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Challenges of Anticoagulation Therapy in Pregnancy

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Opinion statement

Thrombotic complications in pregnancy represent a major cause of morbidity and mortality. Pregnancy is a primary hypercoagulable state due to enhanced production of clotting factors, a decrease in protein S activity, and inhibition of fibrinolysis. These physiologic changes will yield a collective rate of venous thromboembolism (VTE) of about 1–2 in 1000 pregnancies for the general obstetric population, which represents a five- to tenfold increased risk in pregnancy compared to age-matched non-pregnant peers. A select group of women, however, will carry a significantly higher rate of thrombosis due to primary thrombophilia, either inherited or acquired. This introduces a population of women who may benefit from prophylactic anticoagulation, either antepartum or postpartum. The coagulation changes that occur in preparation for the hemostatic challenges of delivery endure for several weeks postpartum. In fact, daily risk for pulmonary embolism (PE) is the highest postpartum. Use of anticoagulation in pregnancy introduces particular risk at the time of delivery, where bleeding and clotting risk collide. Altered metabolism rates of anticoagulants in pregnant women often necessitate closer monitoring than is required outside of pregnancy in order to ensure efficacy and safety. Heparin products are the mainstay of treating VTE in pregnancy, chiefly because they do not cross the placenta. In women with mechanical heart valves, the ideal anticoagulation regimen remains controversial as heparin use has shown inferior outcomes for preventing thromboembolic complications compared to warfarin, but warfarin carries risk for fetal embryopathy. Other populations where a heparin alternative is necessary include women with a history of heparin-associated thrombocytopenia (HIT) or other heparin intolerance. Further challenging the management of anticoagulation in pregnancy is the dearth of randomized clinical trials. The evidence governing treatment recommendations is largely based on expert guidelines, observational studies, or extrapolation from non-pregnant cohorts. A careful critique of a woman's history, as well as the available data, is essential for optimal management of anticoagulation in pregnancy. Such decisions should involve a multidisciplinary team involving obstetrics, hematology, cardiology, and anesthesia.

Introduction

Use of anticoagulation in pregnancy is uniquely challenging due to physiologic changes that may affect both the ability to achieve a desired level of anticoagulation as well as the laboratory measurements used to assess anticoagulation. Anticoagulation also influences the risk of bleeding at the time of delivery, which has implications for anesthesia options and the preferred timing and mode of delivery. Finally, anticoagulation effects on the fetus must be considered when comparing options for anticoagulation in pregnancy.

Pregnancy results in enhanced production of fibrinogen, von Willebrand factor, factors II, VII, VIII, IX, and X, which starts at the time of conception and reaches a peak at the time of delivery. These changes may result in a relative shortening of the PT and PTT, which can complicate monitoring of anticoagulation. There is a 40–60% decrease in protein S activity that results from estrogen-induced decreases in total protein S production, as well as an increase in the C4b binding protein (which binds protein S). Finally, fibrinolysis is inhibited in pregnancy due to increased levels and activity of TAFI, PAI-1, and PAI-2.

Although novel oral anticoagulants have emerged and are now used commonly for treating venous thromboembolism (VTE) or preventing cardioembolism in patients with atrial fibrillation, they also are shown to cross the placenta in animal models and thus not recommended for general use in pregnant women.

Hemostasis at the time of parturition is dependent upon four major factors, typically referred to as the 4Ts: tone (uterine tone/contraction postpartum), trauma (any trauma to the birth canal predisposes to continued postpartum bleeding), tissue (retained placenta or abnormal placentation increases bleeding risk), and thrombin (referring to primary bleeding disorders or the presence of an anticoagulant). Although the contribution of thrombin in achieving postpartum hemostasis is less influential than the other three factors, the presence of a primary bleeding disorder or use of anticoagulation greatly impacts decisions regarding anesthesia options, particularly candidacy for epidural anesthesia.

Treatment

Although women cannot alter the physiologic changes that occur naturally in pregnancy, certain lifestyle factors may serve to decrease their venous clotting risk. It is paramount that all pregnant women be educated regarding the signs and symptoms of thrombosis and instructed to seek medical attention if thrombosis is suspected.

Lifestyle

In all populations, venous stasis is a contributor to venous clotting risk. In pregnancy, pressure exerted by the gravid uterus on the pelvic vasculature and inferior vena cava promotes a slower rate of venous return from the legs, particularly as pregnancy progresses. Additionally, there may be obstetric factors that necessitate bedrest in pregnancy. Women who are able should be encouraged to ambulate frequently, avoiding 2–3-h stretches of immobility during waking hours. Inability to perform this level of activity, such as with strict bedrest, should invite a discussion regarding use of prophylactic anticoagulation. Many women also find use of compression stockings helpful in assisting venous blood return from the legs. Women should also be encouraged to maintain adequate hydration throughout pregnancy. There are no dietary measures that will influence clotting risk, and heparins are not altered

by dietary factors. However, fluctuations in dietary vitamin K will influence the level of warfarin and women must be educated about these factors in the same fashion they would be outside of pregnancy.

Pharmacologic treatment: VTE

Women who will be managed with therapeutic anticoagulation in pregnancy include those who already meet the criteria for systemic anticoagulation before pregnancy, such as those with a history of prior unprovoked thrombosis, recurrent thrombosis or the antiphospholipid antibody syndrome (APLS). In these cases, pregnancy will prompt a transition from oral anticoagulant to a parenteral agent. Systemic anticoagulation will also be initiated with development of acute VTE in pregnancy. In such cases, women should be treated for a minimum of 3 months for a provoked event, but until 6 weeks postpartum to cover the entire window of heightened clotting risk.

Low molecular weight heparin (LMWH)	LMWHs predominantly inhibit FXa, but also work through an antithrombin (AT)-dependent pathway. LMWHs do not cross the placenta and therefore have no associated risk for fetal anticoagulation or embryopathy. Most LMWHs have been used in pregnancy, at the same doses as in non-pregnant patients. These doses are listed below: ● Dalteparin 200 IU per kg body weight daily or 100 IU per kg twice daily ● Enoxaparin 1.5 mg per kg body weight daily or 1 mg per kg body weight twice daily ● Tinzaparin 175 U per kg daily Although once daily dosing exists for each LMWH, the half-life of LMWHs of 4 h makes twice daily dosing more pharmacokinetically appropriate and is thus favored. The anticoagulation level achieved by LMWH can be measured by the anti-Xa level, although there is no adopted standard concerning the need or recommended frequency of monitoring anti-Xa levels in pregnancy. Generally, there is also a lack of evidence to suggest that the anti-Xa level correlates with meaningful clinical endpoints of bleeding or thrombosis. One study sought to investigate whether routine anti-Xa monitoring of pregnant patients with VTE influenced patient outcomes in 26 eligible subjects and found that monitoring anti-Xa versus standard weight-based dosing was not associated with any difference in clinical outcome, including maternal blood loss at delivery or rates of recurrent VTE [1]. Another study focused on the use of anti-Xa monitoring in obese pregnant women [2]. This retrospective study examined 44 pregnant women receiving therapeutic enoxaparin, who were either unmonitored or monitored with anti-Xa levels. Of 14 women with a BMI greater than 30, nine required dosing less than 1 mg/kg twice daily to maintain therapeutic anti-Xa levels. This finding suggests that women at extreme of weight may benefit from closer monitoring of anti-Xa to ensure efficacy and safety of anticoagulation regimens. Although anti-Xa levels may be valuable, they are not readily available in all hospitals. One study examined the use of thromboelastography in pregnancy to assess the anticoagulant effect of dalteparin [3]. In this study of 30 healthy parturients presenting for elective cesarean section, dalteparin was added to whole-blood samples at known concentrations to achieve pre-specified anti-Xa levels. Thromboelastography tracings were able to discriminate the various doses of dalteparin with results available as point-of-care testing. Although this was strictly an ex vivo study, it suggests that this technology has potential to measure anticoagulation in pregnant women using LMWH, with results immediately available to guide clinical decision-making regarding anesthesia options.

	The half-life of most LMWHs is 4 h, which needs to be factored into management plans for labor and delivery. The typical treatment approach is to transition to unfractionated heparin (UFH) closer to term, given the half-life of UFH is 3 h. Ideally, women will not be anticoagulated for the hours of active labor, which ideally would be limited to less than 36 h. For women with acute thromboses within 30 days of delivery, use of intravenous UFH should be considered to facilitate the shortest window off anticoagulation for labor and delivery. For women with labors longer than 36 h, prophylactic dose anticoagulation is usually considered, depending on the indication for anticoagulation and the time lapsed from most recent acute thrombotic event. LMWH does not enter the breast milk, so is safe for nursing mothers. Long-term use in pregnancy has not been shown to cause osteopenia [4]. Overall, LMWHs have the best safety and efficacy profile in pregnancy with predictable degrees of anticoagulation in most women. The dose must be escalated to reflect weight gain throughout gestation. Women who are obese or have altered renal function may benefit from anti-Xa monitoring. Although there is no standard interval for monitoring, once per trimester is reasonable.
UFH	UFH induces a confirmational change in ATIII, which accelerates ATIII's activity against factors IIa and Xa by 1000 fold. UFH also inhibits factors IXa and XIa. Neither LMWH nor UFH cross the placenta, but UFH's effect on anticoagulation is not as predictable as LMWH. The UFH level can be assessed by PTT, but anti-Xa is preferred due to other physiologic changes in pregnancy that can impact the PTT independent of UFH's influence. The starting UFH dose for management of acute VTE is 250 units per kilogram body weight subcutaneously twice daily. With an accepted maximum volume for subcutaneous injection being 1.5 ml, depending on the calculated 24-h UFH dose and available UFH concentration, treatment may require 3 or 4 daily injections. This weight-based calculation is just a starting dose, however, as UFH requires ongoing monitoring and dose adjustment accordingly. It is also recommended to use preservative-free heparin formulations in pregnant women to avoid fetal exposure to benzyl alcohol, which is used in some high-dose UFH preparations and has been associated with a specific neurologic syndrome when administered directly to the neonate. In a 5-year retrospective study of pregnant women receiving LMWH in pregnancy who were transitioned to UFH closer to the time of delivery, it was observed that higher doses of UFH were needed to achieve anticoagulation in patients with a BMI < 30 [5]. This paradoxical relationship is postulated to be due to diminished adiposity or increased renal clearance. The maturing placenta can also degrade heparin and there are changes in the presence of the heparin-binding proteins and coagulation factors throughout pregnancy. While the exact mechanism for the observed paradox is unknown, this finding underscores the need for ongoing monitoring of anti-Xa levels when using UFH. Osteoporosis is also reported to occur in about 2–5% of patients receiving long-term UFH. Although this is believed to be reversible with time removed from UFH, the risk for osteoporotic fractures favors LMWH over UFH in pregnancy [4, 6–8]. UFH at treatment dose also does not come in prefilled syringes, so patients must draw up the medications from vials, which introduces inconvenience and the possibility of dosing errors. UFH does not enter the breast milk, so use can be continued in nursing mothers.
Fondaparinux	While LMWH remains the standard of care for VTE treatment in pregnancy, some women will have intolerance or allergy to heparin. Although there is less available safety data, fondaparinux has been used in pregnancy, with no reported adverse effect. It also offers once daily therapeutic dosing and many women will report less associated injection-site pain. Its longer half-life of 17 h, however, requires a longer elapsed time between dosing and epidural anesthesia. The current recommendation is 5 days. Fondaparinux is recommended by the American College of Obstetrics and Gynecology for anticoagulation in women with a history of HIT. The dosing is the same as for the non-pregnant patient and is weight based:

	- <50 kg–2.5 mg sc daily - 51-75 kg–5 mg sc daily - 76-100 kg–7.5 mg sc daily - >100 kg–10 mg sc daily One study looked at maternal and pregnancy outcomes of 65 pregnancies where fondaparinux was used [9]. The drug was well tolerated, and pregnancy complications were similar to that observed in the general population.
Warfarin	Use of warfarin in pregnant women with mechanical heart valves is discussed below. Due to increased risk for congenital malformations or fetal anticoagulation, warfarin is not recommended for management of VTE in pregnancy and is a category X drug from the Food and Drug Administration (FDA). It can, however, be used in nursing mothers.
Direct thrombin inhibitor (DTI)	Argatroban is an intravenous DTI and therefore has rare application in pregnancy, except possibly at the time of delivery in women being managed for HIT. Theoretically, its short half-life of 40 min should permit a narrow interval between discontinuation and neuraxial anesthesia. However, there is insufficient data in pregnancy to confidently apply this half-life to clinical management. Similar to other direct oral anticoagulants (DOACs) (see below), dabigatran (an oral DTI) has been shown to cross the placenta in ex vivo studies and is therefore not recommended for use in pregnancy.
Direct oral anticoagulants (DOAC)	DOACs have not been used or studied extensively in pregnant women, so are not currently recommended for use. As the use of DOACs in management for VTEs increases, however, there will be cases of inadvertent fetal exposure as anticoagulated women of reproductive age become pregnant while on therapy. Given the lack of safety data available regarding the potential risk of DOAC embryopathy, some women may choose elective termination out of fear of the unknown. Two publications share small numbers of outcomes with inadvertent DOAC exposure in pregnancy. The first includes 137 cases of DOAC exposure in pregnancy [10]. There were 67 live births (48.9%), 31 miscarriages (22.6%), and 39 elective terminations (28.5%). Seven pregnancies (5.1%) had a fetal abnormality, of which 3 (2.2%) could potentially be interpreted as embryopathy. The second publication reviewed 37 pregnancies in Germany with inadvertent DOAC exposure [11]. All women discontinued rivaroxaban as soon pregnancy was recognized, which was in the first trimester for all but one. There were 6 spontaneous abortions, 8 elective terminations, and 23 live births. There was one major fetal malformation, however, in a woman with a history of previous fetal cardiac malformation without rivaroxaban exposure. While these results may provide some reassurance to women with an inadvertent exposure to rivaroxaban in early pregnancy, this limited reported experience cannot rule out an increased risk for fetal embryopathy or endorse the safety of rivaroxaban in pregnancy. Breastfeeding women were excluded from the original trials examining safety and efficacy of DOACs. In absence of rigorous safety data, which is unlikely due to viable and tested alternatives in both warfarin and heparins, use of DOACs while breast feeding cannot be sanctioned as safe.
Thrombolysis	Similar to non-pregnant women, use of thrombolysis in pregnancy should be reserved for life or limb threatening thrombosis. Data from small case series have shown similar complication rates as in non-pregnant patients [12]. An older, but larger series of use of thrombolytics (mostly systemically introduced) in 172 pregnant women was associated with a 1.2% maternal mortality, 5.8% pregnancy loss, and 8.1% hemorrhagic complications [13]. These risks are believed to be further minimized by the use of catheter-directed thrombolysis, but there are no large series or randomized data to generate specific risk information.
Anti-platelet therapy	Indications for anti-platelet therapy may include history of stroke, diabetes or essential thrombocythemia. The FDA classification of aspirin use in pregnancy is largely based on animal models where high-dose aspirin in the third trimester was associated with premature closure of the fetal ductus anteriosus [14]. However, there is no evidence that low-dose

aspirin increases this risk in humans. In fact, numerous large trials of low-dose aspirin for various indications have not shown an increased risk for congenital abnormalities, maternal or fetal bleeding, or complications with neuraxial anesthesia [15–19]. A subgroup analysis of the Maternal-Fetal Medicine Units High-Risk Aspirin study compared aspirin 60 mg daily started before 17 weeks gestation to placebo in women at risk for pre-eclampsia [20]. The data showed that low-dose aspirin started before 17 weeks reduced the risk for late-onset pre-eclampsia by 29% compared to placebo and there were no increased maternal or fetal complications reported.

There is less experience using clopidogrel in pregnancy. There have been no reports of fetal deformity with clopidogrel, which is unlikely to cross the placenta. With lack of dedicated obstetric literature, however, management is based on non-pregnant populations where it is recommended that clopidogrel be held for 7 days before considering neuraxial anesthesia.

Pharmacologic treatment in special circumstances: mechanical heart valves and obstetric antiphospholipid antibody syndrome (APLS)

Mechanical heart valves

The recommendations regarding anticoagulation management in pregnant women with mechanical heart valves are based on data that demonstrate superiority of warfarin for preventing maternal thrombosis, but at a cost of increased fetal complications and embryopathy.

The American Heart Association, American College of Cardiology, and the European Society of Cardiology make a distinction in the safety of warfarin in the first trimester based on the daily dose. In the first trimester, warfarin is advised when the required dose to maintain therapeutic INR is less than 5 mg daily, but dose-adjusted LMWH twice daily is favored if the required warfarin dose exceeds 5 mg daily. Warfarin is recommended in the second and third trimesters regardless of daily dose.

The most recent meta-analysis examining maternal and fetal outcomes of anticoagulated pregnant women with mechanical heart valves included 800 pregnancies and 18 publications [21•]. Similar to prior publications, use of vitamin K antagonist (VKA) throughout pregnancy was associated with the lowest composite maternal risk (5%) compared to LMWH throughout gestation (16%), LMWH in the first trimester followed by VKA for the second and third trimester (16%) or UFH in the first trimester followed by VKA for the second and third trimester (16%). Alternatively, composite fetal risk was lowest in the continuous LMWH managed group (13%) compared with exclusive VKA use (39%), LMWH/VKA hybrid (23%), or UFH/VKA hybrid (34%). A warfarin dose of < 5 mg did not significantly impact fetal risk. Another recent systemic review and meta-analysis compared women receiving VKAs throughout gestation (group 1), heparin in the first trimester followed by VKA for the second and third trimesters (group 2) and UFH or LMWH exclusively throughout gestation (group 3) [22]. The pooled incidence for maternal and fetal outcomes, culled from 46 articles, again demonstrated that VKAs are associated with the fewest maternal complications, but also fewer live births. Respectively in groups 1, 2, and 3, maternal mortality was 0.9, 2.0, and 2.9%; thromboembolic complications occurred in 2.7, 5.8, and 8.7%; and the live birth rate was 64.5, 79.9, and 92%. However, this data demonstrated a difference in outcome depending on warfarin dose. Comparing low dose (< 5 mg/day) versus higher warfarin dosing, there were 83.6 versus 43.9% live births and 2.3 versus 12.4% fetal anomalies. This data shows that although adverse fetal events were decreased when VKA was avoided in the first trimester or the dose was less than 5 mg daily, the risk was not eliminated.

	A similar systemic review and meta-analysis comparing various anticoagulation strategies in women with mechanical heart valves examined four groups: VKA throughout pregnancy (group 1); VKA throughout pregnancy except weeks 6–12 when UFH or LMWH was used (group 2); exclusive LMWH throughout pregnancy (group 3); and exclusive UFH throughout pregnancy (group 4). Fifty-one studies comprising 2113 pregnancies and 1538 women were included [23]. In this review, the exclusive use of UFH throughout gestation was associated with the worst maternal and fetal outcomes. Once again, the rate of fetal loss was significantly higher with a warfarin dose greater than 5 mg daily compared with the lower dose group. The lower dose VKA group was also associated with a significantly lower rate of major maternal thromboembolic events compared to a heparin/VKA hybrid regimen, but with similar fetal outcomes. Similar to other publications, the rate of fetal loss was significantly lower on the LMWH regimen compared with a heparin/VKA hybrid group, but with similar maternal outcomes. The collective data suggest that VKA at low dose may be the optimal regimen in attempting to balance opposing fetal and maternal risks, while a heparin/VKA hybrid may be more appropriate in women requiring more than 5 mg daily of warfarin to maintain therapeutic anticoagulation. In women who refuse warfarin after discussion of these data, LMWH is favored over UFH. While it is appealing to target a higher anti-Xa level with heparins and this practice is recommended by societal recommendation, there is insufficient data to conclude that this practice is associated with improved outcomes.
Obstetric antiphospholipid antibody syndrome (APLS)	APLS is defined as persistently positive antiphospholipid antibodies (lupus anticoagulant, anticardiolipin antibodies, beta 2 glycoprotein antibodies) over 12 weeks and within 5 years of a clinically qualifying event. Women meeting clinical criteria based on arterial or venous thrombosis will be managed with indefinite anticoagulation, which is transitioned to a parenteral heparin in pregnancy. Women with persistently positive antiphospholipid antibodies and a history of pregnancy complications, defined as three consecutive losses before week 10, any pregnancy loss after 10 weeks, or pre-eclampsia or intrauterine growth retardation, are defined as having obstetric APLS. Although this group is not shown to benefit from systemic anticoagulation between pregnancies, meta-analyses combining data from several small trials showed a benefit of combined prophylactic heparin and aspirin compared to aspirin alone in increasing the live birth rate of afflicted women [24, 25]. Extrapolation of data in other series, combined with general superior side effect, safety profile, and ease of use of LMWH compared to UFH, has made use of prophylactic LMWH for obstetric APLS the usual treatment approach. Treatment should be started when pregnancy is detected and continued through 6–8 weeks postpartum.

Anticoagulation prophylaxis

The risk for VTE increases in the puerperium due to the combination of coagulation changes that have not yet returned to pre-pregnancy baseline and the endothelial damage occurring during delivery that further fuels the clotting cascade. In addition to the risk for PE being highest postpartum, this is also a time when the use of anticoagulation no longer impacts the fetus, mode of delivery or candidacy for neuraxial anesthesia. Thus, all women with a history of prior VTE or primary thrombophilia should receive postpartum prophylaxis. For women with a history of VTE in a prior pregnancy, the risk

of recurrence is estimated to be about 6–9% in a subsequent pregnancy [26]. This governs the usual practice of using both antepartum and postpartum prophylaxis in women with a history of an estrogen-associated VTE (prior pregnancy or estrogen-OCP). In these women, LMWH is typically transitioned to UFH closer to term because UFH has a slightly shorter half-life (3 h) compared with LMWH (4 h). This practice increases their candidacy for neuroaxial anesthesia.

The use of antepartum prophylaxis to prevent miscarriage has been hotly debated. After meta-analyses suggested higher live birth rates from heparin and aspirin compared with aspirin alone for women with APLS, heparin prophylaxis for all women with recurrent pregnancy loss became somewhat a commonplace. However, three randomized trials published in 2010–2011 [27–29], most excluding women with APLS, failed to show a benefit of heparin in preventing miscarriage. This finding has not been disputed by any more recent data.

In one double-blind placebo controlled trial, 258 women with a history of 2 or more miscarriages before 15 weeks and a negative thrombophilia work-up were randomized to receive once daily Lovenox 40 mg or placebo through week 35 [30•]. Lovenox use did not improve the live birth rate, which was 66.6% in the Lovenox group versus 72.9% in the placebo group. In another trial, 449 women with 2 or more early term miscarriages were randomized to prophylactic dalteparin or an oral multivitamin through week 24 [31•]. There was also no difference in the live birth rate between groups. In another small study, 32 women with negative thrombophilia screens but with evidence for placental insufficiency in the second trimester were randomized to receive UFH 7500 U twice daily or no active management [32]. Serial placenta ultrasounds were reviewed, finding no difference in either evolution of abnormal placental lesions or maternal vascular underperfusion on histopathology between groups. An open-label multicenter randomized trial comparing the outcome of enoxaparin and aspirin to aspirin alone in 249 women with a history of severe pre-eclampsia diagnosed before 34 weeks gestation showed no significant difference between the groups for maternal death, perinatal death, pre-eclampsia, small for gestational age fetus, or placental abruption [33].

The TIPPS trial randomized women with either primary thrombophilia or a prior placenta-mediated pregnancy complication [34]. In total, 143 women received antepartum dalteparin at 5000 IU daily through week 20 and increased to 5000 IU twice daily through week 37 versus 141 women randomized to the control arm not receiving antepartum LMWH. There was no statistical difference in the occurrence of the composite primary outcome, which included severe or early onset pre-eclampsia, small for gestational age, pregnancy loss, or VTE. There was an increase in minor bleeding in the dalteparin group, but no difference in major bleeding. To address the question of whether women with known thrombophilia and recurrent miscarriage may benefit from Lovenox, the ALIFE2 study is currently open to enrollment [35].

The doses for prophylactic anticoagulation are listed below:

- Enoxaparin 40 mg sc daily
- Dalteparin 5000 U sc daily
- Tinzaparin 4500 U sc daily
- UFH 5000 U sc every 12 h, or to increase each trimester:
  First trimester: 5000–7500 U sc every 12 h
  Second trimester: 7500–10,000 U sc every 12 h
  Third trimester: 10,000 U sc every 12 h, unless PTT is elevated

Obesity may impact the appropriate prophylaxis dosing. One study compared standard enoxaparin prophylactic dosing of 40 mg daily to 50 mg twice daily in 84 post-cesarean women with a BMI greater than 35 [36•]. The standard dosing achieved the intended anti-Xa level only 14% of the time, compared with 88% of women who received weight-based dosing. Regardless of dose, no anti-Xa level reached therapeutic range of anticoagulation. There were no VTE or bleeding complications in either group. Although the small scale and short observation window cannot endorse the practice of one dose over the other, there was no increased bleeding risk in women receiving weight-based dosing.

Anticoagulation at the time of labor and delivery

Although the presence of anticoagulation at the time of delivery will influence bleeding risk less than the factors of uterine tone, trauma to the birth canal or abnormal/retained placenta, it strongly influences decisions regarding mode and timing of delivery, as well as candidacy for epidural anesthesia. One observational study examined disparities between intrapartum anesthesia and delivery modalities in women receiving anticoagulation (n = 203) compared with controls (n = 812) [37]. Of the women receiving anticoagulation, 61.6% received an epidural during childbirth versus 87% of the controls. Alternatively, spinal rates and use of general anesthesia were higher in the anticoagulated group (22.5 versus 1.85% and 5.4 versus 0.7%, respectively). The postpartum hemorrhage rate was similar in both groups.

The actual rates of hemorrhagic complications at the time of delivery in women receiving anticoagulation was examined via a retrospective chart review of 195 pregnancies in 158 women over the course of 9 years [38]. Women receiving therapeutic anticoagulation or prophylactic anticoagulation were included. Both UFH and LMWH were used antepartum, but 87% of women were switched to UFH closer to the time of delivery. The total rate of hemorrhagic complication was 12.8%, with the majority being postpartum hemorrhage (80%). Of these women, 76% received additional therapies, including blood transfusion, surgery or administration of uterotonic agents. However, 77% of women who developed postpartum hemorrhage also had another identified risk factor, and 39% had two or more additional risk factors. Although this total rate of hemorrhagic complication is higher than what is generally reported as the incidence in unselected obstetric cases (3–6%), it was equivalent to the rates of postpartum hemorrhage experienced at the academic center where the study was conducted. Of note, despite the common practice of switching from LMWH to UFH closer to delivery, in this study, the use of therapeutic UFH antepartum was associated with an increased risk of hemorrhagic complication compared to LMWH.

The guidelines regarding neuraxial anesthesia relative to specific anticoagulant and dosing intensity from the American College of Obstetrics and Gynecology is presented below (Table 1).

The recommended longer interval of deferring neuraxial anesthesia in LMWH versus UFH is responsible for the typical practice of transitioning women to UFH closer to term, but remains an open question. Reports of associated bleeding comparing UFH and LMWH do not rigorously support the value of this custom. Local guidelines that are

Table 1. FDA Drug Safety Communication November, 2013; NYP protocol; ASRA guidelines

Antepartum/intrapartum	
UFH ≤ 10,000 IU/day	No contraindications to timing of heparin dose and performance of neuraxial blockade
UFH > 10,000 IU/day	Wait 12 h after the last dose prior to neuraxial blockade or check aPPT
IV heparin	Wait 4–6 h after discontinuation of IV heparin; consider checking aPPT
LMWH prophylaxis	Wait 12 h post the last dose prior to neuraxial blockade
LMWH therapeutic	Wait 24 h post the last dose prior to neuraxial blockade
Postpartum	
UFH ≤ 10,000 IU/day	Heparin may be administered at any time interval after epidural catheter removal or spinal needle placement
UFH > 10,000 IU/day or IV heparin	Wait ≥ 1 h after epidural catheter removal or spinal needle placement
LMWH prophylaxis	Wait ≥ 4 h after epidural catheter removal or spinal needle placement
LMWH therapeutic	Avoid therapeutic dosing with epidural catheter in situ. Wait at least 24 h after catheter removal or spinal needle

interdisciplinary in nature, combining anesthesia, obstetrics, cardiology, and hematology should be developed in order to establish care parameters that are in keeping with the observed bleeding rates and customizable based on each woman's indication for anticoagulation and time elapse from an acute thrombotic event.

Conclusion

While pregnancy is clearly a procoagulant state manifesting as an increased rate of thrombotic complications, there remains limited high-quality evidence to govern the optimal management strategy for anticoagulation.

A summary of the recent data available for the use of anticoagulants in pregnancy is bulleted below:

- LMWH is the preferred anticoagulant for management of VTE in pregnancy.
- Routine monitoring of LMWH with anti-Xa is not supported by the literature, but may be valuable in women at extremes of weight or compromised renal function.
- Acute VTE in pregnancy should be treated for 3–6 months, but at least through 6 weeks postpartum.
- Thrombolysis in pregnancy is reserved for life- or limb-threatening thrombosis.
- Anticoagulation regimens for women with mechanical heart valves remain controversial and must include a detailed discussion with the patient.
- There is insufficient data to support the use of DOACs in pregnancy or with nursing.

- LMWH, UFH, and warfarin can be used in breastfeeding mothers.
- Therapeutic subcutaneous anticoagulation should be discontinued for 24 h prior to neuraxial anesthesia.
- Prophylactic anticoagulation is held for 0, 12, or 24 h prior to neuraxial anesthesia, depending on the specific drug and dose being used, which often motivates a transition to UFH closer to term.
- Use of thromboprophylaxis for women with recurrent miscarriage outside of a diagnosis of APLS has not been shown to significantly improve live birth rate.
- Antepartum prophylaxis should be strongly considered in women with a prior estrogen-associated VTE.
- Postpartum prophylaxis should be used in all women assessed at higher risk for VTE than their peers (including a history of VTE or primary thrombophilia).

Compliance with Ethical Standards

Conflict of Interest
Annemarie E. Fogerty declares no potential conflicts of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:
- • Of importance

1. McDonnell BP, Glennon K, McTiernan A, O'Connor HD, Kirkham C, Kevane B, et al. Adjustment of therapeutic LMWH to achieve specific target anti-Xa acivity does not affect outcomes in pregnant patients with venous thromboembolism. J Thromb Thrombolysis. 2017;43(1):105–11.
2. Petrie S, Barras M, Lust K, Fagermo N, Allen J, Martin JH. Evaluation of therapeutic enoxaparin in a pregnant population at a tertiary hospital. Intern Med J. 2016;46(7):826–33.
3. Chow L, Carr A, MacKenzie L, Walker A, Archer D, Lee A. The effect of dalteparin on thromboelastography in pregnancy: an in vitro study. Int J Obstet Anesth. 2016;28:22–7.
4. Patil AS, Clapp T, Gaston PK, Kuhl D, Rinehart E, Meyer NL. Increased unfractionated heparin requirements with decreasing body mass index in pregnancy. Obstet Med. 2016;9(4):156–9.
5. Patil AS, Clapp T, Gaston PK, Kuhl D, Rinehart E, Meyer NL. Increased unfractionated heparin requirements with decreasing body mass index in pregnancy. Obstet Med. 2016;9(4):156–9.
6. Dahlman T, Lindvall N, Hellgren M. Osteopenia in pregnancy during long-term heparin treatment: a radiological study post partum. Br J Obstet Gynaecol. 1990;97(3):221–8.
7. Dahlman TC. Osteoporotic fractures and the recurrence of thromboembolism during pregnancy and the puerperium in 184 women undergoing thromboprophylaxis with heparin. Am J Obstet Gynecol. 1993;168(4):1265–70.
8. Pettila V, Leinonen P, Markkola A, Hiilesmaa V, Kaaja R. Postpartum bone mineral density in women treated for thromboprophylaxis with unfractionated heparin or LMW heparin. Thromb Haemost. 2002;87(2):182–6.
9. DeCarolis S, di Pasquo RE, Del Sordo G, Buonomo A, Schiavino D, Lanzone A, et al. Fondaparinux in pregnancy: could it be a safe option? A review of the literature. Thromb Res. 2015;135(6):1049–51.

10. Beyer-Westendorf J, Michalski F, Tittl L, Middeldorp S, Cohen H, Abdul Kadir R, et al. Pregnancy outcome in patients exposed to direct oral anticoagulants—and the challenge of event reporting. Thromb Haemost. 2016;116(4):651–8.
11. Hoeltzenbein M, Beck E, Meixner K, Schaefer C, Kreutz R. Pregnancy outcome after exposure to the novel oral anticoagulant rivaroxaban in women at suspected risk for thromboembolic events: a case series from the German Embryotox Pharmacovigilance Centre. Clin Res Cardiol. 2016;105(2):117–26.
12. Leonhardt G, Gaul C, Nietsch HH, Buerke M, Schleussner E. Thrombolytic therapy in pregnancy. J Thromb Thrombolysis. 2006;21(3):271–6.
13. Turrentine MA, Braems G, Ramirez MM. Use of thrombolytics for the treatment of thromboembolic disease during pregnancy. Obstet Gynecol Surv. 1995;50(7):534–41.
14. Heymann MA, Rudolph AM, Silverman NH. Closure of the ductus arteriosus in premature infants by inhibition of prostaglandin synthesis. N Engl J Med. 1976;295:530–3.
15. Askie LM, Duley L, Henderson-smart DJ, Stewart LA, PARIS collaborative group. Antiplatelet agents for prevention of pre-eclampsia: a meta-analysis of individual patient data. Lancet. 2007;369:1791–8.
16. Duley, Henderson-Smart DJ, Meher S, King JF. Antiplatelet agents for preventing pre-eclampsia and its complications. Cochrane Database Syst Rev. 2007;2:CD004659.
17. Kaandorp S, Di Nisio M, Goddijn M, Middeldorp S. Aspirin or anticoagulants for treating recurrent miscarriage in women without antiphospholipid syndrome. Cochrane Database Syst Rev. 2009;1:CD004734.
18. Poutsie VJ, Dodd S, Drakeley AJ. Low-dose aspirin for in vitro fertilization. Cochrane Database Syst Rev. 2007;4:CD004832.
19. CLASP (Collaborative Low-dose Aspirin Study in Pregnancy) Collaborative Group. CLASP: a randomized trial of low-dose aspirin for the prevention and treatment of pre-eclampsia among 9364 pregnant women. Lancet. 1994;343:619–29.
20. Moore GS, Allshouse AA, Post AL, Galan HL, Heyborne KD. Early initiation of low-dose aspirin for reduction in preeclampsia risk in high-risk women: a secondary analysis of the MFMU high-risk aspirin study. J Perinatol. 2015;35(5):328–31.
21.• Steinberg ZL, Dominguez-Islas CP, Otto CM, Stout KK, Krieger EV. Maternal and fetal outcomes of anticoagulation in pregnant women with mechanic heart valves. J Am Coll Cardiol. 2017;69(22):2681–91.
The most recent meta-analysis again demonstrating that VKA use in women with mechanical heart valves is associated with fewer maternal complications, but LMWH throughout gestation is associated with the lowest risk for adverse fetal outcome.
22. D'Souza R, Ostro J, Shah PS, Silversides CK, Malinowski A, Murphy KE, Sermer M, Shehata N. Anticoagulation for pregnant women with mechanical heart valves: a systemic review and meta-analysis. Eur Heart J. 2017.
23. Xu Z, Fan J, Luo X, Zhang WB, Ma J, Lin YB, et al. Anticoagulation regimens during pregnancy in patients with mechanical heart valves: a systemic review and meta-analysis. Can J Cardiol. 2016;32(10):1248.e1–9.
24. Ziakas PD, Pavlou M, Voulgarelis M. Heparin treatment in antiphospholipid syndrome with recurrent pregnancy loss: a systemic review and meta-analysis. Obstet Gynecol. 2010;115:1256–62.
25. Mak A, Cheung MW, Cheak AA, Ho RC. Combination of heparin and aspirin is superior to aspirin alone in enhancing live births in patients with recurrent pregnancy loss and positive anti-phospholipid antibodies: a meta-analysis of randomized controlled trials and meta-regression. Rheumatology. 2010;49:281–8.
26. Bates SM, Greer IA, Middeldorp S, Veenstra DL, Prabulos AM, Vandvik PO. VTE, thrombophilia, antithrombotic therapy, and pregnancy: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141(2. Suppl):e691S–736S.
27. Kaandorp SP, Goddijn M, van der Post JA, Hutten BA, Verhoeve HR, Hamulyak K, et al. Aspirin plus heparin or aspirin alone in women with recurrent miscarriage. N Engl J Med. 2010;362(17):1586–96.
28. Clark P, Walker ID, Langhorne P, Crichton L, Thomson A, Greaves M, et al., Scottish Pregnancy Intervention Study (SPIN) collaborators. SPIN (Scottish Pregnancy Intervention) study: a multicenter, randomized controlled trial of low-molecular-weight heparin and low-dose aspirin in women with recurrent miscarriage. Blood. 2010;115(21):4162–7.
29. Visser J, Ulander VM, Helmerhorst FM, Lampinen K, Morin-Papunen, Bloemenkamp KW, et al. Thromboprophylaxis for recurrent miscarriage in women with or without thrombophilia. HABENOX: a randomized multicentre trial. Thromb Haemost. 2011;105(2):295–301.
30.• Pasquier E, et al. Enoxaparin for prevention of unexplained recurrent miscarriage: a multicenter randomized double-blind placebo-controlled trial. Blood. 2015;125(14):2200–5.
Another randomized trial showing no benefit of enoxaparin in preventing recurrent miscarriage.
31.• Schleussner E, Kamin G, Seliger G, Rogenhofer N, Ebner S, Toth B, et al., ETHIG II group. Low-molecular-weight heparin for women with unexplained recurrent pregnant loss: a multicenter trial with a minimization randomization scheme. Ann Intern Med. 2015;162(9):601–9.
A large trial of 449 women demonstrating no benefit of dalteparin in preventing recurrent miscarriage.
32. D'Souza R, Keating S, Walker M, Drewlo S, Kingdom J. Unfractionated heparin and placenta pathology in high-risk pregnancies: secondary analysis of a pilot randomized controlled trial. Placenta. 2014;35(10):816–23.

33. Haddad B, Heparin-Preeclampsia (HEPEPE) Trial Investigators, et al. Enoxaparin and aspirin compared with aspirin alone to prevent placenta-mediated pregnancy complications: a randomized controlled trial. Obstet Gynecol. 2016;128(5):1053–63.
34. Rodger MA, et al. TIPPS investigators. Antepartum dalteparin versus no antepartum dalteparin for the prevention of pregnancy complications in pregnant women with thrombophilia (TIPPS): a multinational open-label randomized trial. Lancet. 2014;384(9955):1673–83.
35. De Jong PG, et al. ALIFE2 study: low-molecular-weight heparin for women with recurrent miscarriage and inherited thrombophilia—study protocol for a randomized controlled trial. Trials. 2015;16:208.
36.• Stephenson ML, Serra AE, Neeper JM, Caballero DC, McNulty J. A randomized controlled trial of differing doses of postcesarean enoxaparin thromboprophylaxis in obese women. J Perinatol. 2016;36(2):95–9.
A recent publication showing that obesity should be factored when determining the appropriate dose of thromboprophylaxis.
37. Boilot T, Raia-Barjat T, Ollier E, Chapelle C, Laporte S, Chauleur C. Influence of anticoagulant therapy during pregnancy on the peripartum and anesthesia delivery terms. Gynecol Obstet Fertil. 2015;43(7–8):502–8.
38. Wang EHZ, Marnoch CA, Khurana R, Sia W, Yuksel N. Haemorrhagic complications of peripartum anticoagulation: a retrospective chart review. Obstetric Med. 2014;7(2):77–83.