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The Society for Obstetric Anesthesia and Perinatology Consensus Statement on the Anesthetic Management of Pregnant and Postpartum Women Receiving Thromboprophylaxis or Higher Dose Anticoagulants

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Venous thromboembolism is recognized as a leading cause of maternal death in the United States. Thromboprophylaxis has been highlighted as a key preventive measure to reduce venous thromboembolism–related maternal deaths. However, the expanded use of thromboprophylaxis in obstetrics will have a major impact on the use and timing of neuraxial analgesia and anesthesia for women undergoing vaginal or cesarean delivery and other obstetric surgeries. Experts from the Society of Obstetric Anesthesia and Perinatology, the American Society of Regional Anesthesia, and hematology have collaborated to develop this comprehensive, pregnancy-specific consensus statement on neuraxial procedures in obstetric patients receiving thromboprophylaxis or higher dose anticoagulants. To date, none of the existing anesthesia societies' recommendations have weighed the potential risks of neuraxial procedures in the presence of thromboprophylaxis, with the competing risks of general anesthesia with a potentially difficult airway, or maternal or fetal harm from avoidance or delayed neuraxial anesthesia. Furthermore, existing guidelines have not integrated the pharmacokinetics and pharmacodynamics of anticoagulants in the obstetric population. The goal of this consensus statement is to provide a practical guide of how to appropriately identify, prepare, and manage pregnant women receiving thromboprophylaxis or higher dose anticoagulants during the ante-, intra-, and postpartum periods. The tactics to facilitate multidisciplinary communication, evidence-based pharmacokinetic and spinal epidural hematoma data, and Decision Aids should help inform risk–benefit discussions with patients and facilitate shared decision making. (Anesth Analg 2018;126:928–44)

WHY WAS THIS CONSENSUS STATEMENT DEVELOPED?

This consensus statement was commissioned by the Society for Obstetric Anesthesia and Perinatology (SOAP) in anticipation of the expanded 2016 obstetric venous thromboembolism (VTE) prophylaxis guidelines published by the National Partnership for Maternal Safety (NPMS)[1] and the recommendations from the California Maternal Quality Care Collaborative (CMQCC).[2] The primary goal is to provide practical and evidence-based guidance for physician anesthesiologists and other practitioners to help manage a growing number of women receiving antepartum and/or postpartum thromboprophylaxis with increasing doses of unfractionated heparin (UFH) or low molecular weight heparin (LMWH).

WHAT OTHER STATEMENTS OR GUIDELINES ARE AVAILABLE ON THIS TOPIC?

Guidelines on the use of neuraxial anesthesia for anticoagulated patients have been published by several anesthesia professional organizations (Table 1). The American Society for Regional Anesthesia (ASRA) guidelines, first published in 1998, are based on expert consensus opinion, pharmacokinetic principles (such as elimination half-lives), and vigilant tracking of spinal epidural hematoma (SEH) cases; however, these and the other anesthesia recommendations have not differentiated between pregnant and nonpregnant women,[3] despite differences in pharmacokinetics of anticoagulants, competing risks of general anesthesia, and fetal needs.[3,5–8,10] Only the Scandinavian Society of Anaesthesiology and Intensive Care Medicine guidelines incorporate the type of neuraxial procedure performed (ie, single injection spinal versus epidural) and the impact on maternal morbidity and mortality into their recommendations.[9,11]

For LMWH, the general consensus among professional organizations and the US Food and Drug Administration (FDA)[12] is to wait 12 hours after "prophylactic" doses

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The Appendix provides the full list of the SOAP VTE Taskforce members, along with their respective affiliations.

Reprints will not be available from the authors.

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Table 1. Anesthesia Professional Organization Recommendations for Neuraxial Blockade in the Presence of Antithrombotic Therapy or Higher Dose Anticoagulants

	SQ UFH	IV UFH	LMWH	Vitamin K Antagonists	Aspirin and NSAIDs
American Society of Regional Anesthesia and Pain Medicine (2017)[3,4]	Prophylactic low-dose SQ UFH (≤5000 U in a single dose BID or TID and ≤15,000 U in 24 h): -Wait 4–6 h before NB/CR Prophylactic higher dose SQ UFH (>5000 U and ≤10,000 U in a single dose or >15,000 U in 24 h): -Wait 12 h before NB/CR and assess coagulation status. Therapeutic SQ UFH (>10,000 U in a single dose or >20,000 U in 24 h): -Wait 8–12 h before NB/CR and check coagulation status before NB/CR -Subsequent (prophylactic or therapeutic) SQ UFH dose may be administered 1 h after NB/CR For any dosing regimen of SQ UFH administered >4 d, check platelet count before NB/CR	Normalization of coagulation before NB/CR (usually 4–6 h) Delay heparinization for 1 h after NB/CR If administered >4 d, check platelet count before NB/CR	Prophylactic LMWH (eg, dalteparin 5000 U once daily, enoxaparin 30 mg twice daily, or enoxaparin 40 mg once daily): -Any amount greater than prophylactic dosing is considered "therapeutic dosing" -Wait 12 h before NB/CR -No twice daily dosing with indwelling catheter -Avoid concomitant use of other drugs affecting hemostasis -The first postpartum LMWH dose should be administered at least 12 h after NB or 4 h after CR, whichever is greater Therapeutic LMWH (eg, dalteparin 120 U/kg BID or 200 U/kg once daily, enoxaparin 1 mg/kg BID, enoxaparin 1.5 mg/kg once daily, tinzaparin 175 U/kg once daily): -Wait 24 h before NB -The first postpartum LMWH dose should be administered 24 h after NB or 4 h after CR, whichever is greater	-Discontinue 4–5 d and check INR. Normal INR for NB. -Warfarin may be administered with the presence of an indwelling epidural catheter, however, remove catheter before INR >1.4. -INR >1.5 but <3, indwelling catheters may be maintained with caution, based on INR and duration of warfarin therapy. -INR >3, hold warfarin, consider reversal to allow CR. Factor levels may be helpful	No contraindications when used alone Avoid NB in patients on other anticoagulants along with ASA/NSAID No contraindications for COX-2 inhibitors
European Society of Anaesthesiology (2010)[5]	Prophylactic SQ UFH (≤15,000 IU/d or any dose with aPTT in normal reference range): -Wait 4–6 h before NB/CR -Delay dosing 1 h after NB/CR Therapeutic SQ UFH (>15,000 IU/d): -Wait 8–12 h for NB/CR, then check aPTT or anti-Xa for return to normal before NB/CR If administered >5 d, check platelet count before NB/CR	Discontinue IV heparin infusion 4–6 h, then check aPTT or anti-Xa for return to normal before NB/CR If administered for >5 d, check platelet count before NB/CR	Prophylactic LMWH (eg, dalteparin 5000 anti-Xa U once daily; enoxaparin 40 mg once daily; tinzaparin 4500 anti-Xa U once daily; certoparin 3000 anti-Xa U once daily; reviparin 1750 anti-Xa U once daily): -Wait 12 h before NB/CR -Delay dosing 4 h after NB/CR Therapeutic LMWH: -Wait 24 h before NB/CR -Delay dosing 4 h after NB/CR. Consider holding LMWH for 24 h or administering half dose on procedural day	-INR ≤1.4 for NB -No warfarin in combination with indwelling neuraxial catheters -Warfarin may be administered immediately upon CR	No contraindications
Association of Anaesthetists of Great Britain and Ireland (2013)[6]	Prophylactic SQ UFH -Wait 4 h or normalization of aPTT before NB/CR -Delay dosing 1 h after NB/CR	-Wait 4 h or normalization of aPTT before NB/CR Delay heparinization for 1 h after NB/CR	Prophylactic LMWH -Wait 12 h before NB/CR -Postpartum LMWH dose can be administered after 4 h of NB or CR (recommended once daily instead of BID) Therapeutic LMWH -Delay 24 h before NB -The first postpartum LMWH dose can be administered 4 h after NB or CR (wait 24 h if block performance was traumatic)	-INR ≤1.4 for NB -No warfarin in combination with indwelling neuraxial catheters -Warfarin may be administered immediately upon CR	No contraindications

(*Continued*)

Table 1. Continued

	SQ UFH	IV UFH	LMWH	Vitamin K Antagonists	Aspirin and NSAIDs
Belgium Association for Regional Anaesthesia (2011)[7]	Only "intraoperative use" discussed: -Delay dose 1 h after NB/CR except in bloody puncture, then delay dose 1–2 h for NB/CR	Discontinue IV heparin infusion, then check aPTT or ACT for return to normal before NB/CR If dosed >5 d, check platelet count before NB/CR	Prophylactic LMWH (eg, enoxaparin 0.5 mg/kg once daily; dalteparin 5000 IU once daily; nadroparin <5700 IU once daily; tinzaparin 50 IU/kg once daily): -Wait 12 h before NB/CR -Delay dosing 4 h after NB/CR Doses above prophylactic ("intermediate" or "therapeutic"): Delay 24 h from last dose for NB/CR; delay dosing 4 h after NB/CR If dosed for >5 d, check platelet count before NB/CR	INR ≤1.4 for NB or CR	No contraindications
German Society for Anesthesiology and Intensive Care Medicine (2014)[8]	Prophylactic SQ UFH -Wait 4 h before NB/CR -May dose 1 h after NB/CR -For SQ UFH administered >5 d, check platelet count before NB/CR Therapeutic SQ UFH -Wait 8–12 h before NB/CR and check aPTT or ACT and platelet count -May dose 1 h after NB/CR	Wait 4–6 h before NB/CR and check aPTT or ACT and platelet count May dose 1 h after NB/CR	Prophylactic LMWH -Wait 12 h before NB/CR -May dose 4 h after NB/CR For LMWH administered >5 d, check platelet count before NB/CR Therapeutic LMWH -Wait 24 h before NB/CR -May dose 4 h after NB/CR Check platelet count and anti-Xa levels	INR <1.4 for NB or CR	No contraindications for ASA
Scandinavian Society of Anaesthesiology and Intensive Care Medicine (2010)[9]	For doses ≤5000 IU (70 IU/kg) once daily: -Wait 4 h before NB/CR -Delay dose 1 h after NB/CR For doses ≥5000 IU (70–100 IU/kg) once daily: -Wait 4 h from before NB/CR and assure normal aPTT -Delay dose 6 h after NB/CR For doses >100 IU/kg/d: -Wait 4 h before NB/CR and assure normal aPTT -May dose 6 h from NB/CR For all doses given for >5 d, check platelet count before NB/CR	Discontinue IV heparin infusion 4 h, then check aPTT for return to normal before NB/CR Delay infusion 6 h after NB If dosed for ≥5 d, check platelet count before NB/CR	Prophylactic LMWH (eg, dalteparin ≤5000 IU SQ once daily; enoxaparin ≤40 mg SQ once daily): -Wait 10 h before NB/CR -Delay dosing 6 h after NB/CR Any dose greater than prophylactic: -Wait 24 h for NB/CR -Delay dosing 6 h after NB/CR	Recommended INR depends on potential benefit from neuraxial block: If single shot spinal is for: -Comfort only ≤1.4 -Morbidity reduction <1.8 -Mortality reduction <2.2 If epidural or combined spinal–epidural is for -Comfort only ≤1.2 -Morbidity reduction <1.6 -Mortality reduction <1.8	ASA at doses <1 g/24 h: Delay 3 d from last dose before NB/CR ASA at doses >1 g/24 h: Delay 7 d from last dose before NB/CR No delay after NB/CR before dosing ASA Various NSAIDs have different intervals from last dose before NB/CR ranging from 12 h (ibuprofen) to 24 h (ketorolac) to 48 h (naproxen) to 2 wk (piroxicam or tenoxicam) Delay dosing NSAIDs 2 h after NB/CR No contraindications or delays for COX-2 inhibitors

(*Continued*)

Table 1. Continued

	SQ UFH	IV UFH	LMWH	Vitamin K Antagonists	Aspirin and NSAIDs
Sociedade Brasileira de Anestesiologia (2013)[10]	For doses ≤5000 IU BID: -Wait 4 h before NB/CR -Delay dose 1 h from NB/CR If dosed for >5 d, check platelet count before NB/CR	Discontinue IV heparin infusion 4 h, then check aPTT or ACT for return to normal before NB/CR If dosed for ≥5 d, check platelet count before NB/CR	Prophylactic LMWH: -Wait 10–12 h for NB/CR Prophylactic LMWH along with ASA/NSAID: -Delay 24 h for NB/CR Therapeutic LMWH (eg, enoxaparin 1 mg/kg twice daily; dalteparin 120 IU/kg twice daily or 200 IU/kg once daily; tinzaparin 175 IU/kg once daily): -Wait 24 h for NB/CR	Normal INR for NB	No contraindications Additional caution in patients on other anticoagulants along with ASA/NSAID

Abbreviations: ACT, activated clotting time; anti-Xa, antifactor Xa; aPTT, activated partial thromboplastin time; ASA, aspirin; BID, twice daily; COX-2, cyclooxygenase-2; CR, catheter removal; INR, international normalized ratio; IV, intravenous; LMWH, low molecular weight heparin; NB, neuraxial block; NSAID, nonsteroidal anti-inflammatory drug; SQ, subcutaneous; TID, three times daily; UFH, unfractionated heparin.

(eg, enoxaparin ≤40 mg subcutaneous [SQ] once daily or 30 mg SQ twice daily) and 24 hours after "therapeutic" doses (eg, enoxaparin 1 mg/kg SQ twice daily or 1.5 mg/kg SQ once daily) before performing a neuraxial procedure or withdrawing an epidural catheter.

For UFH, there have been some recent modifications. In the first 3 editions of the ASRA guidelines, thromboprophylactic dosing with UFH 5000 U SQ twice daily was not considered to be a contraindication to the placement of a neuraxial anesthetic without delay.[3,13,14] In the forthcoming 2017 update of the ASRA guidelines, the new recommendation is to now wait 4–6 hours after an UFH 5000 U SQ twice daily dose before performing a neuraxial procedure.[4] This practice recommendation was made to be consistent with the European Society of Anaesthesiology guidelines and is not based on reports of new cases of SEH.

HOW DOES THIS 2017 SOAP CONSENSUS STATEMENT DIFFER FROM EXISTING GUIDELINES?

There is no other consensus statement that conclusively addresses thromboprophylaxis and neuraxial anesthesia considerations in the obstetric patient. By engaging the key stakeholders, including the architects of the US obstetric and anesthesia guidelines, and building consensus in areas of differing opinions, this statement helps to minimize provider confusion from disparate recommendations. The statement's Decision Aids for urgent situations can help inform shared decision making between providers and patients with tactics to facilitate multidisciplinary communication, and recommendations for elective cases based on the best available evidence and consensus opinion.

BACKGROUND

VTE is a leading cause of maternal morbidity and mortality in the United States, responsible for 9.2% of maternal deaths,[15] with an observed increase in VTE incidence during vaginal delivery hospitalizations from 15.6 per 100,000 deliveries in 2006 to 29.8 per 100,000 deliveries in 2012.[16] In the United Kingdom, where more women receive pharmacologic prophylaxis, usually with LMWH, the VTE-related maternal mortality decreased from 1.26 per 100,000 births in 2009–2011 to 0.85 per 100,000 births in 2012–2014.[17] The degree to which pharmacologic prophylaxis was responsible for this maternal mortality benefit is unknown. Under the new NPMS and CMQCC obstetric quality of care initiatives, more pregnant and early postpartum women in the United States will now be receiving thromboprophylaxis. Key recommendations include thromboprophylaxis for hospitalized antepartum patients and for women at risk for VTE after cesarean or vaginal delivery.[1] "Thromboprophylactic" doses of UFH can now be as high as 10,000 U SQ twice daily. These significant practice changes increase the chances that a peripartum woman will have recently received UFH or LMWH when she needs labor epidural analgesia or neuraxial anesthesia for cesarean delivery.[18]

There is a myriad of reasons why neuraxial anesthesia continues to be the technique of choice for cesarean delivery and for optimal pain management during labor. Fortunately, the incidence of major complications, specifically SEH with neuraxial anesthesia in the obstetric population, is extremely low (1:200,000–1:250,000),[19,20] compared to

the 1:3600 SEH incidence in the female elderly orthopedic population.[21] In addition to providing excellent labor pain relief, neuraxial analgesia can help to minimize the urge to bear down before complete cervical dilation and decrease circulating catecholamines, both of which are particularly important in facilitating vaginal delivery in select high-risk settings.[22] Despite the overall decrease in anesthetic causes of major maternal morbidity and mortality over recent decades,[23,24] general anesthesia continues to be associated with more maternal anesthesia–related adverse events than neuraxial anesthesia[25] including intraoperative bronchospasm and postoperative hypoventilation (Box 1A). There are also fetal risks associated with maternal general anesthesia, which can include respiratory depression at delivery (Box 1B).

METHODS

The taskforce formulated the consensus statement through a systematic and general review of the relevant literature and a modified Delphi process during an extensive 1.5-year period (Supplemental Digital Content 1, Material 1, http://links.lww.com/AA/C65). Both formal and informal methods were used, including a risk assessment survey using research electronic data capture (REDCap),[42] in-person and telephone meetings, and electronic communications. The taskforce committed to creating a document that reconciled the differences between disparate published guidelines. Differing points of view were discussed in full and when necessary, compromise was attained.

Seventeen taskforce members were identified through literature review of existing anticoagulation guidelines and were invited by e-mail, with a description of the taskforce goals; all agreed to participate except for 1 expert who contributed to only the risk assessment survey. Taskforce members were chosen to include multidisciplinary practitioners with content expertise in obstetric and anesthesia clinical practice, pregnancy-related hematology and pharmacokinetics, and statistical methods. These invited experts were from 3 countries (the United States, Canada, and the United Kingdom), 4 disciplines (anesthesiology, both physician and certified registered nurse anesthetist; obstetrics; hematology; and epidemiology), and 9 institutions. They included members of SOAP, ASRA, NMPS, CMQCC, Obstetric Anaesthetists Association, American Society of Anesthesiologists (ASA), American Association of Nurse Anesthetists, American Congress of Obstetricians and Gynecologists, and hematologic experts. The opinions expressed by individual taskforce members in this statement were their own and did not reflect the views of their institutions or other affiliations.

Box 1A. Maternal Risks Related to General Anesthesia

- Serious adverse events related to induction of general anesthesia (eg, respiratory or cardiac complications, cardiac arrest)[24]
- Failed intubation[19,26,27]
- Cerebrovascular injury from a severe hypertensive response to intubation in women with comorbidities (eg, preeclampsia, cardiac disease)[28]
- Awareness under general anesthesia[29]
- Intraoperative uterine atony and/or increased obstetric hemorrhage[30–32]
- Respiratory depression after emergence from general anesthesia[24]
- Surgical site infection[33]
- Inability to provide neuraxial opioids limiting opioid-sparing postcesarean analgesia[34]
- Persistent pain after delivery[35,36]
- Reduced immediate postdelivery skin-to-skin bonding and breastfeeding[37,38]
- Decreased maternal and paternal participation, and satisfaction with birth experience[37]

Box 1B. Fetal/Neonatal Risks of General Anesthesia

- Respiratory depression at delivery, Apgar <7 at 5 minutes, and admission to neonatal intensive care unit in urgent cases[39]
- In utero exposure to induction/inhalational agents with potential neurobehavioral impact[40]
- Reduced benefits of immediate breastfeeding with decreased likelihood of exclusive breastfeeding[37,41]

Literature and Systematic Review

Published reports on pharmacokinetics and pharmacodynamics of anticoagulation in pregnancy were identified through a literature search of PubMed and MEDLINE (via EBSCOhost). In addition, individual study bibliographies were hand searched. A separate systematic review was conducted to identify cases of SEH in the setting of neuraxial anesthesia in obstetric patients who received thromboprophylactic anticoagulation. Methods and results have been previously published.[43]

Risk Assessment Survey

As SEH event rates were difficult to estimate despite the systematic review, we utilized a 41-question assessment survey of 36 experts in obstetric anesthesia, obstetrics, and hematology to measure their opinion of reasonable clinical practice and of risk.[42] Taskforce members and additional members of SOAP were included. The survey assessed "management of obstetric patients on anticoagulant medications for venous thromboprophylaxis" by asking them to use "clinical intuition to answer" questions about what they would do in different clinical scenarios. In some cases, they were also asked to "estimate the number of additional obstetric patients who would experience a SEH for each million neuraxial procedures" at preselected heparin doses identified in the obstetric guidelines, at varying time intervals since last dose (Supplemental Digital Content 2, Material 2, http://links.lww.com/AA/C66). The contemporary SEH rate of 3–4:1,000,000 in obstetric cases was considered baseline.[19,20] Because the goal of this exercise was to document individual assessment and clinical practice, a single iteration of the survey was deemed to be sufficient.

Consensus Recommendations

The results of the literature review[43] and risk assessment survey[42] helped to guide the development of the consensus statement. Each recommendation was independently reviewed by 5 core members of the SOAP VTE Taskforce (L.L., R.L., K.A., A.B., B.C.) to determine the class (strength of recommendation) and level (quality of the evidence) using the 2015 American Heart Association grading scale.[44] In any case of disagreement, consensus was reached through discussion

between reviewers. Before submission for publication, the consensus statement was approved by all members of the taskforce and endorsed by the SOAP Board of Directors.

RESULTS

Systematic Review: Spinal Epidural Hematoma Risk

The systematic review (covering the years 1952–2016) revealed no case of obstetric SEH after a neuraxial procedure (spinal, epidural, combined spinal–epidural) in pregnant women receiving thromboprophylaxis; however, the total number (denominator) of cases is unknown.[43] Two cases of SEH were reported in the early postpartum period in women who had delivered with neuraxial labor analgesia and then heparin; however, their SEH resulted from other causes. There were also no cases of SEH in the setting of thromboprophylaxis and neuraxial anesthesia in the 546 obstetric-related legal liability claims available for review in the Anesthesia Closed Claims Database (1990–2013).[a] This absence of SEH in pregnant or newly postpartum women with thromboprophylaxis and neuraxial anesthesia is encouraging, although the lack of high-level evidence and denominator data prevents quantitative risk assessment. Additional research and registry data will permit more informed future guidelines.

Risk Assessment Survey: Spinal Epidural Hematoma Risk

Of the 36 experts invited to participate in the risk assessment survey, 27 participants (75% response) responded. Analyses included descriptive statistics appropriate to measurements, including frequency counts (%) and median (interquartile range [ie, 25–75th percentile]). The central tendency (expected value) and variation (95% confidence intervals) in clinical assessments were estimated assuming the distribution of events would follow a negative binomial distribution.

The results were as follows:

- Two-thirds of experts (17/27; 63%) estimated the SEH risk as comparable to baseline risk if the neuraxial procedure was performed 6 hours or more after the UFH 5000 U SQ dose.
- Three-fourths of anesthesia experts (19/25; 76%) said that they would perform the neuraxial procedure within 6 hours of the UFH 5000 U SQ dose without delay. Their estimate of the additional risk was low (median number of SEH +1:1,000,000; interquartile range: 0–2).
- If the parturient receiving the same UFH 5000 U SQ dose was morbidly obese with a category II fetal heart rate tracing (ie, additional maternal and fetal/neonatal risk), 85% of experts indicated that they would proceed with neuraxial labor analgesia within the 6-hour postdose period, and 96% of them would proceed with neuraxial anesthesia for a cesarean delivery.
- With higher UFH doses, only 46% of experts indicated that they would proceed without checking activated partial thromboplastin time (aPTT) if the woman had received UFH 7500 U SQ within 6 hours, and only 8% of them would proceed without checking aPTT if she had received UFH 10,000 U SQ within 6 hours.
- Most surveyed (89%) would not proceed with neuraxial labor analgesia within 10 hours of an enoxaparin 60 mg SQ daily dose.

Literature Review: Pregnancy-Related Coagulation and Pharmacokinetics

Pregnancy is a hypercoagulable state[45] (Box 2A). Inherited thrombophilias, fluid and electrolyte imbalances, and other clinical risk factors such as obesity or age >35 years may contribute to the 5-fold increased risk of VTE during pregnancy and a 60-fold increased risk in the first 3 months postpartum versus nonobstetric patients.[46,47] In addition, physiologic changes during pregnancy modify drug pharmacokinetics including the volume of distribution (Vd), clearance, bioavailability, and drug metabolism[48] (Box 2B).

Pharmacokinetics of UFH

Although limited data exist, it appears that the pharmacokinetics of UFH SQ differ between pregnant and nonpregnant women. In a small number of low-risk pregnant and nonpregnant women receiving a single weight-based dose of UFH SQ (9500 ± 640 U; mean ± standard error),[53] the pregnant women (N = 6) had lower peak plasma heparin concentrations than the nonpregnant control women (N = 6) (0.11 ± 0.017 vs 0.23 ± 0.036 IU/mL, respectively) and shorter times to peak plasma concentrations (113 ± 20 vs 222 ± 20 minutes, respectively) (Figure 1). The overall plasma heparin concentration (ie, the area under the curve) for the pregnant women was only 55% that of the nonpregnant women, and the pregnant women had no significant increase from their baseline aPTT, in contrast to significant increases in the nonpregnant women's aPTT values. Other investigators also reported no significant increases in aPTT or antifactor Xa levels in low to moderate-risk pregnant

Box 2A. Pregnancy-Related Coagulation Changes

- Increase in platelet aggregation after first trimester[49]
- Increase in coagulation factor levels (II, VII, VIII, IX, X, XII, XIII, and von Willebrand Factor)[45]
- Decrease in endogenous anticoagulant effects (increased resistance to activated protein C and decreased free protein S levels)[45,50]
- Modified fibrinolytic capacity.[45,50]

Box 2B. Pregnancy-Related Physiologic Changes and Their Impact on Anticoagulant Pharmacokinetics

- Increase in maternal plasma volume, resulting in increased volume of distribution for water soluble drugs, and decreased peak and steady-state drug concentrations.[48,51]
- Increase in renal blood flow and glomerular filtration rate by the second trimester, causing a more rapid clearance of drugs excreted by the kidney.[48,51]
- Increase in free fraction of highly protein-bound drugs due to lower albumin concentration in pregnancy coupled with the change in drug metabolism, in part related to placental and fetal metabolic effects.[52]

[a]The Anesthesia Closed Claims Database is funded by the Anesthesia Quality Institute (AQI), the quality division of the ASA. Results were obtained via personal communication from Karen Posner, PhD, Laura Cheney, Professor in Anesthesia Patient Safety, Department of Anesthesiology and Pain Medicine, University of Washington, Seattle, WA. Website: www.asaclosedclaims.org.

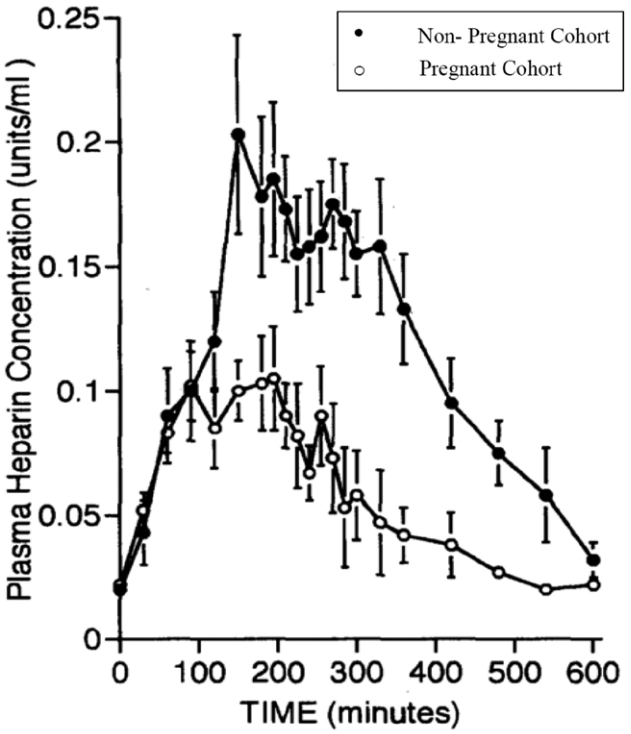

Figure 1. Plasma heparin concentrations in 6 pregnant women at mean gestational age 27 weeks, versus 6 nonpregnant women, after a single dose of weight-adjusted UFH SQ (mean ± standard error of 9500 ± 640 U). SQ indicates subcutaneous; UFH, unfractionated heparin.

women (N = 19) receiving a single dose of UFH 7500 U SQ before cesarean delivery and after neuraxial procedure.[54]

Pregnancy also impacts the linear relationship between plasma heparin concentrations and mean log aPTT; in vitro studies have revealed a "decreased slope" indicating that plasma heparin levels correspond to a lower aPTT in pregnant women compared to nonpregnant women.[55] Proposed mechanisms for this effect include increased binding of circulating nonspecific (heparin neutralizing) proteins and increased levels of factor VIII and fibrinogen in term pregnant women.[55,56]

Although UFH requirements tend to increase in pregnancy with advancing gestation, these requirements can be quite variable. There may be higher heparin requirements in the third trimester, or possibly lower heparin requirements at the end of pregnancy due to a decrease in placental heparinase activity from placental aging.[52] The time interval between the most recent UFH dose (eg, peak versus midinterval) and the laboratory measurements (aPTT or anti-Xa) may impact test results and should be considered when determining UFH requirements.

In summary, these limited data assessing the effect of UFH on coagulation status and laboratory tests in pregnancy, with their inherent limitations of small samples, variability in study designs, and timing of assays, suggest that in pregnant women receiving a single dose of UFH 5000 U, 7500 U, or even 10,000 U SQ, the peak plasma heparin concentration (at approximately 2 hours after the UFH dose) may be at or below the plasma heparin concentration 6 hours after the same UFH dose in nonpregnant women (Figure 1). However, more data are needed for extrapolation to large numbers of pregnant women receiving repeated doses of UFH.

Pharmacokinetics of LMWH

LMWHs are often the drugs of choice for the prevention and treatment of VTE in pregnancy due to ease of administration, a better bioavailability and safety profile, and more predictable dosing compared with UFH.[57,58] Specifically, there is a lower incidence of heparin-induced thrombocytopenia (HIT),[59–61] osteoporosis, and bleeding complications in pregnant women receiving LMWH compared to UFH.[57,58,62–64] Available data suggest that pregnancy impacts the pharmacokinetic profile of commonly utilized LMWHs (such as enoxaparin, dalteparin, and tinzaparin), and some differences exist among the medications due to their different physiochemical structures.[65]

Enoxaparin. Both Vd and clearance of enoxaparin increase during pregnancy. The Vd increase (estimated total increase of 49%) is bimodal, with the largest increase occurring in the third trimester and resolution of these changes occurring a few days postpartum.[66,67] Clearance increases (estimated total increase of 48%) concurrent with the change in glomerular filtration rate and resolves approximately 2 weeks postpartum.[66,68] In 1 study, when pregnant (N = 75) and nonpregnant women (N = 10) received enoxaparin 40 mg SQ daily for thromboprophylaxis throughout pregnancy, the peak anti-Xa activity and global exposure were lower in pregnant women than in nonpregnant women[66] (Figure 2).

In a longitudinal study evaluating the pharmacokinetics of low-dose enoxaparin (40 mg SQ daily; N = 13) at 2 points during pregnancy (12–15 weeks of gestation, 30–33 weeks of gestation) and 6–8 weeks postpartum, the maximum plasma concentration and anti-Xa activity measured were lower during pregnancy compared to the postpartum period.[67]

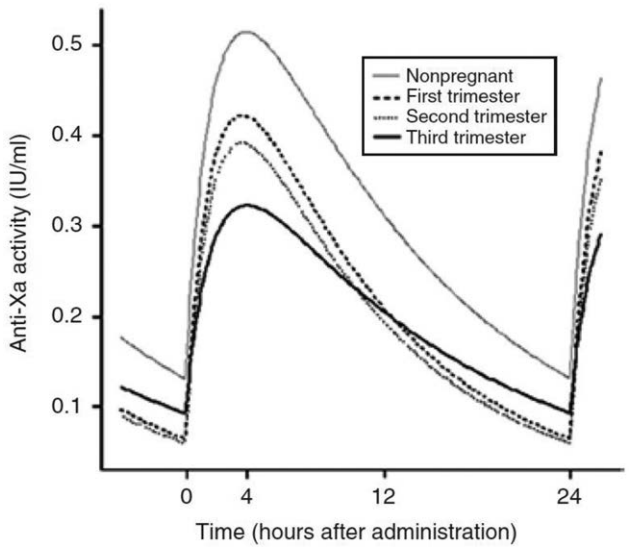

Figure 2. Typical antifactor Xa activity profiles with repeated administration of 40 mg enoxaparin SQ, daily, in pregnant women at each trimester, versus nonpregnant women. SQ indicates subcutaneous.

In summary, these data suggest that in a pregnant cohort, the measured anti-Xa activity of LMWH at 8-hour postdose (during first or second trimester) or 6 hours (during third trimester) may be comparable to the 12-hour postdose activity found in nonpregnant patients.

Dalteparin. In an investigation of the pharmacokinetics of prophylactic, weight-adjusted dosing of dalteparin (5000 U SQ for 50–79 kg) in moderate-risk third trimester pregnant women (N = 17), the mean maximal concentration and area under the curve (0–24 hours)[69] were also lower compared to nonpregnant controls[70] (for mean maximal concentration: 0.21 ± 0.05 vs 0.49 ± 0.13 anti-Xa IU/mL, respectively; for area under the curve: 1.97 ± 0.46 IU vs 3.23 ± 0.85 h/mL, respectively). The average time to peak concentration was 3 hours, and the mean half-lives were 4.9 and 3.9 hours (morning and evening dose) in the pregnant women (N = 17). The results of a similar longitudinal study of moderate-risk pregnant women (N = 24) receiving 5000 U dalteparin SQ once daily showed significantly lower mean anti-Xa levels during pregnancy compared to 6-week postpartum, with the lowest reading at 36 weeks of gestation.[71]

Tinzaparin. Studies examining the pharmacokinetics of tinzaparin in pregnancy do not directly compare pregnant and nonpregnant women.[72–75] In 1 investigation, a cohort of pregnant women at moderate risk for VTE received tinzaparin 50 IU/kg SQ once daily, the recommended prophylactic dose for nonpregnant patients undergoing general surgery. Peak (4 hours) anti-Xa levels were frequently below 0.1 IU/mL and reduced 24-hour anti-Xa levels were found at 36 weeks compared to 28 weeks of gestation.[76] In keeping with other LMWHs, these results suggest an impact of pregnancy on the drug's pharmacokinetics.

Protamine to Reverse Anticoagulation

Protamine sulfate can result in full reversal of UFH and 60%–80% reversal of LMWH[77] (Box 3); however, its use in pregnancy to facilitate neuraxial anesthesia has not been studied. A single case study after a maternal 25 mg intravenous (IV) protamine dose before delivery reported severe neonatal respiratory depression, although a causal relationship was not established.[78]

Assessment of Coagulation Status and Spinal Epidural Hematoma Risk in Pregnancy

Unfortunately, there is currently no standardized test to assess the SEH risk from neuraxial anesthesia in patients receiving anticoagulants as there are no specific data correlating aPTT, anti-Xa assay, or point-of-care test levels with SEH risk (Table 2).[54–56,74,75,80–83] In addition, in pregnancy, the underlying alteration in coagulation status and response to anticoagulation can make interpretation of coagulation tests and risk assessment even more challenging.

- LMWH: The anesthesia professional organizations and the FDA recommend waiting prespecified time intervals (reflecting anticoagulant half-lives) after either low- or high-dose LMWH, rather than ordering laboratory testing and considering cut-offs, to inform decisions about the safe timing of neuraxial procedures (Table 1). A recently published quality initiative identified measurable residual anti-Xa levels beyond 24 hours in older age patients with comorbid disease (eg, cancer, heart disease) who received high-dose enoxaparin.[84] The relevance of this report to pregnant women is uncertain given the anti-Xa levels observed in pregnant women compared with nonpregnant women (Figure 2). The authors raised the question whether anti-Xa levels should accompany the suggested time intervals, although they importantly acknowledge that "we do not know the anti-Xa level below which the risk of bleeding and associated serious sequelae are no higher than usual, and at which it is reasonable to proceed with a neuraxial procedure."[84] We support additional research on this question, specific to the pregnant patient, to help inform future iterations of these guidelines.
- UFH: Interindividual variability in response to UFH compared to LMWH is greater, and the therapeutic index is narrower. Particularly at the intermediate and higher doses of UFH, ASRA and the other anesthesia professional organizations recommend combining time intervals and coagulation status assessment. The current ASRA guidelines do not specify either the preferred coagulation test or the cutoff or threshold for specific laboratory indices before proceeding with a neuraxial procedure. Of the available laboratory tests in the United States, the aPTT is the most frequently used to assess the coagulation status of a patient receiving UFH before neuraxial procedures. Measuring the aPTT is relatively simple and inexpensive, whereas the anti-Xa assay may not be readily available within institutions, overnight, or at all. However, there are also limitations to the aPTT test, such as variable reference ranges (between institutions and different reagents) and the impact of untested anticoagulant factors (eg, lupus anticoagulant). When used, results of the aPTT or anti-Xa assay should be combined with other available information (ie, dose, time since last dose, competing risks) to engage in shared decision making with the pregnant woman.

Box 3. Protamine to Reverse Anticoagulation

- Each 1 mg IV protamine can neutralize 100 U of IV heparin.[79] Reversal of SQ heparin may require repeated doses of IV protamine (half-life approximately 7 minutes).
- Maternal side effects and complications of protamine include, but are not limited to, hypotension from histamine release, hypersensitivity reactions, anaphylaxis, pulmonary hypertension, noncardiogenic pulmonary edema, coagulation disturbance related to thrombocytopenia, altered platelet aggregation, fibrinogen precipitation, and reduced thrombin effect.[79]

RECOMMENDATIONS FOR PHYSICIAN ANESTHESIOLOGISTS AND OTHER PRACTITIONERS

This SOAP consensus statement is not intended to set out a legal standard of care and does not replace medical care or the judgment of the responsible medical professional considering all the circumstances presented by an individual patient. This consensus statement is not intended to ensure a successful patient outcome in every situation and is not a guarantee of any specific outcome. This consensus

Table 2. Applications and Limitations of Coagulation Assessment in Pregnancy

Test	Applications	Limitations
aPTT[55,56]	-Used to adjust high UFH therapy doses to target range -Despite lack of data, aPTT is often used to inform decisions about the safe timing of neuraxial procedures	-Low and varying sensitivity to aPTT for LMWH -Reference range varies in pregnancy and between lab reagents -In term pregnancy, the aPTT response to UFH is ↓ due to ↑ FVIII and fibrinogen, and ↑ nonspecific protein binding
Antifactor Xa[80]	-Used to adjust high LMWH or UFH doses to target range -Undetectable level (eg, <0.01 IU/mL) may be reassuring for neuraxial procedure -Suggests little to no residual effect of UFH or LMWH	-Antithrombin effects of UFH not represented -LMWH have differing affinities for antifactor Xa -May not correlate with actual effect of drug in vivo -Characterize pharmacokinetics not pharmacodynamics -Test may not be rapidly available or available 24/7 -Threshold for safe neuraxial block insertion is unknown
Point-of-care[54,74,75,81–83] Thromboelastography (TEG) Thromboelastometry (ROTEM)	-Some results (related to clot formation) can be available within 15–20 min -Baseline reference ranges for TEG® in pregnancy have been established -Isolated case reports describe use in pregnant patients receiving thromboprophylaxis to determine suitability for neuraxial procedure	-Safe ranges for neuraxial procedures in obstetric patients on thromboprophylaxis have not been established -Tests are not currently widely available within US health care facilities -Recommendation to use these tests to determine fitness for neuraxial procedures cannot be made without additional evidence

Abbreviations: aPTT, activated partial thromboplastin time; FVIII, factor level VIII; LMWH, low molecular weight heparin; UFH, unfractionated heparin.

statement is subject to periodic revision as additional data become available. The recommendations assume normal renal function in the context of pregnancy, body weight >40 kg, and no other contraindications to neuraxial anesthesia.

Antepartum Recommendations

The optimal way to prepare the pregnant woman on thromboprophylaxis or higher dose anticoagulants for delivery is through advanced planning. It is critically important that the multidisciplinary care team knows which women are receiving UFH or LMWH, the time of their last dose, and whether they are appropriate candidates to have their thromboprophylaxis or higher dose anticoagulants held during labor and delivery. Some women may benefit from consultation with a hematologist or thrombosis expert, for example, if there are concerns that she may not be an appropriate candidate for a prolonged interval without antithrombotic medication.

Critical elements of this structured communication may include the following:

- A readily accessible, standardized protocol that outlines which pregnant and newly postpartum women qualify for thromboprophylaxis (eg, NPMS, CMQCC, or other relevant guidelines) (Class I C-EO).
- A system-wide alert (via electronic medical record, if applicable) that flags the record of each woman receiving thromboprophylaxis or higher dose anticoagulants (Class IIa C-EO).
- Predelivery anesthesia consultation

  1. Communication between the obstetric and anesthesia teams about antepartum inpatients receiving thromboprophylaxis or higher dose anticoagulants should occur at 36 weeks of gestation (or earlier if delivery is imminent) (Class IIa C-EO).
  2. Outpatients with additional comorbidities (eg, concomitant medical or obstetric morbidity, difficult airway) who are receiving thromboprophylaxis or higher dose anticoagulants can benefit from referral by their obstetric providers for outpatient antenatal anesthesia consultation (Class IIa C-EO).

- Prompt communication of changes in a pregnant woman's status that increase her risk of imminent or high-risk delivery, by the obstetric team, to the covering anesthesia and nursing teams (Class IIa C-EO). Subsequent trigger of an order to hold anticoagulant dose may be beneficial until further evaluation by the obstetric team (Class IIa C-EO).

Additional antepartum preparation includes the following:

- Adoption of an antepartum thromboprophylactic regimen that facilitates neuraxial procedures (Class IIa C-EO).

  1. For antepartum inpatients requiring thromboprophylaxis, consider using the mechanical thromboprophylaxis or low-dose UFH (eg, 5000 U SQ twice daily) options in the obstetric guidelines, rather than LMWH or higher dose UFH (Class IIa C-EO).
  2. For antepartum outpatients requiring thromboprophylaxis:

     a. Consider switching from LMWH to low-dose UFH 5000 U SQ twice daily, at 36 weeks of gestation or earlier, particularly in women with additional comorbidities (eg, concomitant medical or obstetric morbidity, difficult airway), or women at a high risk for urgent cesarean or preterm labor (Class IIa C-EO).
     b. When the plan is to continue low, intermediate, or high LMWH beyond 36 weeks of gestation, anticipate the need to hold LMWH as described in Intrapartum Recommendations (Class IIa C-EO).
     c. If delivery or other procedure (eg, external cephalic version) is planned, then consider holding UFH or LMWH as described in Intrapartum Recommendations (Class IIa C-EO).

- For all women on UFH for >4 days, check platelet count before neuraxial procedure to rule out HIT (Class I C-EO).[b]

Intrapartum Recommendations

A primary goal in the intrapartum period is to minimize the chance that the pregnant woman has recently received her thromboprophylaxis or higher dose anticoagulants when she desires labor epidural analgesia or needs a neuraxial anesthetic. Key elements in proactive planning include well-established protocols for elective procedures and tools to guide the decision-making process in unplanned circumstances. To facilitate anesthetic decisions in urgent or emergent situations, the SOAP VTE taskforce members have created Decision Aids (Figures 3 and 4) that integrate the ASRA guidelines, pharmacokinetics of anticoagulants in pregnancy, and the competing risks of general anesthesia and fetal well-being.

- Protocols in every unit:
  1. Every unit should have easily accessible protocols available to patients and to all obstetricians, physician anesthesiologists and other practitioners, and nurses involved in their care delineating when pregnant and newly postpartum women should have anticoagulant medications held. These protocols should be incorporated into the medical record, with associated alerts to hold anticoagulant if patient is admitted for delivery. The drug hold should trigger an obstetric evaluation and a plan for appropriate next management steps (Class IIa C-EO).
  2. Similarly, every unit should have standardized protocols to ascertain when women receiving thromboprophylaxis or higher dose anticoagulants are eligible for neuraxial anesthesia. These protocols should be shared with patients, obstetricians, and nurses so that all members of the care team develop consensus on the available analgesic or anesthetic options (Class I C-EO).
- Preprocedure huddles and daily multidisciplinary rounds should emphasize the mode of thromboprophylaxis, timing and amount of the most recent anticoagulant dose, and plans for reinitiating therapy for all relevant patients (Class IIa C-EO).
- Time intervals between anticoagulant dosing and neuraxial procedure:

  Elective obstetric procedures (eg, cerclage, induction of labor, planned cesarean delivery, external cephalic version, or postpartum bilateral tubal ligation):

  1. Both the magnitude of each individual dose and the total daily dose are considered in the recommended time intervals between the last dose and the neuraxial procedure. These time intervals also apply to removal of an epidural catheter. All

[b]Pregnant patients receiving LMWH heparin without additional risk factors have <1% risk of HIT, and therefore routine monitoring of platelet counts is not recommended.

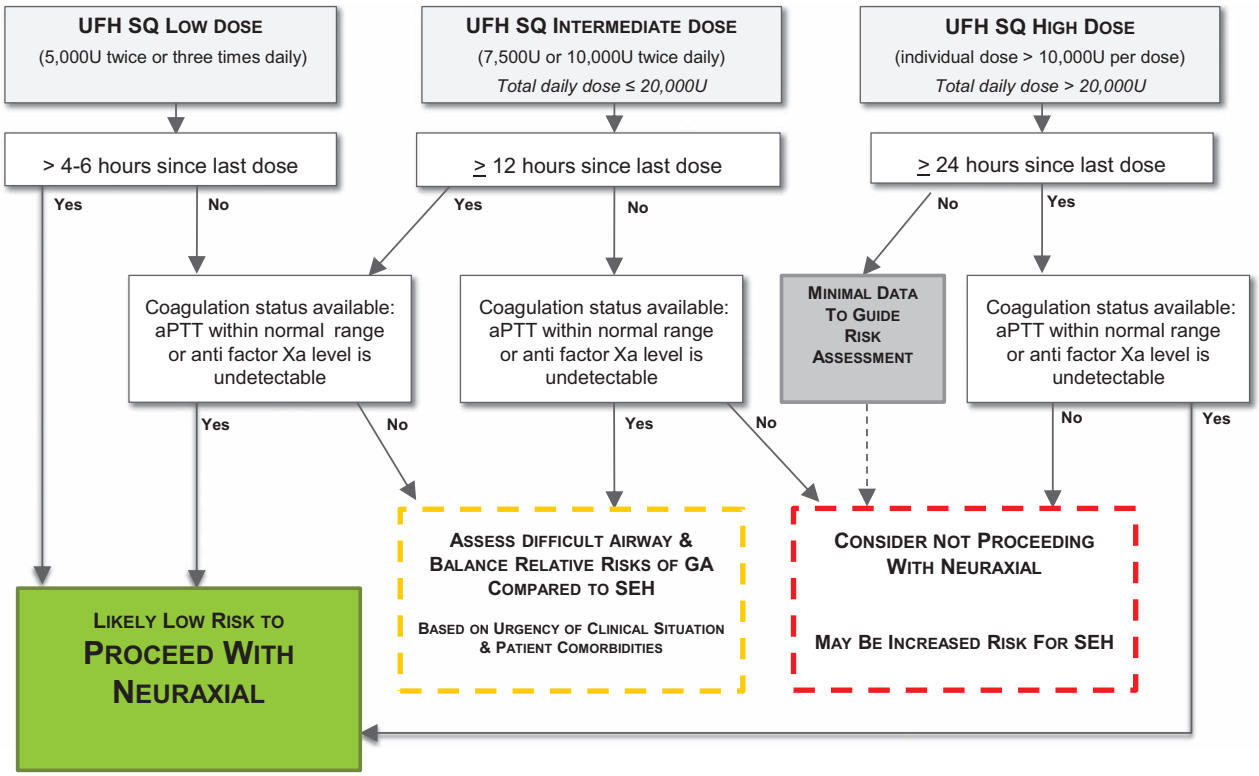

Figure 3. Decision aid for urgent or emergent neuraxial procedures in the obstetric patient receiving UFH. *Assume normal renal function, body weight > 40 kg, and no other contraindications to neuraxial anesthesia. aPTT indicates activated partial thromboplastin time; GA, general anesthesia; SEH, spinal epidural hematoma; SQ, subcutaneous; UFH, unfractionated heparin. Note: This SOAP consensus statement is not intended to set out a legal standard of care and does not replace medical care or the judgment of the responsible medical professional considering all the circumstances presented by an individual patient.

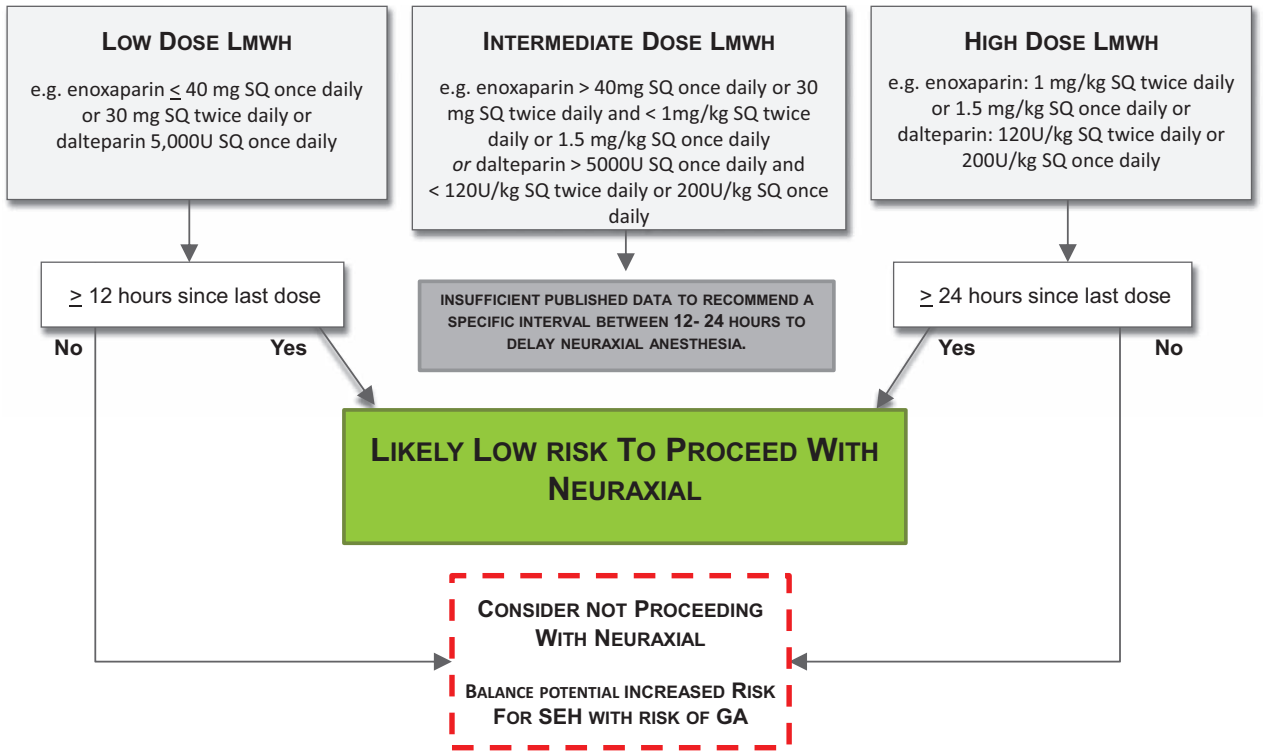

Figure 4. Decision aid for urgent or emergent neuraxial procedures in the obstetric patient receiving LMWH. *Assume normal renal function, body weight >40 kg, and no other contraindications to neuraxial anesthesia. GA indicates general anesthesia; LMWH, low molecular weight heparin; SEH, spinal epidural hematoma; SQ, subcutaneous. Note: This SOAP consensus statement is not intended to set out a legal standard of care and does not replace medical care or the judgment of the responsible medical professional considering all the circumstances presented by an individual patient.

recommendations assume the absence of other contraindications to neuraxial anesthesia, renal insufficiency, or body weight <40 kg.

Unfractionated Heparin

a. For low-dose UFH thromboprophylaxis (ie, 5000 U SQ twice daily or 3 times daily), consider holding the dose for 4–6 hours before placing neuraxial anesthetic or assessing coagulation status, as per ASRA recommendations, for elective procedures (Class IIa C-EO).
b. For intermediate-dose UFH thromboprophylaxis, (eg, 7500 U SQ twice daily or 10,000 U SQ twice daily), consider holding the dose 12 hours and assessing coagulation status before placing a neuraxial anesthetic (Class IIa C-EO).
c. For high-dose UFH (eg, individual dose >10,000 U SQ per dose, or >20,000 U SQ total daily dose), consider holding the dose 24 hours before placing a neuraxial anesthetic and assessing coagulation status to help guide anesthetic management (Class IIa C-EO).
d. For IV heparin, consider stopping the infusion 4–6 hours and then assessing coagulation status before placing a neuraxial anesthetic (Class IIa C-EO).

Low Molecular Weight Heparin

e. For low-dose LMWH thromboprophylaxis (eg, enoxaparin ≤40 mg SQ once daily or 30 mg SQ twice daily, or dalteparin 5000 U SQ once daily), consider holding the dose ≥12 hours before placing a neuraxial anesthetic as recommended by the FDA and ASRA (Class I C-EO).
f. For intermediate-dose LMWH thromboprophylaxis (eg, enoxaparin >40 mg SQ once daily or 30 mg SQ twice daily and <1 mg/kg SQ twice daily or 1.5 mg/kg SQ once daily or dalteparin >5000 U SQ once daily and <120 U/kg SQ twice daily or 200 U/kg SQ once daily), there are insufficient published data to recommend a specific interval between 12 and 24 hours to wait before proceeding with neuraxial anesthesia (Class IIb C-EO).
g. For higher dose LMWH (eg, enoxaparin 1 mg/kg SQ twice daily or 1.5 mg/kg SQ once daily; dalteparin 120 U/kg SQ twice daily or 200 U/kg SQ once daily), consider holding the dose ≥24 hours before placing a neuraxial anesthetic as recommended by the FDA and ASRA (Class I C-EO).

2. ***Urgent and emergent obstetric procedures:***

a. Educate the pregnant woman to hold UFH or LMWH dose if she suspects that she is in labor, has rupture of membranes, and/or if she has vaginal bleeding, pending timely discussion with her obstetrician about appropriate next steps (Class IIa C-EO).
b. SOAP Neuraxial Anesthesia Decision Aid for UFH (Figure 3)
   i. For low-dose UFH thromboprophylaxis (ie, 5000 U SQ twice or 3 times daily), the 2017 ASRA guidelines now suggest waiting 4–6 hours after

the last dose before placing the neuraxial anesthetic or assessing coagulation status.
-However, in urgent cases, with greater competing risks of general anesthesia compared to the risk of SEH from neuraxial blockade, the placement of neuraxial anesthesia without delay may be appropriate. Although high level data are lacking, a systematic review of cases, expert opinion, and the updated ASRA guidelines support this practice if needed (Class IIa C-EO).

ii. For intermediate-dose UFH thromboprophylaxis (eg, 7500 U SQ twice daily or 10,000 U SQ twice daily), ASRA guidelines suggest waiting 12 hours after the last dose before neuraxial anesthesia and assessing coagulation status.
-However, in urgent cases, with greater competing risks of general anesthesia compared to the risk of SEH from neuraxial blockade, the placement of neuraxial anesthesia without delay may be appropriate (Class IIa C-EO).

iii. For high-dose UFH (eg, individual dose >10,000 U SQ per dose, or >20,000 U SQ total daily dose), if ≥24 hours since dose and normal coagulation assessment (eg, aPTT within normal range or anti-Xa result is "undetectable" or below the limits of the assay), likely low risk to proceed with neuraxial anesthesia. Otherwise, there are insufficient data to recommend proceeding with the neuraxial procedure (Class IIb C-EO).

iv. Protamine should only be considered in situations where UFH needs to be urgently reversed (Class IIb C-EO).

c. SOAP Neuraxial Anesthesia Decision Aid for LMWH (Figure 4):

i. For low-dose LMWH thromboprophylaxis (eg, enoxaparin ≤40 mg SQ once daily or 30 mg SQ twice daily, or dalteparin 5000 U SQ once daily), if given ≥12 hours ago, likely low risk to proceed with neuraxial anesthesia (Class I C-EO).

ii. For low-dose LMWH thromboprophylaxis (eg, enoxaparin ≤40 mg SQ once daily or 30 mg SQ twice daily, or dalteparin 5000 U SQ once daily), if given <12 hours before planned neuraxial anesthetic, there are insufficient data to recommend proceeding with neuraxial anesthesia.
-However, in circumstances involving select high-risk parturients receiving low-dose LMWH thromboprophylaxis and urgent intervention for maternal or fetal indications, the risk of general anesthesia may be higher than the risk of SEH with neuraxial anesthesia (Class IIb C-EO).

iii. For intermediate-dose LMWH thromboprophylaxis (eg, enoxaparin >40 mg SQ once daily or 30 mg SQ twice daily and <1 mg/kg SQ twice daily or 1.5 mg/kg SQ once daily or dalteparin >5000 U SQ once daily and <120 U/kg SQ twice daily or 200 U/kg SQ once daily), there are insufficient published data to recommend a specific interval between 12 and 24 hours to wait before proceeding with neuraxial anesthesia (Class IIb C-EO).

iv. For higher dose LMWH (eg, enoxaparin 1 mg/kg SQ twice daily or 1.5 mg/kg SQ once daily; dalteparin: 120 U/kg SQ twice daily or 200 U/kg SQ once daily) given ≥24 hours, likely low risk to proceed with neuraxial anesthesia (Class I C-EO).

v. For higher dose LMWH (eg, enoxaparin 1 mg/kg SQ twice daily or 1.5 mg/kg SQ once daily; dalteparin: 120 U/kg SQ twice daily or 200 U/kg SQ once daily) given <24 hours, there are insufficient data to recommend proceeding with neuraxial anesthesia (Class IIb C-EO).

Postpartum Recommendations

- For SQ UFH thromboprophylaxis, wait ≥1 hour after neuraxial procedure (if no signs of postpartum hemorrhage) and ≥1 hour after epidural catheter removal before initiating or restarting thromboprophylaxis.

  1. Indwelling catheters can be maintained with low-dose UFH (specifically 5000 U SQ twice daily). Nonsteroidal anti-inflammatory agents (NSAIDs) (including aspirin), but not acetaminophen, with an in situ epidural and thromboprophylaxis may increase the risk of bleeding complications. Catheter removal can occur ≥4–6 hours after a dose of UFH and subsequent UFH dosing should occur ≥1 hour after catheter removal (Class IIb C-EO).

- For IV UFH, wait ≥1 hour after neuraxial block (if no signs of postpartum hemorrhage) before initiating or restarting anticoagulation (Class IIb C-EO).

- For low-dose LMWH thromboprophylaxis (eg, enoxaparin ≤40 mg SQ once daily or 30 mg SQ twice daily, or dalteparin 5000 U SQ once daily), wait ≥12 hours after the neuraxial procedure and ≥4 hours after the epidural catheter removal before initiating or restarting LMWH thromboprophylaxis.

  1. Indwelling catheters can be maintained with low-dose LMWH. NSAIDs (including aspirin), but not acetaminophen, with an in situ epidural and thromboprophylaxis may increase the risk of bleeding complications. Catheter removal can occur ≥12 hours after a LMWH dose and subsequent LMWH dosing should occur ≥4 hours after catheter removal (Class I C-EO).

- For higher dose LMWH (eg, enoxaparin 1 mg/kg SQ twice daily or 1.5 mg/kg SQ once daily; dalteparin 120 U/kg SQ twice daily or 200 U/kg SQ once daily), consider waiting ≥24 hours after the neuraxial procedure and ≥4 hours after epidural catheter removal before initiating or restarting LMWH therapy (Class I C-EO).

- For a few select circumstances, there may be a benefit to bridging with UFH 5000 U SQ (twice or 3 times daily) instead of LMWH because of its shorter duration of action and because it can be restarted sooner than LMWH (1 vs 4 hours) (Class IIb C-EO).

Table 3. The SOAP Consensus Statement on the Anesthetic Management of Pregnant and Postpartum Women Receiving Thromboprophylaxis or Higher Dose Anticoagulants

	Intrapartum		Postpartum
SOAP (2017)	**ELECTIVE**	**URGENT AND EMERGENT**	
Subcutaneous UFH	For low-dose UFH thromboprophylaxis: (ie, 5000 U SQ BID or TID) • Consider holding dose for 4–6 h before NB or assessing coagulation status (Class IIa C-EO) For intermediate-dose UFH thromboprophylaxis (eg, 7500 U SQ BID or 10,000 U SQ BID) • Consider holding dose 12 h and assessing coagulation status before NB (Class IIa C-EO) For high-dose UFH (eg, individual dose >10,000 U SQ per dose, or >20,000 U SQ total daily dose) • Consider holding dose 24 h before NB and assessing coagulation status (Class IIa C-EO)	For low-dose UFH thromboprophylaxis:(ie, 5000 U SQ, BID or TID) • ASRA suggests waiting 4–6 h after last dose before NB or assessing coagulation status. -However, in urgent cases, with greater competing risks of GA compared to the risk of SEH from neuraxial procedure, the placement of neuraxial anesthesia without delay may be appropriate (Class IIa C-EO) For intermediate-dose UFH thromboprophylaxis (eg, 7500 U SQ BID or 10,000 U SQ BID) • ASRA suggests waiting 12 h after last dose before NB and assessing coagulation status. -However, in urgent cases, with greater competing risks of GA compared to the risk of SEH from neuraxial procedure, the placement of neuraxial anesthesia without delay may be appropriate (Class IIa C-EO) For high-dose UFH (eg, individual dose >10,000 U SQ per dose or >20,000 U SQ total daily dose) • If ≥ 24 h since dose and normal coagulation assessment (eg, aPTT within normal range or undetectable antifactor Xa level), likely low risk to proceed with NB. Otherwise, insufficient additional data to recommend proceeding with NB (Class IIb C-EO)	For SQ UFH thromboprophylaxis: (ie, regardless of dose) • Wait ≥1 h after NB and after CR before initiating or restarting UFH • Indwelling catheters can be maintained with low dose (specifically UFH 5000 U SQ BID): -CR can occur ≥4–6 h after a dose of UFH and subsequent UFH dosing should occur ≥1 h after CR (Class IIb C-EO) • Consider holding NSAIDs (including aspirin), but not acetaminophen, until CR if receiving thromboprophylaxis (Class IIa C-EO)
Intravenous UFH	• Consider stopping infusion 4–6 h and then assessing coagulation status before placing NB (Class IIa C-EO)		• Wait ≥1 h after NB before initiating or restarting anticoagulation (Class IIb C-EO)
LMWH	For low-dose LMWH thromboprophylaxis (eg, enoxaparin ≤40 mg SQ once daily or 30 mg SQ BID, or dalteparin 5000 U SQ once daily) • Consider holding dose ≥12 h before placing NB (Class I C-EO) For intermediate-dose LMWH thromboprophylaxis (eg, enoxaparin >40 mg SQ once daily or 30 mg SQ BID and <1 mg/kg SQ BID or 1.5 mg/kg SQ once daily or dalteparin >5000 U SQ once daily and <120 U/kg SQ BID or 200 U/kg SQ once daily) • Insufficient data to recommend specific interval between 12 and 24 h to delay before NB (Class IIb C-EO) For higher dose LMWH (eg, enoxaparin 1 mg/kg SQ BID or 1.5 mg/kg SQ once daily; dalteparin: 120 U/kg SQ BID or 200 U/kg SQ once daily) • Consider holding dose ≥24 h before placing NB (Class I C-EO)	For low-dose LMWH thromboprophylaxis (eg, enoxaparin ≤40 mg SQ once daily or 30 mg SQ BID; or dalteparin 5000 U SQ once daily) • If given ≥12 h ago, likely low risk to proceed with NB (Class I C-EO) • If given <12 h before planned NB: insufficient additional data to recommend proceeding with NB -However, in high-risk circumstances where urgent intervention is needed for maternal or fetal indications, risk of GA may be higher than the risk of SEH with NB (Class IIb C-EO) For intermediate-dose LMWH thromboprophylaxis (eg, enoxaparin >40 mg SQ once daily or 30 mg SQ BID and <1 mg/kg SQ BID or 1.5 mg/kg SQ once daily or dalteparin >5000 U SQ once daily and <120 U/kg SQ BID or 200 U/kg SQ once daily) • Insufficient data to recommend specific interval between 12 and 24 hours to delay before NB (Class IIb C-EO) For higher dose LMWH (eg, enoxaparin 1 mg/kg SQ BID or 1.5 mg/kg SQ once daily; dalteparin: 120 U/kg SQ BID or 200 U/kg SQ once daily) • If given ≥24 h, likely low risk to proceed with NB (Class I C-EO) • If given <24 h, insufficient additional data to recommend proceeding with NB (Class IIb C-EO)	For low-dose LMWH thromboprophylaxis (eg, enoxaparin <40 mg SQ once daily or 30 mg SQ BID; or dalteparin 5000 U SQ once daily) • Wait ≥ 12 h after NB and ≥4 h after CR before initiating or restarting LMWH thromboprophylaxis • Indwelling catheters can be maintained with low-dose LMWH: -CR can occur ≥12 h after a LMWH dose and subsequent LMWH dosing should occur ≥4 h after CR (Class I C-EO) • Consider holding NSAIDs (including aspirin), but not acetaminophen, until CR if receiving thromboprophylaxis (Class IIa C-EO) For higher dose LMWH (eg, enoxaparin 1 mg/kg SQ BID or 1.5 mg/kg SQ once daily; dalteparin: 120 U/kg SQ BID or 200 U/kg SQ once daily) • Consider waiting ≥24 h after NB and ≥4 h after CR before initiating or restarting LMWH thromboprophylaxis (Class I C-EO)

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Abbreviations: aPTT, activated partial thromboplastin time; ASRA, American Society of Regional Anesthesiology and Pain Medicine; BID, twice daily; CR, catheter removal; GA, general anesthesia; LMWH, low molecular weight heparin; NB, neuraxial block; NSAID, nonsteroidal anti-inflammatory drug; SEH, spinal epidural hematoma; SOAP, Society for Obstetric Anesthesia and Perinatology; SQ, subcutaneous; TID, three times daily; UFH, unfractionated heparin.

These scenarios could include the following:

1. Early postcesarean delivery thromboprophylaxis (<12 hours after surgery)
2. Risk of postpartum hemorrhage after cesarean delivery
3. Planned postpartum surgical procedure (eg, tubal ligation) and/or neuraxial procedure (eg, epidural blood patch)
4. Presence of an indwelling, postpartum, epidural catheter to facilitate removal

- NSAIDs, along with acetaminophen, are key components of an effective postcesarean delivery pain management plan. In the absence of other contraindications, women who received a neuraxial procedure and no longer have an epidural catheter in situ should receive NSAIDs and acetaminophen even if they will be receiving low-dose thromboprophylactic UFH or LMWH doses.

1. Consider holding NSAIDs (including aspirin), but not acetaminophen, until the epidural catheter is withdrawn if patient is receiving thromboprophylaxis with UFH SQ or LMWH SQ (Class IIa C-EO).

Quality Assurance

The integrity and continued growth of the multidisciplinary care team depends, in part, on a culture that promotes nonjudgmental debriefings of cases.

- Successful and challenging cases involving thromboprophylaxis or higher dose anticoagulant therapy with or without neuraxial procedures should be formally discussed on a routine basis to identify potential areas for improvement in systems, communication, and clinical care (Class IIb C-EO).
- Systems to identify, treat, and report complications (eg, SEH) and near misses (eg, failures to recognize that women were receiving UFH or LMWH) are likely to be beneficial.

1. The patient, nurses, obstetricians, physician anesthesiologists, and other providers should all be aware of possible signs and symptoms of SEH including back pain, extremity numbness, and weakness, particularly after a block has initially resolved (Class I C-EO).
2. Institutional pathways to obtain urgent magnetic resonance imaging and appropriate consultation need to be defined and readily available for bedside clinicians (Class 1 C-EO).
3. Confirmed cases of SEH should be reported through institutional quality assurance as per protocol, as well as through the ASA AQI and its Anesthesia Incident Reporting System[c] and MedWatch[d] (Class I C-EO).

- SOAP Consensus statement ante-, intra-, and postpartum recommendations for neuraxial anesthesia in the setting of UFH and LMWH are summarized in Table 3.

CONCLUDING REMARKS

In conclusion, the use of anticoagulant thromboprophylaxis will likely increase in pregnant and postpartum women in the United States in response to recent guidelines and recommended practice changes. The SOAP consensus statement lays the foundation for proactive planning, and multidisciplinary team communication to ensure that pregnant women who qualify for thromboprophylaxis or higher dose anticoagulants will continue to safely benefit from neuraxial anesthesia without an increased risk of SEH.

The taskforce committed to attaining full consensus, in light of the limited available evidence and the potential confusion created by disparate published guidelines on this topic. This approach was particularly controversial for women receiving UFH 5000 U SQ twice daily. Many of the taskforce experts endorsed proceeding with neuraxial anesthesia without a time delay citing the favorable, albeit limited, pharmacokinetic data and the historical lack of reported SEH in this setting. However, some experts felt that there were insufficient data to assess the population risk of SEH with expanded use of thromboprophylaxis, and therefore, it was appropriate to err on the side of being more conservative. In response, the updated ASRA and the SOAP consensus recommendations incorporated language acknowledging that in some instances, the risks of SEH in a pregnant woman receiving neuraxial anesthesia may be lower than the risks of general anesthesia and it may be appropriate to proceed with a neuraxial procedure without delay. All parties agreed that more studies are needed to effectively assess the effects of UFH and LMWH on coagulation in pregnant women and the incidence of SEH in this context.

In urgent clinical settings where pregnant women have received recent thromboprophylaxis or higher dose anticoagulants, the Decision Aids and detailed commentary can help clinicians, in discussion with their patients, make better informed decisions about the competing risks of neuraxial compared to general anesthesia. Further research and rigorous reporting of complications and missed opportunities for neuraxial anesthesia are needed to inform future guidelines in this area.

APPENDIX

The full list of members of the SOAP VTE Taskforce is as follows: Chairs of the SOAP VTE Taskforce are as follows: Lisa Leffert, MD, Co-Chair (Department of Anesthesia, Critical Care and Pain Medicine, Massachusetts General Hospital, Boston, Massachusetts) and Ruth Landau, MD, Co-Chair (Department of Anesthesiology, Columbia University College of Physicians and Surgeons, New York, New York). Members of the SOAP VTE taskforce are as follows: Katherine Arendt, MD, (Department of Anesthesiology and Perioperative Medicine, Mayo Clinic, Rochester, Minnesota); Shannon M. Bates, MDCM, MSc (Department of Medicine, Thrombosis and Atherosclerosis Research

[c]The AQI, established in 2008, created the National Anesthesia Clinical Outcomes Registry in 2010 to assess adverse events and improve quality of anesthetic care. The National Anesthesia Clinical Outcomes Registry reports on 45 metrics, such as admission, perioperative mortality, and pain measures.

[d]MedWatch, founded by the US FDA, is an online, voluntary, adverse event–reporting system available to health professionals and patients.

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DISCLOSURES

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