CME CREDIT ***EDUCATIONAL OBJECTIVE:*** To confidently prescribe anticoagulants to pregnant women based on a careful assessment of the risks to mother and fetus

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Anticoagulants and pregnancy: When are they safe?

ABSTRACT

Prescribing anticoagulants to pregnant women can be difficult and stressful. Fortunately, low-molecular-weight heparins (LMWHs) and unfractionated heparin are quite safe and efficacious when properly selected, dosed, and monitored. Maternal and fetal concerns must be considered at all times, with a careful assessment of the risks and benefits of anticoagulant therapy in each patient. Further research should help to clarify who should receive thromboprophylaxis, how to prevent adverse pregnancy outcomes in women with various thrombophilias, and how best to treat pregnant women who have a prosthetic heart valve.

KEY POINTS

Pregnancy is a hypercoagulable state. Thrombotic risk in an individual pregnancy depends on many maternal and situational factors.

When indicated, careful anticoagulation can proceed with minimal risk to the mother and fetus.

Heparins, especially LMWHs, are the main anticoagulants used in pregnancy. Dosing depends on the clinical indications and on the agent selected.

If anticoagulation is absolutely necessary and LMWH is contraindicated, a newer, alternative anticoagulant should be considered.

Warfarin should not be used in pregnancy in any but the highest-risk situations.

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Anticoagulation is essential in a wide variety of conditions in women of childbearing age. Some, such as venous thromboembolism, occur more often during pregnancy. Others, such as recurrent fetal loss in the setting of antiphospholipid antibodies, are specific to pregnancy.

While anticoagulants are useful in many circumstances, their use during pregnancy increases the risk of hemorrhage and other adverse effects on the mother and the fetus. Treatment with anticoagulants during pregnancy must therefore be carefully considered, with judicious selection of the agent, and with reflection on the physiologic changes of pregnancy to ensure appropriate dosing. In this article, we review these issues.

WHY IS THROMBOTIC RISK HIGHER DURING PREGNANCY?

Venous thromboembolism is among the leading causes of maternal death in developed countries.[1–3] Modern care has dramatically reduced the risk of maternal death from hemorrhage, infection, and hypertension, but rates of morbidity and death from thrombosis have remained stable or increased in recent years.[4]

Pregnancy is a period of increased risk of thrombotic complications (**TABLE 1**), owing to hypercoagulability, venous stasis, and vascular damage—the three elements of Virchow's triad.[5] Several changes to the maternal coagulation system increase clotting risk:

- Much higher levels of fibrinogen and factors VII, VIII, IX, and X
- Lower levels of protein S and increased resistance to activated protein C
- Impaired fibrinolysis, due to inhibitors derived from the placenta.

TABLE 1

Factors that increase thrombotic risk in pregnancy

Increased maternal clotting factors
Fibrinogen and factors VII, VIII, IX, and X

Reduction in maternal levels of protein S

Impaired fibrinolysis
Placenta-derived fibrinolytic inhibitors

Venous stasis and blood pooling
Progesterone-mediated venous dilation
Compression of the inferior vena cava by the uterus in later pregnancy

Endothelial disruption of the pelvic vessels
Cesarean section

Acquired antithrombin deficiency
High-proteinuric states such as nephrotic syndrome or preeclampsia

Excessive elevation of pregnancy hormones
Ovarian hyperstimulation syndrome, multiple gestation

Other maternal risk factors
Thrombophilia
Family history of venous thromboembolism
Age > 35 years
Parity > 3
Obesity
Immobilization
Smoking
Varicose veins with phlebitis

Other maternal medical conditions
Hyperemesis gravidarum
Infection
Inflammatory bowel disease
Any condition necessitating a chronic indwelling catheter

Acquired antithrombin deficiency may also occur in high-proteinuric states such as nephrotic syndrome or preeclampsia, further increasing thrombotic risk. Pooling of venous blood, caused by progesterone-mediated venous dilation and compounded by compression of the inferior vena cava by the uterus in later pregnancy, also increases thrombotic risk. And endothelial disruption of the pelvic vessels may occur during delivery, particularly during cesarean section.

Additional factors that increase thrombotic risk include immobilization, such as bed rest for pregnancy complications; surgery, including cesarean section; ovarian hyperstimulation during gonadotropin use for in vitro fertilization; trauma; malignancy; and hereditary or acquired hypercoagulable states.[6] These hypercoagulable states include deficiencies of antithrombin or the intrinsic anticoagulant proteins C or S; resistance to activated protein C, usually due to the factor V Leiden mutation; the PT20210A mutation of the prothrombin gene; hyperhomocystinemia due to mutation of the methyltetrahydrofolate reductase (MTHFR) gene; and the sustained presence of antiphospholipid antibodies, including lupus anticoagulant antibodies, sometimes also with moderately high titers of anticardiolipin or beta-2-glycoprotein I antibodies.

Other conditions that increase thrombotic risk include hyperemesis gravidarum, obesity, inflammatory bowel disease, infection, smoking, and indwelling intravenous catheters.[6] Given the multitude of risk factors, pregnant women have a risk of thrombotic complications three to five times higher than nonpregnant women.[7]

HEPARIN USE DURING PREGNANCY

Low-molecular-weight heparins (LMWHs)[8] and unfractionated heparin bind to antithrombin and thus change the shape of the antithrombin molecule, dramatically increasing its interaction with the clotting factors Xa and prothrombin (factor II). The enhanced clearance of these procoagulant proteins leads to the anticoagulant effect. Unfractionated heparin has roughly equivalent interaction with factors Xa and II and prolongs the activated partial thromboplastin time (aPTT), which is therefore used to monitor the intensity of anticoagulation.

LMWHs, on the other hand, interact relatively little with factor II and do not predictably prolong the aPTT. Monitoring their effect is therefore more difficult and requires direct measurement of anti-factor-Xa activity. This test is widely available, but it is time-consuming (it takes several hours and results may not be available within 24 hours if the test is requested "after hours"), and therefore it is of limited use in the acute clinical setting. While weight-based dosing of LMWHs is reliable and safe in nonpregnant patients, it has not yet been validated for pregnant women.

TABLE 2

Anticoagulant dosing in pregnancy

MEDICATION	ACTION	INDICATIONS IN PREGNANCY	RECOMMENDED DOSAGE
Low-molecular-weight heparin (LMWH)	Potentiates antithrombin action, inactivates factor Xa much more than factor II (prothrombin)	To treat acute venous thromboembolism (VTE) Ongoing anticoagulation in women on long-term anticoagulation	**Therapeutic use** Enoxaparin (Lovenox) 1 mg/kg twice daily Dalteparin (Fragmin) 100 IU/kg twice daily Tinzaparin (Innohep) 175 IU/kg once daily
		To prevent VTE To prevent recurrent miscarriage (with aspirin) in antiphospholipid antibody syndrome	**Prophylactic use** Enoxaparin 30 mg twice daily, or 40 mg once daily Dalteparin 5,000 IU once daily Tinzaparin 75 IU/kg once daily, or 4,500 IU/ once daily
Unfractionated heparin (UH)	Potentiates antithrombin action, inactivates factor Xa and factor II	To treat acute VTE Ongoing anticoagulation in women on long-term anticoagulation	**Therapeutic use** Intravenous: 80 U/kg bolus, then 18 U/kg/hour, adjusted to an activated partial thromboplastin time (aPTT) of 60–80 sec Subcutaneous: initial dose of 216 U/kg every 12 hours, adjusted to a mid-interval (6-hour) aPTT of 60–80 sec
		To prevent VTE To prevent recurrent miscarriage (with aspirin) in antiphospholipid antibody syndrome	**Prophylactic use** 5,000 U twice daily in first trimester 7,500 U twice daily in second trimester 10,000 U twice daily in third trimester
Warfarin (Coumadin), other coumarins	Reduce hepatic synthesis of factors II, VII, IX, and X by inhibiting vitamin K	To prevent valve thrombosis and thromboembolism in women with a mechanical heart valve, gestational weeks 12 to 36 Postpartum anticoagulation for any indication	Initial dose 5–10 mg once daily, adjusted to an international normalized ratio of 2.0–3.0
Aspirin	Inhibits platelet aggregation	To prevent recurrent miscarriage (with LMWH or UH) in antiphospholipid antibody syndrome To prevent preeclampsia in high-risk women	81 mg once daily

Unfractionated heparin has been used for decades for many indications during pregnancy. It is a large molecule, so it does not cross the placenta and thus, in contrast to the coumarin derivatives, does not cause teratogenesis or toxic fetal effects. Its main limitations in pregnancy are its inconvenient dosing (at least twice daily when given subcutaneously) and its potential maternal adverse effects (mainly osteoporosis and heparin-induced thrombocytopenia).

Over the last 10 years LMWHs have become the preferred anticoagulants for treating and preventing thromboembolism in all patients. They are equivalent or superior to unfractionated heparin in efficacy and safety in the initial treatment of acute deep venous thrombosis[9,10] and pulmonary embolism[11,12]

outside of pregnancy. While comparative data are much less robust in pregnant patients, several series have confirmed the safety and efficacy of LMWHs in pregnancy.[13–15] LMWHs do not cross the placenta[15–17] and thus have a fetal safety profile equivalent to that of unfractionated heparin.

Pregnancy alters metabolism of LMWHs

The physiologic changes of pregnancy alter the metabolism of LMWH, resulting in lower peak levels and a higher rate of clearance,[18,19] and so a pregnant woman may need higher doses or more frequent dosing.

Recent evidence suggests that thromboprophylaxis can be done with lower, fixed, once-daily doses of LMWH throughout pregnancy,[20] although some clinicians still prefer twice-daily dosing (particularly during the latter half of pregnancy).

For therapeutic anticoagulation, however, the dose of LMWH required to achieve the desired level of anti-factor-Xa activity appears to change significantly over the course of pregnancy in many women.[18] Therapeutic dosing of LMWH may also require twice-daily dosing, depending on the agent used (**TABLE 2**).

Pregnancy increases the risk of thrombosis three to five times

Pending more research on weight-based dosing of LMWH in pregnancy, anti-factor-Xa activity levels should be measured after treatment is started and every 1 to 3 months thereafter during pregnancy.[21] Doses should be adjusted to keep the peak anti-Xa level (ie, 4 hours after the dose) at 0.5 to 1.2 U/mL.[22]

Heparin-induced thrombocytopenia

Type-2 heparin-induced thrombocytopenia is an uncommon but serious adverse effect of unfractionated heparin therapy (and, less commonly of LMWH), caused by heparin-dependent immunoglobulin G (IgG) antibodies that activate platelets via their Fc receptors, potentially precipitating life-threatening arterial or venous thrombosis.

In a trial in nonpregnant orthopedic patients,[23] clinical heparin-induced thrombocytopenia occurred in 2.7% of patients receiving unfractionated heparin vs 0% of those receiving LMWH; heparin-dependent IgG was present in 7.8% vs 2.2%, respectively.

Fortunately, heparin-induced thrombocytopenia seems to be very rare in pregnancy: two recent prospective series evaluating prolonged LMWH use in pregnancy[13,15] revealed no episodes of this disease. Nonetheless, it is reasonable to measure the platelet count once or twice weekly during the first few weeks of LMWH use and less often thereafter, unless symptoms of heparin-induced thrombocytopenia develop. In pregnant women with heparin-induced thrombocytopenia or heparin-related skin reactions, other anticoagulants must be considered[24] (see discussion later).

Heparin-induced osteoporosis

Heparin-induced osteoporosis, a potential effect of prolonged heparin therapy, is of concern, given the prolonged duration and high doses of unfractionated heparin often needed to treat venous thromboembolism during pregnancy. Several studies found significant loss of bone mineral density in the proximal femur[25] and lumbar spine[26] during extended use of unfractionated heparin in pregnancy.

Fortunately, LMWH appears to be much safer with respect to bone loss. Three recent studies[27–30] evaluated the use of LMWH for extended periods during pregnancy, and none found any greater loss of bone mineral density than that seen in normal pregnant controls. Giving supplemental calcium (1,000–1,500 mg/day) and vitamin D (400–1,000 IU/day) concomitantly with unfractionated heparin or LMWH in pregnancy is advisable to further reduce the risk.

Interrupt heparin to permit regional anesthesia

Heparin therapy should be temporarily stopped during the immediate peripartum interval to minimize the risk of hemorrhage and to permit regional anesthesia. Because of the theoretical risk of paraspinal hemorrhage in women receiving heparin who undergo epidural or spinal anesthesia, many anesthetists will not perform neuraxial regional anesthesia in women who have recently received heparin.

Since unfractionated heparin has a relatively short duration of action, the American Society of Regional Anesthesia states that subcutaneous unfractionated heparin prophylaxis is not a contraindication to neuraxial regional anesthesia.[31] However, LMWHs should be stopped for at least 12 to 24 hours before re-

gional anesthesia can be considered safe. This issue is discussed in more detail in the section on peripartum and postpartum management of anticoagulation, below.

In summary, LMWH during pregnancy offers a number of advantages over unfractionated heparin: equivalent efficacy, once- or twice-daily dosing, lower risk of heparin-induced thrombocytopenia and osteoporosis, and less-intensive monitoring. Unfractionated heparin can be offered to women who cannot afford LMWH (which costs four to five times more), and it may be used peripartum to reduce hemorrhagic risk and to permit regional anesthesia.

COUMARINS

Coumarins are the mainstay of anticoagulant therapy in most nonpregnant women beyond the immediate thrombotic period.

Warfarin (Coumadin) is the most widely used coumarin because it has a predictable onset and duration of action and excellent bioavailability.[32] Others, such as acenocoumarol (Sintrom) and phenprocoumon (Marcoumar), are used more outside the United States but can be ordered or brought into the United States.

Coumarins interfere with vitamin K metabolism, inhibiting the generation of vitamin-K-dependent procoagulant proteins (factors II, VII, IX, and X) and thereby preventing clotting. They also inhibit the formation of the vitamin-K-dependent intrinsic anticoagulant proteins C and S.

Major bleeding is the most significant side effect of coumarin therapy, occurring at a rate of 4% to 6% over 3 months when the prothrombin time is maintained at an international normalized ratio (INR) of 2 to 3,[33] and more often if the INR is higher.

Other issues with warfarin are the effect of variations in dietary vitamin K intake on anticoagulation and potential drug interactions that may alter the anticoagulant effect. Thus, the INR needs to be monitored closely.

Risks to the fetus and the mother

Unlike the heparins, coumarins freely cross the placenta and thus pose a risk of teratogenicity. A cluster of fetal malformations including "warfarin embryopathy" (nasal bone hypoplasia and chondrodysplasia punctata) can occur when the drug is used between 6 and 12 weeks of gestation. Warfarin embryopathy may be avoided by stopping warfarin prior to 6 weeks from the onset of the last menstrual period (ie, 6-week "menstrual age" or 4-week gestational age[34]).

Later in pregnancy, warfarin is associated with potential fetal bleeding complications leading to central nervous system abnormalities, increased rates of intrauterine fetal death, and pregnancy loss. In pregnant women with mechanical cardiac valve prostheses who received oral anticoagulants throughout pregnancy, the incidence of congenital anomalies was 6.4% to 10.2%.[35] Fetal demise (spontaneous abortion, stillbirth, neonatal death) was also very common (29.7% to 33.6% of pregnancies) in coumarin-treated women.

Severe maternal hemorrhage may also occur in pregnant women on oral anticoagulants, particularly those who remain fully anticoagulated around the time of labor and delivery.

General caveats to warfarin in pregnancy

Because of the many maternal and fetal concerns, oral anticoagulant use in pregnancy is largely restricted to women with older-generation prosthetic heart valves in whom the very high maternal thrombotic risk may outweigh the risk of maternal and fetal side effects.

Fortunately, heparin-induced thrombocytopenia seems to be very rare in pregnancy

While there are limited data on warfarin use in pregnant women with antiphospholipid syndrome,[36] warfarin use in such patients should be considered only for those at highest risk and with careful informed consent. These issues are discussed further below in the section on mechanical heart valve prostheses.

ANTIPLATELET DRUGS

Aspirin is an antiplatelet agent rather than an anticoagulant. Although considered inadequate for preventing venous thrombosis in high-risk groups when used alone, aspirin can moderately reduce the risk of deep venous thrombosis and pulmonary embolism in nonpregnant patients.[37] It also has a well-accepted role in preventing arterial thrombotic events, ie, coronary artery disease and stroke.[38]

Low-dose aspirin (≤ 100 mg/day) has been extensively evaluated during pregnancy[39–41]

TABLE 3

Newer anticoagulants and pregnancy

AGENT	ADMINISTRATION	MONITORING	CLEARANCE	HALF-LIFE	COMMENTS
Heparinoids					
Danaparoid (Orgaran)	Intravenous (IV) bolus, followed by subcutaneous (SC) injections	Anti-Xa levels	Renal	25 ± 100 hours[47]	Probably the preferred newer drug in pregnancy, per preliminary reports Not available in the United States Possible 5% to 10% risk of cross-reactivity with antibodies generated in heparin-induced thrombocytopenia (HIT)[43,48] Expensive
Direct thrombin inhibitors					
Lepirudin (Refludan)	IV infusion	Activated partial thromboplastin time (aPTT)	Renal	60 minutes	Recombinant hirudin Approved for treatment of HIT Unlike the heparins, this agent binds both free and clot-bound thrombin Does not cause HIT and works in patients with antithrombin deficiency
Bivalirudin (Angiomax)	IV infusion	Activated clotting time aPTT Prothrombin time	Renal	25 minutes	Approved only for patients with unstable angina undergoing coronary angioplasty Human pregnancy data extremely limited
Argatroban	IV infusion	aPTT	Hepatic (no renal adjustment needed)	28 minutes	Human pregnancy data limited, but given its low molecular weight, it probably crosses the placenta readily
Direct factor Xa inhibitor					
Fondaparinux (Arixtra)	SC injections once daily	Anti-Xa level	Renal	17–21 hours	Placental transfer appears to be minimal,[49,50] suggesting this may be the best newer anticoagulant for pregnant patients with HIT when there is no access to danaparoid

and has been shown to be safe and effective in reducing the risk of preeclampsia in high-risk women[39] and in treating women with antiphospholipid antibodies and recurrent pregnancy loss[42] (in conjunction with prophylactic doses of heparin). Although higher doses of aspirin and other nonsteroidal anti-inflammatory drugs can be toxic to the fetus, low doses have been shown to be safe throughout pregnancy.[43]

Dipyridamole (Persantine) has been studied extensively in pregnancy, and while it appears to be safe, it has not found a well-defined therapeutic role.

Other antiplatelet drugs have been only rarely used, and data on their safety and efficacy during pregnancy are limited to case reports, for example, on ticlopidine[44] (Ticlid) and clopidogrel[45,46] (Plavix) given during pregnancy in women with cardiac disease. These drugs do not appear to be major teratogens or to cause specific fetal harm. Their use may be reasonable in some high-risk situations, such as recurrent thrombotic stroke despite aspirin therapy. They may be used alone or with other anticoagulants in women with a coronary or other vascular stent if fetal safety is uncertain or if there is an increased risk of maternal bleeding.

NEWER ANTICOAGULANTS

Several newer anticoagulants can be used in pregnancy (TABLE 3).[47–50]

Danaparoid

The heparinoid danaparoid (Orgaran) is an LMWH, a combination of heparan, dermatan, and chondroitin sulfate. Since it is derived from heparin, in theory it can cross-react with antiheparin antibodies, but this is generally not a problem. Danaparoid inhibits factor Xa, and monitoring is via measurement of anti-factor-Xa activity levels. It has been shown to be safe and effective in nonpregnant patients with heparin-induced thrombocytopenia.[51]

Although no controlled study has been published on danaparoid in pregnancy, at least 51 pregnancies in 49 patients treated with danaparoid have been reported.[52] Thirty-two of the patients received danaparoid because of heparin-induced thrombocytopenia and 19 because of heparin-induced skin intolerance. These reports suggest that danaparoid does not cross the placenta[53] and that it may be effective and safe during pregnancy.[54] For this reason, it is probably the preferred anticoagulant in pregnant patients with heparin-induced thrombocytopenia or other serious reactions to heparin.

Unfortunately, danaparoid has two major disadvantages. First, it has a prolonged half-life and no effective reversing agent, which makes its use problematic close to the time of delivery. Second, and perhaps more relevant to this discussion, it is not readily available in the United States; it was removed from the market by its manufacturer in April 2002 for business reasons rather than because of concerns over toxicity. It is still available in Canada and Europe, and it can be obtained in special circumstances in the United States via the US Food and Drug Administration (FDA); this may be worthwhile in pregnant patients who require a non-urgent alternative to heparin.

Direct thrombin inhibitors

Lepirudin (Refludan), bivalirudin (Angiomax), and argatroban are direct thrombin inhibitors and exert their anticoagulant effect independently of antithrombin. They are given by continuous intravenous infusion, and they have a very short half-life.

Lepirudin and argatroban are typically monitored via the aPTT. Bivalirudin can be monitored with the activated clotting time, partial thromboplastin time, or INR, depending on the circumstances. None of these agents generates or cross-reacts with antibodies generated in heparin-induced thrombocytopenia. None has an antidote, but the short half-life usually obviates the need for one.

Unfortunately, pregnancy data are very sparse for all three of these new agents. Argatroban has a low molecular weight and likely crosses the placenta. Also, because these agents are given intravenously, they are not practical for long-term use in pregnancy.

Fondaparinux

Fondaparinux (Arixtra), a direct factor Xa inhibitor, binds to antithrombin, causing an irreversible conformational change that increases antithrombin's ability to inactivate factor Xa (as do the heparins). It has no effect on factor IIa (thrombin) and does not predictably affect the aPTT. Its half-life is 17 hours, and no agent is known to reverse its anticoagulant effect, although some experts would recommend a trial of high-dose recombinant factor VIIa (NovoSeven) in uncontrolled hemorrhage.

While not FDA-approved for treating heparin-induced thrombocytopenia, it has been used for this in some patients.[55–58] Animal studies and in vitro human placental perfusion studies suggest that fondaparinux does not cross the placenta in significant amounts.[49] Since danaparoid is not available in the United States, fondaparinux would likely be the first choice among the newer anticoagulants when treating heparin-induced thrombocytopenia in pregnancy.

INDICATIONS FOR ANTICOAGULANTS DURING PREGNANCY

Pregnant women with a prior thrombotic event and a thrombophilia need thromboprophylaxis

Acute deep venous thrombosis and pulmonary embolism

If acute deep venous thrombosis or pulmonary embolism is confirmed or strongly suspected in a pregnant woman, therapeutic anticoagulation should be started promptly (TABLE 4). In most cases, the woman should probably be hospitalized, given the complex maternal and fetal concerns that include adequate maternal dosing and the potential for fetal harm in the setting of significant hypoxia.

Anticoagulant therapy should begin as full doses of either LMWH or intravenous un-

TABLE 4

Indications for anticoagulation in pregnancy by risk category

PREGNANCY RISK CATEGORY	RECOMMENDED ANTICOAGULATION
High risk	
Current arterial or venous thromboembolism (VTE)	Therapeutic low-molecular-weight heparin (LMWH) or adjusted-dose unfractionated heparin (UH)
Prior recurrent VTE, on long-term anticoagulation	Therapeutic LMWH or adjusted-dose UH
Antiphospholipid (APL) syndrome with prior VTE	Therapeutic LMWH or adjusted-dose UH ± aspirin
Mechanical heart valve	Aggressive-dose therapeutic LMWH or adjusted-dose UH ± aspirin, consider warfarin between 12 and 36 weeks of gestation
Moderate risk	
Single prior VTE with thrombophilia	Prophylactic LMWH or UH
Prior idiopathic VTE, no thrombophilia	Prophylactic LMWH or UH
Antithrombin deficiency, no VTE	Prophylactic or therapeutic LMWH or UH
Combined thrombophilias or homozygous thrombophilic mutation, no VTE	Prophylactic LMWH or UH
APL syndrome on the basis of adverse pregnancy outcomes*	Prophylactic LMWH or UH plus aspirin
Low risk	
Prior VTE with resolved temporary risk factor, no thrombophilia	Clinical surveillance or prophylactic LMWH or UH
Single thrombophilia (other than antithrombin deficiency), no VTE	Clinical surveillance, consider aspirin
Prior adverse pregnancy outcome with thrombophilia (other than APL), no VTE	Aspirin, consider prophylactic LMWH or UH

*Three or more unexplained consecutive spontaneous abortions before the 10th week of gestation, or one or more unexplained deaths of morphologically normal fetuses at or after the 10th week of gestation; or one or more premature births of morphologically normal neonates at or before the 34th week of gestation

fractionated heparin. We prefer starting with LMWH, as it can be started rapidly with less need for nursing care (eg, no need to start and maintain an intravenous line and monitor the aPTT) and has excellent safety. If LMWH is selected, initial dosing should be based on the current weight (TABLE 2). Subsequent monitoring of the peak anti-factor-Xa activity levels (ie, 4 hours after the dose) is recommended, with the first level drawn in the first few days of treatment, and repeat levels every 1 to 3 months for the rest of treatment. As mentioned earlier, weight-based dosing has not been systematically evaluated in pregnancy.

If unfractionated heparin is the initial agent, it should be given as a bolus followed by a continuous infusion, ideally utilizing a weight-based nomogram to estimate required doses, with adjustment of the infusion rate to maintain the aPTT at 1.5 to 2.5 times the baseline value (obtained during pregnancy). After several days, the heparin may be switched to LMWH in therapeutic doses (TABLE 2).

Alternatively, in women approaching term or who cannot afford LMWH, anticoagulation may be continued as adjusted-dose subcutaneous unfractionated heparin, ie, two or three large daily doses of subcutaneous heparin to

provide therapeutic levels of anticoagulation. The starting dose can be calculated as the total units of heparin required to maintain full anticoagulation intravenously over 24 hours, given as two or three divided doses (TABLE 2). The aPTT at the mid-dosing interval (eg, 6 hours after the subcutaneous dose during every-12-hour dosing) should be monitored and the dose adjusted to maintain the aPTT at 1.5 to 2.5 times the baseline value.

A therapeutic level of anticoagulation should be maintained for at least 3 months after an acute thrombotic event during pregnancy, though many physicians prefer to continue full anticoagulation for a total of 6 months. Beyond this interval, if the woman is still pregnant, the anticoagulation may be reduced in intensity, perhaps even to a prophylactic level for the duration of the pregnancy (see discussion below on prior venous thromboembolic events) (TABLE 2). Peripartum and postpartum anticoagulation are discussed further below.

PRIOR VENOUS THROMBOEMBOLIC EVENT

While all pregnant women are at higher risk of venous thrombosis, the overall incidence of thromboembolism is only about one event per 1,000 pregnancies. Routine thromboprophylaxis in all pregnant women is therefore not justified. However, women who have previously had a venous thromboembolic event are at a substantially higher risk of recurrent thrombosis and should be considered for thromboprophylaxis in all subsequent high-risk situations, including pregnancy.

For women on indefinite therapeutic anticoagulation (ie, because of recurrent thrombosis), full therapeutic anticoagulation with LMWH or adjusted-dose unfractionated heparin should be maintained throughout pregnancy, as described above.

Which other women should receive prophylactic anticoagulation is a topic of ongoing debate and controversy.

How great is the risk of recurrent thromboembolism?

A small observational study[59] examined the risk of recurrent venous thromboembolism during subsequent pregnancies in women with a prior thrombotic event. Anticoagulation was withheld during the antepartum period and restarted briefly after delivery. Among the 125 women enrolled, recurrent venous thromboembolism occurred in 4.8%, with half of the events occurring during the antepartum period. Among those with underlying thrombophilia, the rate of recurrent venous thromboembolism was 13% (95% confidence interval [CI] 1.7%–40.5%) to 20% (95% CI 2.5%–56.5%), and those with a prior idiopathic clot without thrombophilia had an event rate of 7.7% (95% CI 0.01%–25.1%). The subgroup with a prior reversible risk factor (at the time of their initial venous thromboembolic event) and without detectable thrombophilia had no recurrent events.

This study suggests that women with prior venous thromboembolism and thrombophilia or a prior idiopathic thrombotic event are at a substantial risk of recurrent thrombotic events during pregnancy. And other data confirm the high risk of recurrent venous thromboembolism in thrombophilic pregnant women.[60] These women should all be offered active antepartum and postpartum thromboprophylaxis with LMWH or unfractionated heparin (TABLES 2 AND 4). Women without thrombophilia but with a history of venous thromboembolism related to pregnancy or oral contraceptive use also have a substantial risk of recurrent venous thrombosis and should be offered antepartum and postpartum thromboprophylaxis.[61] In contrast, women with a prior "secondary" clot, no thrombophilia, and no additional current risk factors (TABLE 1) appear to be at low risk of recurrent venous thromboembolism.

The puerperium is the time of highest day-to-day thrombotic risk

The risks should be discussed with these women, with an option for close clinical surveillance during pregnancy (TABLE 4), but with a low threshold to investigate any worrisome symptoms. Such women may also elect to take LMWH or unfractionated heparin during pregnancy.

Which heparin to use?

Prophylactic anticoagulation during pregnancy can be with either LMWH or unfractionated heparin. For most women this involves "prophylactic" dosing with the goal of maintaining a mid-interval anti-factor-Xa activity level of approximately 0.05 to 0.2 U/mL. Thromboprophylaxis with LMWH can be

with lower, fixed, once-daily doses throughout pregnancy[20] (TABLE 2), although some clinicians still prefer twice-daily dosing. The heparin should be started as soon as pregnancy is confirmed, as the pregnancy-associated increase in thrombotic risk begins by the middle of the first trimester.

To maintain effective prophylactic levels, the dose of unfractionated heparin should be increased sequentially over the trimesters[62,63]: approximately 5,000 units subcutaneously twice daily in the first trimester, then 7,500 units twice daily in the second trimester, and 10,000 units twice daily in the third trimester for a woman of average size.

When to add low-dose aspirin

Women with antiphospholipid antibodies, particularly those with prior recurrent pregnancy loss or fetal demise, should receive aspirin 81 mg/day in addition to heparin.[39] The aspirin may be started prior to conception or when pregnancy is confirmed.

Other measures

Women on anticoagulant therapy who are at risk of recurrent venous thromboembolism should be encouraged to wear elastic compression stockings. Intermittent pneumatic compression of the legs via automated devices may be considered for women hospitalized for any reason or on bedrest.

Whichever measures are used, a high index of suspicion and a low threshold for investigating for recurrent thrombosis should be maintained throughout pregnancy and the puerperium.

Heparin therapy must be stopped peripartum to permit regional anesthesia

PERIPARTUM AND POSTPARTUM MANAGEMENT OF ANTICOAGULATION

Heparin therapy must be interrupted temporarily during the immediate peripartum interval to minimize the risk of hemorrhage and to allow for the option of regional anesthesia. As mentioned earlier, because of the theoretical risk of paraspinal hemorrhage in women receiving heparin who undergo epidural or spinal anesthesia, the American Society of Regional Anesthesia guidelines advise waiting to insert the needle at least 10 to 12 hours after the last prophylactic dose of LMWH, and at least 24 hours after the last therapeutic dose.[31]

The guidelines state that neuraxial anesthesia is not contraindicated in patients on prophylactic unfractionated heparin.[31]

To facilitate use of regional anesthesia in these women, therefore, options include:

- Electively stopping LMWH 24 hours before planned induction of labor
- Electively stopping prophylactic-dose LMWH or unfractionated heparin at about 38 weeks of gestation, to await spontaneous labor, or
- Switching therapeutic or prophylactic LMWH to unfractionated heparin at about 36 weeks of gestation, with instructions to discontinue the injections in the earliest stages of spontaneous labor. This aims to shorten the heparin-free period required before neuraxial anesthesia while minimizing maternal thrombotic risk.

Additional advantages to using unfractionated heparin peripartum include the option of obtaining a rapid aPTT measurement to confirm the absence of a significant ongoing heparin effect prior to regional anesthesia or delivery, and the ability to completely reverse the heparin effect with protamine sulfate if major bleeding occurs. LMWHs are only partially reversible.[64]

Interrupting anticoagulation after an initial thrombotic event

If therapeutic anticoagulation must be interrupted for labor within 1 month of the initial thrombotic event, the risk of recurrent thrombotic complications is high[65]; these women must be observed very carefully and may benefit from intravenous heparin before and after delivery. They may even merit placement of a temporary vena cava filter (particularly if less than 2 weeks have elapsed since the venous thromboembolic event and in women with a large deep venous clot burden), a procedure that has been used safely but little studied in pregnant women.[66]

Fluoroscopic guidance may be needed for filter placement. This exposes the fetus to radiation, but the low-level exposure at this late gestational age is unlikely to pose a significant risk. The filter may be removed within 1 to 2 weeks postpartum, assuming there are no ongoing contraindications to anticoagulation.

In the rare woman with antithrombin

deficiency and a recent or prior thrombotic event, giving antithrombin concentrate during the peripartum (heparin-free) interval has been described and may be considered under the guidance of a hematologist.[67]

Ongoing anticoagulation is essential postpartum, as the puerperium is the period of highest day-to-day risk of thromboembolic events: about one-third of pregnancy-associated events occur during these 6 to 12 weeks.[2] Heparin should be resumed 6 to 12 hours after delivery, once hemostasis is confirmed.

Options for women requiring ongoing therapeutic anticoagulation include intravenous heparin started without a bolus, to minimize bleeding risk, with aPTT measured 12 hours later, or an initial prophylactic dose of LMWH 6 to 12 hours postpartum, with therapeutic dosing resumed on postpartum day 1. If prophylactic dosing is desired, unfractionated heparin or LMWH may be given subcutaneously starting at about 6 hours postpartum.

Warfarin in the puerperium

Women may subsequently be maintained on either LMWH or unfractionated heparin, or switched to an oral anticoagulant such as warfarin. Although warfarin may appear in minute amounts in breast milk, it has not been associated with adverse events in newborns and is considered compatible with breastfeeding.[68] Heparin should be continued during the initial days of warfarin therapy, until the INR is at a therapeutic level for 24 hours. Some physicians prefer to delay warfarin for several days, giving LMWH alone in the immediate postpartum period, to allow wound-healing and to reduce bleeding risk.

Postpartum, anticoagulation should be continued for at least 6 to 12 weeks, at which point the physiologic changes in the coagulation system related to pregnancy will have returned to normal.

THROMBOPHILIA WITHOUT A PREVIOUS THROMBOEMBOLIC EVENT

Over the last 5 to 10 years, practitioners have been seeing many more young women with genetic or acquired thrombophilias who have never had a venous thromboembolic event. Physicians must advise these women about their risk of thromboembolic events during pregnancy and about the appropriateness of anticoagulant use.

Thrombophilias are often detected in women who develop venous thrombosis during pregnancy,[69–71] but they are also very common in the general population (around 15%). While women with thrombophilia are at above-average risk of venous thromboembolism during pregnancy, the magnitude of risk in an individual patient is often difficult to estimate.

Data suggest that some types of thrombophilia confer greater thrombotic risk than others. McColl et al[72] derived risk estimates for a primary event in women with several of the disorders: 0.23% in women heterozygous for the factor V Leiden mutation, 0.88% in women with protein C deficiency, and 2.4% to 35.7% in women with antithrombin deficiency. A case-control study[70] found that all thrombophilic states were more common in women with pregnancy-associated venous thromboembolism than in healthy pregnant controls, except those with the MTHFR mutation and protein S deficiency. The estimated risk during pregnancy was 0.03% in women with no defect, 0.1% in women with protein C deficiency, 0.25% in women with the factor V Leiden mutation, 0.4% in those with antithrombin deficiency, 0.5% in those with the prothrombin gene mutation, and 4.6% in those with both factor V Leiden and prothrombin gene mutations.

Warfarin is considered compatible with breastfeeding

Routine anticoagulation not advised in pregnant thrombophilic women

Because the risk of a primary venous thromboembolic event is less than 1% for most thrombophilic women, routine anticoagulant therapy does not seem prudent for this indication. Given the low absolute risk of venous thromboembolism, the cost and potential side effects of anticoagulant use are difficult to justify.

The women who seem at higher risk and in whom anticoagulation should be considered include those with antithrombin deficiency; those with high-titer anticardiolipin antibodies or a lupus anticoagulant antibody (treat with heparin and low-dose aspirin); those with combined thrombophilic defects or who are homozygotes for the factor V Leiden or

prothrombin gene mutations; and those with multiple other current risk factors for venous thromboembolism (TABLE 1).

Since anticoagulants for primary prevention of adverse pregnancy outcomes in thrombophilic women have not yet been shown to have a definitive benefit, they are not recommended for this purpose.

ADVERSE PREGNANCY OUTCOMES IN WOMEN WITH THROMBOPHILIAS

Women with antiphospholipid antibodies and a previous poor obstetric outcome are clearly at increased risk of recurrent adverse pregnancy outcomes such as recurrent spontaneous abortion, unexplained fetal death, placental insufficiency, and early or severe preeclampsia. In such women who have both antiphospholipid antibodies and a history of venous thromboembolism or adverse pregnancy outcome, treatment during subsequent pregnancy with low-dose aspirin and prophylactic-dose LMWH or unfractionated heparin improves pregnancy outcomes.[36–42] Women with antiphospholipid antibodies without previous thrombosis or pregnancy complications may also be at increased risk, but it is unclear whether thromboprophylaxis improves their outcomes.

Some types of thrombophilia may be riskier than others

Recent epidemiologic data reveal that women with other thrombophilic conditions also are at increased risk of early, severe preeclampsia[73] as well as other pregnancy complications, including recurrent pregnancy loss, placental abruption, fetal growth restriction, and stillbirth.[74] A recent meta-analysis[75] looked at individual thrombophilias and found that factor V Leiden and prothrombin gene mutations were associated with recurrent fetal loss, stillbirth, and preeclampsia; that protein S deficiency was associated with recurrent fetal loss and stillbirth; that antiphospholipid antibodies were associated with recurrent pregnancy loss, preeclampsia, and intrauterine growth restriction; that the MTHFR mutation (homozygous) was associated with preeclampsia; and that protein C and antithrombin deficiencies were not significantly associated with adverse pregnancy outcomes. Data were scant for some of the rarer thrombophilias.[75]

Several recent small studies[76–78] suggest that anticoagulants may improve pregnancy outcomes in women with genetic thrombophilias and recurrent pregnancy loss. These findings have not yet been confirmed in high-quality clinical trials, but such trials are under way. It is still unclear whether anticoagulants also reduce the risk of other adverse pregnancy outcomes associated with thrombophilias.

The current American College of Chest Physicians guidelines recommend testing of women with adverse pregnancy outcomes (recurrent pregnancy loss, prior severe or recurrent preeclampsia, abruptions, or otherwise unexplained intrauterine death) for congenital thrombophilias and antiphospholipid antibodies, and offering treatment to such women, if thrombophilic, with low-dose aspirin plus prophylactic heparin (unfractionated or LMWH).[22] The authors of the guidelines admit that the evidence for this recommendation is weak, but they argue that the heparin will also serve as thromboprophylaxis in this high-risk group. Hopefully, the randomized clinical trials currently under way will provide clearer guidance regarding the most appropriate therapy in this difficult clinical situation.

MECHANICAL HEART VALVES

Internists may occasionally encounter a woman with a mechanical heart valve prosthesis who is either pregnant or is planning a pregnancy and therefore needs advice regarding optimal anticoagulant management. This should generally be undertaken in a multidisciplinary fashion, with input from cardiology, hematology, and maternal-fetal medicine. The substantial maternal and fetal risks and the lack of definitive data on which to base treatment decisions make it a treacherous and stressful undertaking. Nonetheless, all internists should have a basic understanding of the complex issues regarding this management.

Outside of pregnancy, oral anticoagulants are the mainstay of therapy for patients with mechanical heart valves. Unfortunately, as discussed above, the use of these agents during pregnancy carries a risk of teratogenicity and toxic fetal effects and increases the risk of pregnancy loss and maternal hemorrhage. Heparins have been used in this setting for many years, but data on their efficacy and safety are very limited, and there are numer-

ous reports of catastrophic maternal thrombotic complications.[79,80]

A systematic review of anticoagulation in pregnant women with prosthetic heart valves[34] found very limited data on heparin use throughout pregnancy. Women maintained on warfarin vs heparin between pregnancy weeks 6 and 12 had higher rates of congenital anomalies (6.4% with warfarin vs 3.4% with heparin) and total fetal wastage (33.6% vs 26.5%). The warfarin group had fewer maternal thromboembolic complications (3.9% vs 9.2%), however, and a slightly lower rate of maternal death (1.8% vs 4.2%). Most of the women had higher-risk older-generation valves in the mitral position.

Recent data on LMWH consist mainly of case reports and case series,[81] with a likely bias to publication of worse outcomes. Controlled trials in this area will be difficult to conduct. Still, aggressive anticoagulation with LMWH or unfractionated heparin, with close monitoring of the intensity of anticoagulation, may be safe and effective for pregnant women with newer-generation mechanical heart valves.[82] A recent consensus statement[22] suggested several regimens for pregnant women with mechanical heart valves:

- Twice-daily LMWH throughout pregnancy, with the dose adjusted either by weight, or to keep the 4-hour postinjection anti-factor-Xa activity level around 1.0 to 1.2 U/mL
- Aggressive adjusted-dose unfractionated heparin throughout pregnancy, given subcutaneously every 12 hours and adjusted to keep the mid-interval aPTT at least twice the control value or to attain a mid-interval anti-factor-Xa activity level of 0.35 to 0.70 U/mL
- Unfractionated heparin or LMWH (as above) until gestation week 13, then warfarin until the middle of the third trimester, and then heparin again.[22]

The authors also recommended adding low-dose aspirin (75–162 mg/day) in high-risk women.[22]

These options all seem reasonable, given our current knowledge, though warfarin use during pregnancy should be restricted to very-high-risk situations, such as women with older-generation mitral prostheses. LMWHs may become the preferred therapy for this indication once further controlled data regarding their efficacy and safety become available.

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