Shall we rethink the timing of epidural anesthesia in anticoagulated obstetrical patients?

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Phylopathic anticoagulation is indicated during pregnancy for patients with a history of venous thromboembolism (VTE), high-risk thrombophilia, and obstetrical antiphospholipid syndrome.1,2 Other pregnant patients necessitate maintaining long-term therapeutic anticoagulation (eg, for atrial fibrillation, congenital cardiopathies, or recurrent VTE).3,4 The drugs of choice are usually low-molecular-weight heparins (LMWHs) as they do not cross the placenta or have teratogenic effects and have stable pharmacokinetics, together with a large body of data supporting their favorable risk-benefit balance.5,6 Continuous intravenous infusion of unfractionated heparin (UFH) might represent an alternative for the inpatient setting (prophylactic or therapeutic indications), although subcutaneous UFH administration is sometimes substituted for prophylactic LMWHs.

Various scientific societies have issued guidelines on the management of anticoagulation in pregnancy, notably around the time of labor and for the use of epidural anesthesia,4–8 which is the favored mode of pain management with an enhanced safety profile.9 The guidelines uniformly recommend waiting 24 hours for “epidural” catheter placement since the last administration of therapeutic-dose LMWH (regardless of whether it is administered once or twice daily), although a 12-hour delay is deemed sufficient in case of prophylactic dosage. We hereby propose a collection of arguments to reduce this delay to 12 hours for twice-daily therapeutic dosage, similar to prophylactic doses, therefore allowing quicker access to adequate pain management for these patients.

Except for the Society for Obstetric Anesthesia and Perinatology,7 these recommendations indiscriminately apply to all patients, although the obstetrical population represents a distinct demographic subgroup of younger and otherwise healthy individuals. Outside of rare, well-recognized conditions, such as preeclampsia in which renal function may deteriorate rapidly and patients with chronic renal insufficiency, the risk of LMWH accumulation is exceedingly uncommon in pregnant patients. Furthermore, minimal residual anticoagulant activity might be compensated by a pregnancy-associated hypercoagulable state.10 The incidence of spinal or “epidural” hematoma with neuraxial anesthesia has been shown to be 5 to 10 times lower in the obstetrical population (with an estimated incidence of 3:1,000,000 to 4:1,000,000) than in the general population.5,11–14 Furthermore, given that 1 large study reported no complication in the obstetrical subgroup, the aforementioned cumulative incidence is likely overestimated.15

General anesthesia usually represents a valid alternative to “epidural” anesthesia in most clinical situations. However, it poses specific maternal and fetal risks (difficult airway management, aspiration risk, and exposure of the fetus to anesthetic agents, among others). In addition, it hampers the initial fetomaternal interaction (reduced immediate post-delivery skin-to-skin bonding and breastfeeding initiation with decreased likelihood of exclusive breastfeeding).16,17 Depriving a pregnant patient of adequate management of labor pain (with “epidural” if wished) is equally unacceptable.

Most guidelines recommend splitting therapeutic dosage to twice-daily dosing starting at 36 weeks of gestation. The aim is to reduce anti-activated factor X (anti-Xa) peak levels and consequentially the associated bleeding risk during delivery. However, the twice-daily regimen prevents most patients going into spontaneous labor from benefiting from timely anesthesia. The median time from admission to delivery varies with parity and dilation at admission, approximately 12 to 20 hours,18 noticeably less than the prescribed 24-hour...
safety interval. Some international or local guidelines suggest circumventing this issue with planned delivery (induction labor) for patients receiving therapeutic-dose LMWHs, allowing earlier discontinuation of anticoagulant therapy. However, this point remains controversial and supported by only low-level evidence.3,4 The induction of labor is associated with prolonged duration of labor and bed rest in the peripartum, thus representing an additional prothrombotic factor for these high-risk patients.19 There are benefits to waiting for spontaneous labor, particularly for women with a strong wish to do so and to avoid induction of labor.20 Reducing the prerequisite waiting delay between LMWH injection and “epidural” catheter placement would allow more patients to undergo safer natural labor.

The dichotomous awaiting period proposed by the current guidelines does not fit with another specificity of the pregnant population, which is the wider array of dosing schemes, that is, fixed-dose classical prophylaxis, weight-adjusted prophylactic doses, intermediate strength prophylaxis, and weight-adjusted once- or twice-daily therapeutic usage (Table). Moreover, as pregnant patients come in all shapes, sizes, and body weights, the expected trough anti-Xa levels largely overlap, blurring the distinction among categories.

In pharmacokinetic studies, observed levels of anti-Xa activity after the administration of LMWHs in different populations are already substantially reduced after 12 hours, regardless of subcutaneous or intravenous administration.21—23 This can be explained by the short half-life of LMWHs ranging from approximately 3 to 8 hours allowing the elimination of approximately 90% to 75% of the administrated dose (which is equivalent to 4 to 2 half-lives) within 12 hours in the general population.24,25 The half-life of LMWHs is expected to be further reduced in pregnancy because the renal blood flow and glomerular filtration rate increase by 50%, as early as 14 weeks of gestation.26 In addition, a pregnancy-related increase in blood volume is expected to expand considerably the volume of distribution of LMWHs, decreasing their plasma levels.5,27,28 Some experts even recommend a dose adjustment in pregnancy to prevent infra-therapeutic levels if using dosages developed for the general population.20 Regrettably, there is currently no validated laboratory test to assess the individual bleeding risk from “epidural” anesthesia in patients receiving anticoagulants.5 Pharmacokinetic-pharmacodynamic data correlating levels of anti-Xa activity and residual bleeding risk are lacking. The establishment of a “safe” anti-Xa cutoff allowing the administration of “epidural” anesthesia is unlikely for several factors. Applying data from other medical fields is of limited value as the relationship between “epidural” hemostata and bleeding complications, in general, has not been established. Furthermore, there are conditions where anti-Xa activity may underestimate the anticoagulant effect of LMWHs (antiphospholipid syndrome, hypertriglyceridemia, etc.). Moreover, the in vitro chromogenic anti-Xa activity assay, in platelet-poor plasma, only reflects LMWH concentration, which is distinct from LMWH in vivo activity. Finally, LMWH preparations vary in their composition and may, theoretically, have some residual direct thrombin

**TABLE**

<table>
<thead>
<tr>
<th>Substance (all subcutaneous administration route)</th>
<th>Prophylactic</th>
<th>Intermediate</th>
<th>Therapeutic (BID)</th>
<th>Therapeutic (once daily)</th>
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</thead>
<tbody>
<tr>
<td>Enoxaparin 30—40 mg once daily</td>
<td>60 mg once daily, increase as pregnancy progresses to 1 mg/kg once daily</td>
<td>1 mg/kg BID</td>
<td>1.5 mg/kg once daily</td>
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<tr>
<td>0.5 mg/kg once daily</td>
<td>30—40 mg BID</td>
<td>&lt;1 mg/kg BID</td>
<td>&lt;1.5 mg/kg once daily</td>
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<tr>
<td>Dalteparin 5000 U once daily</td>
<td>&gt;5000 U once daily and 200 U/kg once daily</td>
<td>100—120 U/kg BID</td>
<td>200 U/kg once daily</td>
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<tr>
<td>Dalteparin 5000 U once daily</td>
<td>50 U/kg once daily</td>
<td></td>
<td>175 U/kg once daily</td>
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<tr>
<td>Tinzaparin 4500 U once daily</td>
<td>86 U/kg BID</td>
<td>171 U/kg once daily</td>
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<tr>
<td>Nadroparin &lt;5700 U once daily</td>
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<tr>
<td>Certoparin 3000 U once daily</td>
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<tr>
<td>Reviparin 1750 U once daily</td>
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</table>

BID, twice daily.

* Some scientific societies do not recognize the intermediate dosing category and consider any amount greater than prophylactic dosing as “therapeutic” for epidural placement; 5 Prophylactic dosing may require modifications for extremes of body weight.

inhibition not accounted for in the anti-Xa assay. “Thromboelastometry, with a short turnaround time and whole blood analysis, may represent an attractive option. However, in vivo data validating its use for LMWH therapeutic monitoring and for assessing the procoagulant state of late pregnancy are still preliminary.” Therefore, to date, the precautious approach applied in the different guidelines is reasonable, and prespecified safety time intervals (reflecting the actual anticoagulant half-lives in the concerned population) remain the most practical management option.

These elements constitute in the authors’ view a bundle of arguments in favor of rethinking the current approach to suggest a delay of 12 hours for prophylactic and intermediate strength prophylaxis and spliced, twice-daily, therapeutic dosage while keeping the 24-hour delay for the once-daily therapeutic dosage. In line with the 2018 American Society of Hematology Guidelines,4 we agree that a multidisciplinary, individualized approach should be used when decisions are made about delivery plans and anesthetic options for patients receiving anticoagulants. We go beyond and argue that pregnant patients’ specifics in terms of demographics, procoagulant state, and LMWH pharmacokinetics and the risks of general anesthesia for both mother and offspring warrant caution against overestimating the LMWH-associated bleeding, and we suggest that a 12-hour delay for twice-daily therapeutic LMWH dosage should be sufficiently safe. Regrettably, to date, there is insufficient experimental prospective data to validate definitively this attitude, as high-quality evidence in this distinct subpopulation is largely lacking. Therefore, prospective scrupulous clinicobiological documentation (laboratory values at the time of epidural anesthesia, including thromboelastography if available, and clinical outcome), preferably in a multicentric setting, is called for to gather additional knowledge and help inform the future updates of the guidelines. We believe that these data will be essential for (1) a tailored dosage of LMWH during pregnancy and (2) a refined definition of the secure conditions for “epidural” placement, both being equally relevant toward better, safer, patient-oriented obstetrical and perinatal care.

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