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Management of Venous Thromboembolism in Pregnancy

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Abstract

Purpose of review This manuscript addresses the risks for venous thromboembolism (VTE) during pregnancy and the associated challenges of both diagnosis and treatment.
Recent findings The obstacles to diagnosis given lack of specificity of typical biomarkers to predict VTE in pregnancy, as well as the unique fetal and bleeding risks introduced by managing massive pulmonary embolism (PE) with thrombolytics or thrombectomy are highlighted.
Summary VTE during pregnancy and the postpartum window occurs at a 6–10-fold higher rate compared with age-matched peers and is a major cause of morbidity and mortality. Hypercoagulability persists for 6–8 weeks after delivery with the highest risk of PE being postpartum. The lack of randomized trials in pregnant women leads to variability in practice, which are largely based on expert consensus or extrapolation from non-pregnant cohorts. The standard treatment of VTE in pregnancy is anticoagulation with low molecular weight heparin (LMWH), which like unfractionated heparin does not cross the placenta and is not teratogenic. LMWH is preferred given the negligible risk for heparin-induced thrombocytopenia and osteoporosis, better bioavailability, and a predictive dose response. Depending on the severity of the VTE, additional treatments including thrombolysis, thrombectomy, inferior vena cava filter placement, or venous stenting may be used. Management requires balancing the competing bleeding and thrombotic risks during labor and delivery and factoring the impact of treatment on the fetus. A multidisciplinary team involving hematology, obstetrics, anesthesia, vascular medicine, and cardiology is critical for safe and timely management. The design and execution of prospective, randomized trials to specifically address optimal diagnosis and management are a top priority in obstetric hematology.

Introduction

Thrombophilia in pregnancy results from increased production of clotting factors, decreased protein S activity, and inhibition of fibrinolysis, which collectively contribute to a prothrombotic state. Anatomically, there is a decreased rate of venous return from the legs due to hormonal changes decreasing venous tone, obstruction by the gravid uterus, and endothelial damage to pelvic veins at the time of delivery due to venous hypertension. Readers are referred to a recent publication detailing the associated normal physiologic changes to the coagulation system [1].

Diagnosis of VTE, both antepartum and postpartum, can be challenging because presenting symptoms (fatigue, shortness of breath, leg swelling) may overlap with those of normal pregnancy. A few distinctions should be noted. While pregnant women commonly report dyspnea on exertion, this rarely involves pleuritic pain. The dyspnea of healthy pregnancy typically recovers quickly with rest, where persistence after rest or progressive dyspnea upon less strenuous exertion may suggest PE. Leg swelling in normal pregnancies is typically symmetric and painless, often resolving with leg elevation. In contrast, a deep venous thrombosis (DVT) is generally unilateral (the left leg in 85–90% of cases) and causes progressive edema and pain that persists despite elevation or rest. Isolated iliac vein thrombosis, rare outside of pregnancy, accounts for 17% of events in pregnancy [2]. It often presents as abdominal or back pain and may be attributed incorrectly to musculoskeletal pain until substantial swelling involves the entire leg.

VTE prediction scores are less reliable in pregnancy. A recent publication [3] summarized seven working guidelines, noting that prediction tools determining pretest probability of PE are derived from studies that specifically excluded pregnant women. Moreover, some risk factors (older age, cancer) that are included in traditional scoring systems are rarely present in pregnancy and other factors (leg edema and tachycardia) are common in normal pregnancies. A recent study compared biomarkers in pregnant or postpartum women with confirmed VTE compared to those without and found low predictive value for PT, aPTT, BNP, CRP, fibrinogen, DDimer, prothrombin fragment 1 + 2, thrombin generation, soluble tissue factor, or troponin [4•]. Another group reported that the sensitivity, specificity, positive predictive, and negative predictive values of the Wells score applied to pregnancy were 41, 82, 44, and 79% and of the Revised Geneva Score were 63, 59, 35, and 82%, respectively [5].

Given the above, imaging is usually required to diagnose or exonerate clinically suspected VTE in pregnancy. Pregnant women with clinically suspected PE should first undergo leg ultrasound since anticoagulation management of DVT is the same as for PE. This approach minimizes radiation exposure. If pelvic DVT is suspected and not visualized on leg ultrasound, pelvic imaging with MRI should be performed.

Lung imaging must be performed when a PE is clinically suspected and there is no DVT. The optimal imaging modality in pregnancy remains an area of debate. Some guidelines recommend ventilation-perfusion (V/Q) scan. V/Q scan interpretation depends on a clear chest X-ray, which is likely in pregnant women. The chest tomography pulmonary angiogram (CTPA) may show less contrast enhancement secondary to physiologic changes in lung perfusion in pregnancy, but can offer valuable alternative diagnostic data even when PE is not shown. CTPA results in less fetal radiation than chest X-ray plus V/Q scan, but more maternal radiation. There is theoretic concern that breast tissue in pregnancy may be particularly sensitive to radiation damage. Nevertheless, chest X-ray, V/Q scan, and CTPA combined result in < 50 mGy of fetal radiation exposure, a value associated with negligible fetal risk for teratogenic or other complications [6]. Although the ideal diagnostic strategy is not known, there is agreement that adequate diagnostic testing should be pursued until VTE is satisfactorily exonerated or documented given the serious consequences of VTE in pregnancy.

Treatment

Heparin remains the mainstay for management of VTE in pregnancy. Oral direct thrombin and factor Xa inhibitors are not used in pregnancy since they cross the

placenta in animal models. VTE in pregnancy is usually treated with anticoagulation alone; however, massive PE, extensive DVT, or progressive VTE despite anticoagulation may necessitate additional interventions—such as thrombectomy or thrombolysis.

Lifestyle

Although women cannot alter the physiologic changes of pregnancy, certain lifestyle factors may decrease venous clotting risk. Venous stasis can be somewhat ameliorated by frequent ambulation, compression garments, adequate hydration, and elevation of the legs. There are no dietary measures that will influence clotting risk or the degree of anticoagulation achieved with heparins. Because the most important strategy to reduce VTE complications is prompt diagnosis and treatment, all pregnant women should be educated to the signs and symptoms of thrombosis and encouraged to seek prompt medical evaluation if thrombosis is suspected.

Pharmacologic treatment: VTE

Once a VTE is diagnosed in pregnancy, treatment with a therapeutic heparin should be initiated urgently. VTEs in pregnancy are classified as provoked, therefore treated with a finite duration of anticoagulation. There is agreement (in the absence of prospective trials) that a minimum of 3 months of anticoagulation is indicated (more commonly 6 months) and that treatment should include the first 6 weeks postpartum to cover the entire window of increased clotting risk. Because a primary hypercoagulable disorder will be identified in roughly 50% of women with VTE in pregnancy, screening should be considered.

Low molecular weight heparin (LMWH)	LMWHs enhance antithrombin III (AT)-mediated inhibition of coagulation factors, predominantly factor Xa. A lower affinity for binding to proteins other than AT renders LMWH more predictable and bioavailable compared to UFH. LMWHs do not cross the placenta and therefore have no associated risk for fetal anticoagulation or embryopathy. LMWHs are generally used in pregnancy at the same doses as in non-pregnant patients. They are administered subcutaneously as listed below: • Enoxaparin 1 mg per kg body weight twice daily; or 1.5 mg per kg daily • Dalteparin 100 IU per kg body weight twice daily; or 200 IU per kg body weight daily • Tinzaparin 175 U per kg body weight daily • Nadroparin 86 U per kg body weight twice daily; or 171 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. Adjusting the LMWH dose in pregnant women based on anti-Xa levels has not been shown to affect maternal or fetal outcomes. The target anti-Xa for therapeutic LMWH is 0.5–1.0 IU/mL. One study of 26 patients found that monitoring anti-Xa versus standard weight-based dosing was not associated with any difference in maternal blood loss at delivery or rates of recurrent VTE. [7•]. In another study, 144 women with primary thrombophilia and prior placenta-mediated pregnancy complications were managed with prophylactic LMWH in effort to reduce recurrent fetal complications. Women were managed with either fixed dosing LMWH or anti-Xa adjusted LMWH; there was no difference in clinical outcomes. [8]

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	There is minimal data regarding dosing of LMWH in obese pregnant women. One small retrospective study of 14 women with a body mass index > 30 showed that most required less than weight-based dosing to achieve a therapeutic anti-Xa level, but there was no significant difference in clinical outcomes among those managed with anti-Xa monitoring. [9] Overall LWMHs carry the best safety and efficacy profile in pregnancy with predictable degrees of anticoagulation achieved in most women. The dose should be escalated commensurate with weight gain throughout pregnancy. Women who are obese or have altered renal function may benefit from anti-Xa monitoring once per trimester. LMWH is usually transitioned to UFH closer to term to prepare for labor and delivery and possible neuroaxial anesthesia. When acute thrombosis is within 2–4 weeks of delivery, intravenous UFH can facilitate the shortest window off anticoagulation. If delivery has not occurred after 36 h of anticoagulation interruption, prophylactic anticoagulation should be considered. 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. [10]
Unfractionated heparin (UFH)	UFH induces a conformational change in AT, which accelerates AT- inhibition of factors IIa and Xa by 1000-fold. UFH also enhances AT- inhibition of factors IXa and XIa and prevents conversion of fibrinogen to fibrin. UFH does not cross the placenta. The anticoagulation effect of UFH can be assessed by the aPTT, but anti-Xa testing (when available) is preferred to measure heparin intensity given physiologic changes in pregnancy that can affect the aPTT independent of the UFH level. UFH is available subcutaneously and intravenously. The recommended subcutaneous dose for acute VTE is 250 units per kilogram body weight twice daily. However, this weight-based calculation may necessitate 3 or 4 times daily injection since the maximum volume for any subcutaneous injection is 1.5 mL. Importantly, UFH must be monitored and dose adjusted – starting about 48 h after the initial weight based dose. Both anti-Xa and aPTT should be assessed 3–4 h after an injection. The target anti-Xa level is 0.3–0.7 IU/mL; the target aPTT is 60–80 s. If the results are out of range, the dose should be adjusted and testing repeated until the therapeutic range is achieved. Anti-Xa and aPTT may not be concordant, but anti-Xa is a more accurate measure of heparin level and is thus preferred for judging dose adjustments. Preservative-free heparin formulations are preferred in pregnancy to avoid fetal exposure to benzyl alcohol, used in some UFH preparations and associated with a specific neurologic syndrome when administered directly to the neonate. A 5-year retrospective study of pregnant women receiving LMWH in pregnancy who were transitioned to UFH closer to delivery found that higher doses of UFH were needed to achieve anticoagulation in patients with a BMI < 30. [11]. Diminished adiposity or increased renal clearance have been proposed mechanisms for this paradoxical relationship. Regardless, the finding highlights the need for monitoring UFH. Osteoporosis is reported to occur in 2–5% of patients receiving long term UFH. Although considered reversible after UFH is discontinued, sequelae from any fracture that may result is possible. [10, 12–14] Another disadvantage is that weight-based UFH is not available in prefilled syringes, which is inconvenient and may result in dosing errors. Use of intravenous UFH is restricted to hospitalized patients, and therefore has limited application in pregnancy. It is used in combination with additional interventions (such as thrombectomy or thrombolysis) or to minimize the time without anticoagulation in women with VTE 2–4 weeks prior to delivery. When used for acute management of VTE, standard weight based dosing with adjustment per aPTT/anti-Xa as used outside of pregnancy is appropriate: 80 U/kg body weight bolus followed by 18 U/kg/h continuous infusion. Assess aPTT 6 h after starting and with every dose change to ensure appropriate intensity. UFH does not enter the breast milk, so use can be continued in nursing mothers.

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Fondaparinux	Fondaparinux is a pentasaccharide resulting in selective factor Xa inhibition by AT. Although there is less available safety data compared with LMWH, a review of 65 pregnancies where fondaparinux was used showed that the drug was well tolerated with pregnancy complication rates similar to the general population. [15] Fondaparinux has been shown to cross the placenta, although in small quantities and with no documented fetal consequence [16]. Given its unknown fetal risk, however, avoidance in the first trimester is prudent if possible. Its longer half-life of 17 h has the advantage of once daily therapeutic dosing, but also necessitates the longest elapsed time (5 days) prior to epidural anesthesia. Fondaparinux is recommended by the American College of Obstetrics and Gynecology for anticoagulation in women with a history of heparin induced thrombocytopenia (HIT). The treatment-intensity dosing is the same as in non-pregnant patients and is weight based: - < 50 kg to 2.5 mg sc once daily - 51–75 kg to 5 mg sc once daily - 76–100 kg to 7.5 mg sc once daily - > 100 kg to 10 mg sc once daily There are no published data regarding Fondaparinux levels in human breast milk. However, significant absorption by the nursing infant is unlikely since oral bioavailability is low.
Warfarin	Given fetal exposure and therefore 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 and bivalirudin are DTIs available only intravenously and therefore have rare application in pregnancy, except possibly peripartum in women with HIT. HIT is uncommon in pregnancy, given predominant use of LMWH. One systemic review identified only 12 reported cases. [17] It is not known if intravenous DTIs cross the placenta. The estimated threshold for human placental transfer is 1000 Da. [18] The molecular weight of bivalirudin is 2180 Da, rendering it less likely to transfer placentally compared with argatroban with a molecular weight of 527 Da. [19, 20] The oral DTI, dabigatran, has been shown to cross the placenta in animal models and is therefore not recommended for use in pregnancy.
Director oral anticoagulants (DOAC)	DOACs are increasingly used to treat VTE, but have been insufficiently studied in pregnancy and therefore not recommended. Given increasing use among reproductive aged women, there are cases of inadvertent DOAC exposure in pregnancy. Limited recent literature describing outcomes of such pregnancies has been summarized. [1] All women discontinued DOAC upon pregnancy detection. However, in the absence of safety data, roughly one fourth of women elected pregnancy termination. With small numbers, the risk for embryopathy was generally similar to that of warfarin. [21, 22] Nursing mothers were excluded from the original trials examining safety and efficacy of DOACs. One case report demonstrated small amounts of rivaroxaban in breast milk. [23]. Although safety or harm could not be assessed, the availability of alternative safe anticoagulants disfavors use of DOACs in nursing women.
Thrombolysis	There are no available data from randomized trials to assess thrombolysis in pregnancy, which should be reserved for life or limb threatening thrombosis. Data from small series have shown similar complication rates in pregnant women compared to non-pregnant patients [24]. A recent publication culled 65 articles describing outcomes when thrombolysis was used in pregnancy, including management for VTE and CVA. In 141 pregnant women, the rates of complications included: 2.8% maternal deaths, 8.5% major bleeding, 9.2% mild bleeding, 1.4% fetal deaths, 0.7% newborn death, 6.4% miscarriage and 9.9% preterm delivery. [25] An older series describing use of thrombolytics in 172 pregnancies showed similar

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complications rates: 1.2% maternal mortality, 5.8% pregnancy loss and 8.1% hemorrhagic complications. [26]. Although not evidence-based, current practice would favor catheter-directed thrombolysis instead of systemic administration to minimize the associated risk. A publication from 1970 demonstrated minimal transplacental passage of tPA or streptokinase [27].

A more recent systemic review described the management and outcomes of 127 cases of severe PE during pregnancy or within 6 weeks of delivery (83% massive PE and 23% with cardiac arrest). Of note, about half of the cases occurred within 24 h of delivery. Management included thrombolysis and/or surgical thrombectomy. Of the 83 women managed with thrombolysis, maternal survival was 94%, with an associated major bleeding risk of 17.5% antepartum and 58.3% postpartum. Fetal death occurred in 12% of cases, attributed to PE or its treatment. [28•]

Pharmacologic treatment in special circumstances: AT III deficiency

AT-III (AT) deficiency	AT is a natural anticoagulant that inhibits factor IIa (thrombin), factor Xa, and other serine proteases in the coagulation cascade. In the absence of AT, heparin has little effect as an anticoagulant. AT deficiency, a rare primary thrombophilia, is associated with an increased risk of VTE, particularly during pregnancy. A recent review pooling data from 7 publications estimated an odds ratio of 6.09 for VTE in pregnancy in women with AT deficiency [29], supporting use of thromboprophylaxis in pregnancy even without a personal thrombosis history. A challenge, however, is that heparins exert their anticoagulant affect via binding with AT. UFH is the most reliant on AT for its anticoagulant effect. A single case report describes a woman with AT deficiency who developed acute VTE in pregnancy despite use of weight-based LMWH at recommended therapeutic dose. [30] In this case, supplemental AT infusions were used to achieve normal AT levels such that heparin could achieve a therapeutic level of anticoagulation. This publication also contained a review of the literature, including 439 publications of either cases reports or reviews. When AT concentrate was used, typical loading doses were 30–50 IU/kg with a targeted AT level of 80–120%. The maintenance dose is typically given every 2–3 days. An analysis combining data from 2 clinical trials examined use of recombinant human antithrombin (rhAT) to prevent VTE in women with inherited AT deficiency. [31] A total of 21 women were enrolled and received rhAT to achieve an AT level of 80–120%. There were no VTEs during rhAT treatment. There were 2 postpartum VTEs that occurred after discontinuing rhAT in women receiving prophylactic doses of UFH or LMWH. This limited series is insufficient to inform universal practice, but suggests that AT replacement with heparin or switching to a DTI may be required to achieve therapeutic anticoagulation in AT deficient patients. Of note, this is one disease where anti-Xa levels may be less useful in monitoring the degree of anticoagulation since some assays add AT, which could render a false report of anticoagulation intensity in the AT deficient patient.

Interventions and surgical procedures

The majority of women will be adequately managed for VTE with anticoagulation alone. Massive PE, however, defined as causing systemic hypotension or shock, may necessitate additional therapies. These therapies could include thrombolysis (discussed above) or thrombectomy. While use of inferior vena cava (IVC) filters is also rarely necessary, placement has been considered in cases of acute DVT when anticoagulation is held for labor and delivery. Venous stenting is also considered if anticoagulation fails to alleviate vascular congestion, as may occur with May-Thurner syndrome.

Surgical thrombectomy	Surgical thrombectomy is reserved for management of massive PE. In a series of 127 pregnant or peripartum women with massive PE, 36 were managed with surgical thrombectomy. Maternal survival was 86%, major bleeding was 20% and fetal deaths were 20% [28•]. Although few patients were studied, this series showed less maternal bleeding with surgery compared with thrombolytics: 20 vs 75%. However, maternal survival was less with surgery: 86 vs 94%. The data are insufficient for strong recommendations and the treatment of massive PE in peripartum women may depend on local resources and experience.
Inferior vena cava (IVC) filters	IVC filters are considered when anticoagulation therapy is not tolerated, is ineffective, or must be discontinued. Placement requires radiation exposure, which should be minimized in pregnancy except where benefit clearly outweighs this risk. There are no randomized trials specific to pregnant women. A recent publication reported the experience of a single center over a 10-year period that included IVC filter placement in 10 pregnant and 14 postpartum women. The most common indication for antepartum use was allowing anticoagulation interruption at delivery with acute VTE (40%) and for postpartum use was an adjunct to catheter-directed thrombolysis (64%). The overall complication rate was 29.2% and successful retrieval was 79% [32]. Another recent study reviewed outcomes for 43 pregnant women who received IVC filters and compared outcomes to the general population. In this series, there were no reported PEs in pregnant or postpartum women. Although not reaching statistical significance, filter complication rates were higher in pregnant women compared with the baseline population: filter thrombosis (2.3 vs 0.9%), IVC perforation (7 vs 4.4%), and failure to retrieve the filter (26 vs 11%) [33]. Although this limited experience may reflect publication bias that favors reporting complications, the overall limited benefit seen with IVC filters combined with these complications rates certainly gives pause before considering use in pregnancy. Most women, even with acute VTE within several weeks of delivery, will tolerate anticoagulation interruption for several hours to permit delivery such that the benefit of an IVC filter would not outweigh the risks. Shortened windows of anticoagulation interruption can be achieved with intravenous UFH (see above). It has been postulated that suprarenal placement of IVC filters in pregnant women would significantly decrease the risks compared to infrarenal placement due to separation from direct pressure on the filter exerted by the growing or contracting uterus. However, a large published review totaling 135 pregnancies managed with both suprarenal and infrarenal placement reported complications in both positions [34].
Catheter-directed thrombolysis	A commonly cited concern in management of proximal DVTs is the risk of developing post-thrombotic syndrome (PTS), even in cases where anticoagulation was initiated early. The risk for PTS is higher in proximal versus distal events. Given the relative young age of pregnant women (therefore more years in which to develop PTS) and

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	that proximal/pelvic events occur more commonly in pregnancy than in the general population, the role of catheter-directed thrombolysis to prevent PTS has been debated. Although excluding pregnant women, the recent publication of the ATTRACT trial investigators would challenge the value of routine catheter-directed thrombolysis for management of proximal events. In this trial, 692 patients were randomized to anticoagulation alone versus anticoagulation plus catheter-directed thrombolysis. There was no difference in rates of PTS (48 vs 47%) at 6 months or recurrent VTE (8 vs 12%) at 24 months in anticoagulated alone versus anticoagulation plus catheter-directed thrombolysis groups. Although severity scores for PTS were less in the thrombolysis group, quality of life scores did not differ. Use of thrombolysis was associated with a higher major bleeding risk (1.7%) compared to anticoagulation alone (0.3%) [35].
	These data suggest that catheter-directed thrombolysis should not be used routinely in the management of pregnant women with proximal DVT, but rather reserved for symptomatic DVT that is unresponsive to systemic anticoagulation. Catheter-directed thrombolysis should generally be avoided in the first trimester since use requires radiation, which can be teratogenic at a time of organogenesis. If deemed clinically necessary, pregnant women require careful education regarding these risks.
Pneumatic compression devices	Use is generally recommended for pregnant women during the window when anticoagulation is held for labor and delivery, although there is no rigorous data demonstrating benefit.

Anticoagulation management: labor and delivery

The prime factors affecting bleeding risk at the time of delivery are uterine tone; trauma to the birth canal; or abnormal placentation or retained placental tissue. While systemic anticoagulation contributes much less to these bleeding risks, the timing and intensity of anticoagulation weigh heavily on decisions regarding anesthesia options. One observational study examined disparities between intrapartum anesthesia and delivery modalities in women receiving anticoagulation compared with controls [36]. Of the 203 women receiving anticoagulation, 61.6% received an epidural during childbirth versus 87% of the 812 controls. Use of general anesthesia was higher in the anticoagulated group: 5.4% versus 0.7%. The postpartum hemorrhage rate was similar in both groups.

The half-life of subcutaneous UFH is about 3 h where the half-life for LMWH is about 4 h. Despite this minor variation, the recommended delay for neuraxial anesthesia from time of last injection is 12 h for subcutaneous UFH and 24 h for LMWH. These guidelines have led to the common practice of transitioning women to UFH closer to term, although there is little data to show this practice decreases bleeding complications. In fact, one publication showed an increased risk for hemorrhagic complications in women receiving therapeutic UFH antepartum compared with LMWH [37].

The recommendations of different medical societies regarding management of therapeutic anticoagulation and timing of neuraxial anesthesia are presented below. Not all societies provide specific guidance for all anticoagulants, but

there is general consensus that therapeutic LMWH requires a 24 h hold before neuroaxial anesthesia. Use of intravenous UFH can shorten the required window off anticoagulation prior to neuroaxial anesthesia to 4–6 h, provided that the aPTT is normal (Table 1).

Given these challenges, it is important that an interdisciplinary team consisting of representatives from anesthesia, obstetrics, cardiology, and hematology work together to establish guidelines that govern management of anticoagulation at the time of labor and delivery. It is also important that patients are informed of the complexity of management and the possibility that despite careful planning, neuraxial anesthesia may not be possible. Patients likely benefit from an anesthesia consultation prior to labor and delivery to discuss alternative pain management strategies should neuraxial anesthesia not be deemed safe.

Table 1. Societal recommendations regarding anticoagulation and neuraxial anesthesia

Society	UFH	LMWH
American College of Obstetricians and Gynecologists (ACOG) [38, 39]		Withhold for 24 hours before neuraxial anesthesia (level C)
American College of Chest Physicians (ACCP) [40]	If laboratory data allows for rapid assessment of heparin level, testing can be considered and used to guide anesthesia management	Discontinue at least 24 hours prior to induction of labor or cesarean section (grade 1B) If spontaneous labor occurs on therapeutic anticoagulation, neuroaxial anesthesia should not be used
Society of Obstetricians and Gynaecologists of Canada (SOGC) [41]	Neuroaxial anesthesia can be administered: - without delay following prophylactic dose of 10,000 units/day (grade IIIB) - 4 hours after stopping therapeutic intravenous infusion (and when PTT is normal) (grade IIIB) - 12 hours or longer after last therapeutic subcutaneous dose (and when PTT is normal) (grade IIIB)	Wait at least 24 hours after the last therapeutic dose (grade IIIB)
Royal College of Obstetricians and Gynaecologists (RCOG) [42, 43]		Where delivery is planned, discontinue LMWH 24 hours prior to delivery (no grade) Defer neuroaxial anesthesia at least 24H from the last LMWH dose (no grade)
Australia/New Zealand [44]	For prophylactic unfractionated heparin (less than 10,000 units/day), wait at least 6 hours after last dose For therapeutic UFH IV, stop 4–6 hours prior to neuroaxial blockade (and documented normal PTT) (no grade)	Minimum of 24 hours after last LMWH dose is required (no grade)

Anticoagulation management: postpartum

Women with a VTE diagnosed in pregnancy will resume anticoagulation postpartum once hemostasis has been achieved and at least 4 h after neuraxial anesthesia is discontinued. For a provoked event, women should complete 3–6 total months of anticoagulation. If these 6 months are completed at the time of delivery, transitioning to prophylactic anticoagulation for the 6–8 weeks postpartum is reasonable. If the VTE was within 6 months of delivery, they would normally resume therapeutic level anticoagulation for 6–8 weeks postpartum (6 weeks for vaginal delivery and 8 weeks for cesarean delivery). With a history of pregnancy-associated VTE, antepartum and postpartum VTE prophylaxis is recommended for future pregnancies.

Conclusion

Pregnancy is a well-characterized thrombophilic condition due to both changes in coagulation as well as the venous system. These changes yield an increased risk of VTE by 6–10-fold in pregnancy, with risk extending (and in fact increasing) into the postpartum 6–8 weeks. Although this association is well known, there is a dearth of high-quality evidence to guide the diagnosis and optimal management strategy for VTE. It is critical that both providers and pregnant women be educated on the risk of VTE, remain vigilant for symptoms, work expeditiously to evaluate suspected VTE, and initiate appropriate therapy promptly.

A summary of the recent data available regarding management of VTE in pregnancy is below:

- Traditional biomarkers and PE scoring symptoms used in non-pregnant populations have poor positive and negative predictive value in pregnancy.
- Leg ultrasound is the preferred radiographic modality for investigating suspected VTE in pregnancy, but use of pelvic MRI or CTPA is appropriate if VTE is suspected but not identified on ultrasound.
- 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 impaired renal function.
- There is insufficient safety data to support the use of DOACs in pregnancy or nursing.
- LMWH, UFH, and warfarin can be used in nursing mothers.
- VTE diagnosed in pregnancy is classified as provoked and should be treated for a total of 3–6 months, but include all of pregnancy and at least 6 weeks postpartum.
- LMWH and subcutaneous UFH anticoagulation at therapeutic doses should be discontinued for 24 and 12 h prior to neuraxial anesthesia, respectively.

- Thrombolysis in pregnancy is reserved for life or limb threatening thrombosis; it is associated with increased risk for postpartum hemorrhage.
- Surgical thrombectomy can also be considered for management of massive PE, with small studies showing inferior maternal outcomes, but less postpartum bleeding when compared to thrombolysis.

Compliance with Ethical Standards

Conflict of Interest
The authors declare that they have no 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.

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