Wallis testing demonstrated significant variance between the end dose of subcutaneous UFH required to reach therapeutic anticoagulation and BMI, but not the time to achieve therapeutic anticoagulation by BMI group (Table 1). The BMI >35 group had a significantly lower end dose ($p=0.02$) compared to the BMI <30 group (17.6 vs. 25.3 U/kg/h). Patients in the BMI 30–35 range were not significantly different from either group, but more closely compared to the BMI >35 group (20.4 U/kg/h). Additional demographic and anticoagulation parameters were analyzed by BMI groups (<30, 30–35, and >35), as detailed in Table 1.

Patient race and method of conversion (subcutaneous only vs. intravenous then subcutaneous) did not vary by BMI group. Mode of delivery trended towards significance ($p=0.08$), with a greater proportion of Cesarean sections performed in the BMI >35 group. Clinical outcomes were similar when compared by BMI, including occurrence of pre-eclampsia, placement of epidural occurrence of thromboembolism, and blood loss during delivery.

Figure 1. Regression analysis of BMI vs. end-dose subcutaneous UFH required to achieve therapeutic anticoagulation, defined as three consecutive aPTT values within therapeutic range ($R^2 = 0.132$, $p = 0.04$).

Table 1. Demographics and anticoagulation characteristics by BMI group.

BMI group	<30	30–35	>35	P value
Number of subjects	11	10	10	NS
Age (years)	27.7 ± 5.8	24.9 ± 4.4	26.3 ± 6.1	NS
Admit gestational age (weeks)	35.2 ± 3.8	35.9 ± 1.5	36.1 ± 0.3	NS
Discharge gestational age (weeks)	35.9 ± 3.6	37.1 ± 1.5	36.7 ± 0.5	NS
End-dose UFH (U/kg/h)	25.3 ± 8.0	20.4 ± 3.9	17.6 ± 4.2	0.02
Time to Therapeutic aPTT (h)	35.0 ± 18.6	49.6 ± 29.5	41.3 ± 30.3	NS

BMI: body mass index; UFH: unfractionated heparin; aPTT: activated partial thromboplastin time. P values reflect the results of Kruskal–Wallis testing (nonparametric one-way ANOVA) for variance in selected parameters by BMI group.

Conclusion

Efficient conversion from LMWH to UFH reduces the risk of thromboembolic events during the transition period. Our study demonstrated an inverse relationship between BMI and final subcutaneous UFH dose needed to achieve goal (therapeutic) aPTT levels. The BMI >35 group achieved therapeutic aPTT levels (approximately 18 U/kg/h) closest to the established dosing guidelines, while the BMI <30 group required significantly more UFH to achieve therapeutic levels (25 U/kg/h). These findings suggest that use of BMI-based targets for UFH anticoagulation may improve the efficiency of the conversion process.

Guidelines from the American College of Chest Physicians (ACCP) have emphasized the use of LMWH as a standardized approach to antenatal anticoagulation.¹⁰ ACCP guidelines recommend discontinuation of UFH or LMWH anticoagulation approximately 24 h prior

to a planned induction of labor or cesarean delivery, though individuals at high risk for recurrent thrombosis may continue intravenous UFH in labor.¹⁰ In practice, a variety of strategies exist for the management of anticoagulation in anticipation of labor.^{11–13} Traditionally, patients have been transitioned from LMWH to UFH around 36 weeks gestation to minimize the risk of obstetric hemorrhage or complications of neuraxial blockade.^{14–16} However, many practitioners have adopted a practice of continuing LMWH until shortly before a scheduled delivery or the onset of signs of early labor. A recent study of anticoagulant management in 101 subjects delivered at a tertiary care obstetric unit documented persistence of these divergent management approaches: 39% of subjects were anticoagulated with LMWH only, while 52% of subjects were converted from LMWH to UFH (intravenous or subcutaneous) prior to delivery.¹⁷ Clinicians' continued practice of converting patients from LMWH to UFH prior to labor underscores the need to optimize this process.

The physiologic changes of pregnancy can make management of anticoagulation challenging to manage, including the conversion from LMWH to UFH. Several of the pertinent changes in pregnancy include a 50% increase in cardiac output, 1.5 L increase in blood volume, 50% increase in glomerular filtration rate (GFR), and altered protein binding of heparin.¹ Concentrations of specific coagulation factors are also altered, including increases in factors VII, VIII, X, von Willebrand factor, and fibrinogen.² UFH works through varied mechanisms such as heparin-antithrombin complexes, inactivation of thrombin and other coagulation enzymes, inhibition of platelet function, and modulation of endothelium cell function. The changes in physiology that occur in pregnancy make empiric titration of UFH a necessary, though time-consuming, part of care.

Our study cohort was balanced between BMI groups (<30, 30–35, and >35), allowing us to analyze the relationship between BMI and final subcutaneous UFH dose needed to achieve goal aPTT levels. Our use of BMI at the time of the conversion process is a surrogate for changes in maternal body composition including increased adipose tissue and increased blood volume. The inverse relationship demonstrated between maternal BMI and final therapeutic subcutaneous UFH dose may be explained by physiologic changes of pregnancy altering the pharmacokinetics of UFH. In subjects with BMI > 35, the standard non-pregnant dosing regimen of 18 U/kg/h appears sufficient to achieve therapeutic anticoagulation. One potential explanation for this consistency with drug behavior in non-pregnant subjects is a slower rate of absorption of UFH from the subcutaneous fat into the systemic circulation. Over time, a 'depot effect' may occur with consistent absorption of UFH maintaining anticoagulation at the standard dose of 18 U/kg/h. In contrast, subjects with BMI < 30 group required a significantly higher dose of UFH (25 U/kg/h) to achieve sustained therapeutic anticoagulation. We suspect that diminished subcutaneous fat increases drug absorption, in combination with efficient clearance of UFH from the increased GFR, leading to the need for a higher dose to achieve therapeutic levels.

Although our study is limited by small sample size and retrospective design, it does provide clinically applicable conclusions. Our findings suggest an inverse relationship between BMI and the dose of subcutaneous UFH necessary to achieve anticoagulation. While this may initially appear paradoxical, the anticipated physiologic changes of pregnancy provide a reasonable explanation for the observed drug behavior. A larger prospective study is needed to evaluate the impact of initiating subcutaneous UFH at 25 U/kg/h in patients with BMI < 30 on clinical practice, with a focus on the time needed to achieve therapeutic levels and the associated cost of care. Adherence to traditional dosing guidelines of 18 U/kg/h UFH continues to be appropriate for BMI > 30.

Acknowledgements

We would like to acknowledge Andra James, MD, for providing editorial support in the preparation of this manuscript.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Ethical approval

Obtained from the University of Tennessee Health Science Center and Regional Medical Center Institutional Review Boards. Due to the retrospective study design, the requirement for informed consent was waived by the respective IRBs.

Guarantor

ASP.

Contributorship

Study design – ASP, TC, PKG, ER, and NLM; Data collection – TC, PKG, and ER; Data analysis – ASP and DK; Manuscript preparation – ASP, TC, PKG, DK, ER, and NLM.

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