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Novel Antithrombotic Agents in Pregnancy Anticoagulants and Antiplatelet Agents

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Abstract: Increasing rates of thromboembolic complications have required increasing use of anticoagulant and antiplatelet agents during and after pregnancy. Furthermore, thromboembolism is both a cause and a complication of severe maternal morbidity requiring intensive care. As a consequence, almost all patients admitted to intensive care units receive an anticoagulant or an antiplatelet agent (or both) for either treatment or prevention of thromboembolism. In this review, we summarize commonly used anticoagulants and antiplatelet agents and outline the potential role of newly developed (novel) antithrombotic agents for pregnant and postpartum patients.

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Key words: clopidogrel, direct oral anticoagulant, direct thrombin inhibitor, fondaparinux, factor XI inhibitor, pregnancy

Introduction

Increasing rates of thromboembolic complications have required increasing use of anticoagulant and antiplatelet agents during and after pregnancy. Furthermore, thromboembolism is a both a cause and a complication of severe maternal morbidity requiring intensive care. As a consequence, almost all patients admitted to the intensive care units receive an anticoagulant or an antiplatelet agent (or both) for either treatment or prevention of thromboembolism. On the basis of several population studies from North America, intensive care unit admissions for obstetric reasons range from 3.2 to 15.4 per 1000 pregnancies.[1–3]

During such intensive care unit admissions and other less critical situations, obstetricians are called upon to make recommendations about anticoagulants and antiplatelet agents. The purpose of this review is to describe the range of antithrombotic agents that are used to treat both venous and arterial thromboembolism with an emphasis on the new or novel antithrombotic agents and their implications for pregnancy and the postpartum period.

Venous and Arterial Thromboembolism—Mechanisms

An understanding of the process of normal coagulation is necessary for understanding anticoagulants and antiplatelet agents. Physiological coagulation involves the formation of a protective clot at the site of blood vessel injury. Formation of the clot involves 2 steps—(1) the development of a platelet plug, and (2) the formation of a fibrin net that stabilizes the platelet plug. The development of a platelet plug is triggered by disruption of the endothelium, which exposes collagen and releases von Willebrand factor from Weibel-Palade bodies. The path of smooth, discoid platelets is altered, their internal cytoskeletons are disrupted, and platelet membrane receptors are exteriorized. This allows von Willebrand factor to attach to the glycoprotein (Gp) Ib-IX-V receptors on the platelets and connect the platelets to the underlying collagen (platelet adhesion). Fibrin attaches to the Gp IIb/IIIa receptors on the platelets binding them together (platelet aggregation) and forming a net that further holds the platelets in place. The formation of this fibrin net from soluble fibrin in the presence of thrombin is the end point of the coagulation cascade. The coagulation cascade is initiated when factor X is activated (factor Xa) by activated factor VII and tissue factor, which has also been exposed at the time of blood vessel injury. The reaction is amplified and propagated by activated factor VIII and activated factor IX, resulting in the generation of large amounts of thrombin which propel clot formation.[4] Normally, the process is contained and confined to the site of injury by the activation of the natural anticoagulants (protein C, protein S, tissue factor pathway inhibitor, and antithrombin) and by the antifibrinolytic system.

Thrombosis is an abnormal clot that partially or completely obstructs a blood vessel.

Arterial thromboembolism (heart attack or myocardial infarction, stroke or cerebral vascular accident, and peripheral arterial disease) differs from venous thromboembolism (deep vein thrombosis, pulmonary embolism, cerebral vein thrombosis, or splanchnic vein thrombosis) in terms of mechanisms and risk factors. Consequently, the proportion of thromboembolic events that are either arterial or venous differ by age group. Arterial thromboembolism, which usually occurs in the setting of atherosclerosis and plaque, increases exponentially with age. Classic risk factors for arterial thromboembolism include hyperlipidemia, smoking, diabetes, hypertension, and obesity.[5] The prevalence of these risk factors are increasing in the reproductive-aged population and obstetricians can expect to see more pregnant women with arterial thromboembolism or a history of an arterial thromboembolic event in the future.

Overall, arterial thromboembolism is more common and more lethal than venous thromboembolism, but in the reproductive-aged population, venous thromboembolism is more common than arterial thromboembolism and accounts for 80% of thromboembolic events.[6] Classical risk factors for venous thromboembolism include trauma, cancer, surgery,

immobility, hormonal contraceptives, menopausal hormone therapy, pregnancy, the postpartum period, a history of venous thromboembolism, and other causes of hypercoagulability such as thrombophilia.[5]

Traditional Anticoagulants

Heparin, the first anticoagulant used therapeutically, was discovered in 1916 by a second year medical student, Jay McLean,[7] while working in the laboratory of Dr William Henry Howell.[8] Heparin's commercial potential was immediately recognized, but it took until 1939 to develop a purified product, which was suitable to be marketed as a pharmaceutical.[9] In 1960, Barritt and Jordan published a small randomized trial, which quickly established heparin's efficacy in the treatment of acute venous thromboembolism and pulmonary embolism. In the 1970's Kakkar et al[10] established the efficacy of low doses of subcutaneous heparin in the prevention of postoperative deep vein thrombosis. In the 1970's and 1980's, heparin's chemical structure was elucidated, chemically cleaved low molecular weight heparins (LMWH) were developed as a separate drugs, and the unique pentasaccharide antithrombin binding site was sequenced and synthesized.[9] In 1982, Kakkar et al[11] established the efficacy of low dose LMWH, also administered subcutaneously, to prevent postoperative deep vein thrombosis.

Heparins, unfractionated heparin (UFH) and LMWH, are the preferred anticoagulants to prevent and treat venous thromboemoblism in pregnancy and as an adjunct in the prevention of recurrent arterial thromboembolism. Neither UFH nor LMWH crosses the placenta,[12] and both are considered safe for mother and fetus.[12] Furthermore, neither UFH nor LMWH are orally bioavailable and breastfeeding is considered safe.[13] The mechanism for both UFH and LMWH is potentiation of the natural anticoagulant antithrombin. Because of fewer side effects and a longer half-life, LMWHs are preferred to UFH.[14] Both, however, require parenteral administration—subcutaneous in the case of LMWH and intravenous (IV) or subcutaneous in the case of UFH. There are circumstances, however, in which an alternative to heparins may be desirable or necessary. These circumstances include:

(1) Preconception—as long as the anticoagulant is not a known teratogen
(2) Postpartum—if the anticoagulant does not pass into breast milk or if a patient is not breastfeeding
(3) Heparin resistance—which if clinically significant in pregnancy is almost always due to congenital antithrombin deficiency and requires consideration of antithrombin concentrate
(4) Heparin allergy manifesting as heparin-induced skin reactions or heparin-induced thrombocytopenia
(5) The presence of a mechanical heart valve—where warfarin is the preferred anticoagulant

From time to time, the obstetrician is called on to make recommendations about anticoagulants in pregnancy, including in circumstances in which an alternative to heparin has been suggested or is necessary.

Warfarin, the first alternative to heparin and the first oral anticoagulant, was discovered in the 1920's after previously healthy cattle in North America began dying of internal bleeding.[15] A desperate Wisconsin farmer presented biochemist Karl Link with a milk can full of unclotted blood.[16] By 1940, after 6 years' work, Link and colleagues established that the causative agent was a naturally occurring coumarin that was present in moldy hay. After evaluating many different coumarins, they identified a potent one and named it warfarin after the funding

agency, the Wisconsin Alumni Research Foundation. Warfarin was successfully synthesized in 1948, marketed as a rodenticide in 1952 and approved for human use as an oral anticoagulant in 1954.[15]

Warfarin, along with other vitamin K antagonists used elsewhere in the world, crosses the placenta, increases the risk of miscarriage, increases the risk of congenital anomalies, and increases the risk of fetal hemorrhage. In a multicenter, observational, prospective study of 666 pregnant women exposed to the vitamin K antagonists phenprocoumon (n = 280), acenocoumarol (n = 226), fluindione (n = 99), warfarin (n = 63), and phenindione (n = 2) compared with a nonexposed control group (n = 1094), the miscarriage rate reached 42% versus 14% (hazard ratio 3.36; 95% confidence interval (CI) 2.28-4.93) and the rate of major birth defects after first trimester exposure was significantly increased (odds ratio 3.86, 95% confidence interval 1.86-8.00).[17] For this reason, warfarin is considered to be relatively contraindicated during conception and pregnancy, with its use limited to a few select indications in which the risks of thrombosis are exceptionally high (such as the presence of a mechanical heart valve). Warfarin is considered safe, however, during lactation. Little warfarin appears in breast milk and infants have never been affected.[18,19]

Novel Anticoagulants

Fondaparinux is a synthetic version of heparin's unique pentasaccharide antithrombin binding site and is technically a LMWH. It is administered subcutaneously. The prophylactic dose is 2.5 mg daily and the therapeutic dose is 7.5 mg daily, increasing to 10.0 daily with body weight > 100 kg and decreasing to 5.0 mg with body weight < 50 kg.[20] It does not cross-react with heparin-induced thrombocytopenia antibodies and has little placental transfer.[21] Adverse pregnancy outcomes have not been reported with fondaparinux.[22] It is used during pregnancy in cases of heparin-induced skin reactions or heparin-induced thrombocytopenia.[23] Whether fondaparinux is present in breast milk is unknown, but if it were, fondaparinux is only partially orally bioavailable,[24] so breastfeeding should be safe.

Besides warfarin, there are 4 other oral anticoagulants, all direct oral anticoagulants or DOACs, currently on the market. Dabigatran (a direct thrombin inhibitor), was the first to be approved by the United States Food and Drug Administration (FDA) in 2010.[25] The other 3 DOACs currently on the market are rivaroxaban,[26] apixaban,[27] and edoxaban (all antifactor Xa inhibitors). Betrixaban was removed from the market in 2020 for commercial reasons. Compared with warfarin, DOACs require less monitoring, require fewer follow-up visits, have fewer food and drug interactions and have more immediate drug onset and offset, which is important for patients who are bleeding or are undergoing procedures.[25] All are indicated for the treatment of venous thromboembolism and for the prevention of stroke in nonvalvular atrial fibrillation. Rivaroxaban has an indication in coronary artery and peripheral arterial disease.[28] Largely because of its gastrointestinal side effects and partly because of the requirement for initial treatment with parenteral heparin, dabigatran is prescribed less often than the factor Xa inhibitors. Edoxaban also requires initial treatment with parenteral heparin and is also prescribed less often. Apixaban, in particular, may have the most favorable bleeding profile based on indirect comparisons.[29] Thus, rivaroxaban and apixaban are currently the most commonly prescribed DOACs in the United States.[30]

There are few data that suggest that DOAC exposure adversely affects the fetus, but at the present time, all DOACs are presumed to cross the placenta and are all likely to be present in breast milk,

so they should not be prescribed during pregnancy or lactation.[31] Evidence of the fetal effects of DOACs is limited to animal models, case reports, case series,[32] and a Danish nationwide cohort study.[33] The largest series of cases was presented at the International Society on Thrombosis and Haemostasis (ISTH) Congress in 2020. In summary, 588 cases of DOAC exposure in pregnancy were identified from various data sources including questionnaires, pharmacovigilance databases, and the European Medicines Agency.[34] Of the 313 cases with data on pregnancy outcome, 23% were electively terminated, 22% ended in miscarriage, and 55% ended with live birth. Nineteen cases (6.1%) exhibited congenital abnormalities, of which 12 (3.8%) could potentially be related to DOAC exposure. A Danish nationwide cohort study included only a limited number of women who received DOACs and did not allow any evidence-based conclusions.[33]

There are 2 very new and very novel anticoagulants, abelacimab and milvexian, that are factor XI inhibitors. Evidence suggests that targeting factor XI reduces the risk of thromboembolism without disrupting normal hemostasis. Patients with congenital factor XI deficiency are at a lower risk of venous thromboembolism than patients with normal factor XI levels, yet they are not at an increased risk of bleeding.[35] Abelacimab is a human monoclonal antibody that binds to the active site of factor XI and locks it in an inactive precursor conformation, thereby preventing its activation by factor XIIa or thrombin. A recent randomized trial with a single IV dose (the half-life is 25 to 30 d) after total knee arthroplasty demonstrated that abelacimab was effective for the prevention of venous thromboembolism and was associated with a low risk of bleeding.[35,36] Milvexian, another factor XI inhibitor, is a small molecule that selectively binds to the active site of factor XI.[37] Another recent randomized trial with once or twice daily postoperative doses of milvexian for 10 to 14 days after total knee arthroplasty demonstrated that the drug was effective for the prevention of venous thromboembolism and was also associated with a low risk of bleeding.[38] Although factor XI inhibitors may ultimately provide anticoagulation without an increased risk of bleeding and wound complications, neither abelacimab with its long half-life nor milvexian as small molecule which could cross the placenta are good candidates for anticoagulation during pregnancy or the peripartum period.

Specialized Anticoagulants Used Exclusively in the Acute or Critical Care Settings

Anticoagulants used exclusively in the acute care setting include 2 IV direct thrombin inhibitors—argatroban and bivalirudin. Heparin has been the traditional anticoagulant used in the acute or critical care settings because it is relatively easy to titrate and providers are familiar with its use. Recently, bivalirudin, has been used as an alternative to heparin especially in patients resistant to heparin[39,40] or with heparin-induced thrombocytopenia.[41] Although indicated for use in percutaneous coronary interventions, it is utilized off-label for heparin-induced thrombocytopenia and mechanical circulatory support. A literature search published in 2021 identified 10 studies in which bivalirudin was used in extracorporeal membrane oxygenation and 5 studies in which it was used in ventricular assist devices.[42] Bivalirudin is a semisynthetic derivative of hirudin, a modified component of leech saliva,[43] which was first used as an alternative to heparin in the management of acute coronary syndromes.[43] As a direct thrombin inhibitor, bivalirudin inactivates thrombin directly, rather than indirectly through antithrombin, as heparin does.

TABLE 1. Mechanism, Molecular Weight, Dose, Route of Delivery, Placental Transfer, Use in Pregnancy, Safety in Pregnancy, and Safety in Breastfeeding for New Anticoagulants

Anticoagulant	Mechanism	Molecular Weight in Daltons (g/mol)	Dose	Route of Delivery	Placental Transfer	Use in Pregnancy	Safety in Pregnancy	Safety in Breastfeeding
Fondaparinux	Potentiates antithrombin	1727	2.5 mg qd prophy 7.5 mg qd treatment 10.0 mg if > 100 kg 5.0 mg if < 50 kg	SC	Little	In exceptional circumstances	Unknown	Yes
Dabigatran	Direct thrombin inhibitor	628	150 or 220 mg qd prophy 150 mg bid treatment	Oral	Yes	Not recommended	Unknown	Unknown
Rivaroxaban	Anti-Xa inhibitor	436	10 mg qd prophy 20 mg qd treatment	Oral	Yes	Not recommended	Unknown	Unknown
Apixaban	Anti-Xa inhibitor	459	2.5 mg bid prophy 5.0 mg bid treatment	Oral	Yes	Not recommended	Unknown	Unknown
Edoxaban	Anti-Xa inhibitor	548	15-30 mg qd prophy 60 mg qd treatment	Oral	Yes	Not recommended	Unknown	Unknown
Abelacimab	FXI inhibitor	Large molecule	Not established yet	IV	Unknown	Not reported	Unknown	Unknown
Milvexian	FXI inhibitor	626.4	Not established yet	Oral	Presumed	Not reported	Unknown	Unknown
Bivalirudin	Direct thrombin inhibitor	2180	0.15-0.2 mg/kg/h IV; adjust to aPTT 1.5-2.5 times baseline value	IV	Unknown	Not reported	Unknown	Unknown
Argatroban	Direct thrombin inhibitor	527	25 mcg/kg/min after bolus of 350 mcg/kg	IV	Presumed	Reported	Unknown	Unknown

IV indicates intravenous; SC, subcutaneous.

Compared with heparin, bivalirudin and other direct thrombin inhibitors have activity against cell- and clot-bound thrombin, not just free thrombin.[44] Consequently, bivalirudin and other direct thrombin inhibitors are not impacted by low antithrombin levels and are not subject to heparin resistance.[43] As for its possible use in pregnancy, bivalirudin, with a molecular weight of 2180 Daltons,[45] is larger than the placental transfer threshold of 1000 Daltons,[46] and may or may not cross the placenta. Animal studies reveal no evidence of fetal harm, but there are no data in humans and no reported cases of its use in pregnancy.[45]

Argatroban is another direct thrombin inhibitor, which has been used in critically ill patients unresponsive to heparin.[47] Argatroban was first used in Japan and was approved by the FDA as an alternative anticoagulant for the treatment and prevention of thrombosis in heparin-induced thrombocytopenia. Argatroban has also been used as an alternative anticoagulant in vaccine-induced immune thrombotic thrombocytopenia,[48] acute stroke,[49] and extracorporeal membrane oxygenation.[50] Similar to bivalirudin, argatroban is not subject to heparin resistance. Argatroban, however, is a relatively small molecule, with a molecular weight

of 527 Daltons,[51] and, as the molecular weight is less than the placental transfer threshold of 1000 Daltons, is much more likely to cross the placenta. Animal studies reveal no evidence of fetal harm, but there are limited data in humans, except for a few case reports.[52,53] The novel anticoagulants are summarized in Table 1.

Traditional Antiplatelet Agents

Whereas the mainstay of venous thromboembolism treatment is anticoagulation, the mainstay of arterial thromboembolism treatment is antiplatelet therapy and the prototypic antiplatelet agent is aspirin. Naturally occurring salicylates have been used for centuries to treat muscle and joint pain. The first published report of the use of salicylates was in 1876 when salicin, derived from white willow bark, was used to treat the fever, pain, and inflammation associated with rheumatic fever. After salicylic acid was synthesized in 1874, the Bayer pharmaceutical company developed acetylsalicylic acid, a derivative with fewer gastrointestinal side effects in 1897 and named it "Aspirin". It was not until 1971, however, that aspirin's mechanism of action was discovered to be blockade of prostaglandin synthesis.[54] A single dose of 100 mg of aspirin results in inhibition of platelet cyclooxygenase activity and almost complete suppression of the synthesis of thromboxane A2, [55] which would otherwise induce platelet aggregation and vasoconstriction.[56] Because platelets lack the ability to synthesize new cyclooxygenase, the defect induced by aspirin is irreversible.

Novel Antiplatelet Agents

The current management of arterial thromboembolic events includes "dual antiplatelet therapy" with aspirin and a newer antiplatelet agent. The first of these newer antiplatelet agents was ticlopidine whose antiplatelet properties were serendipitously discovered by Dr Fernand Eloy in 1972 during his investigation of the derivatives of thienopyridine compound, tinoridine, an anti-inflammatory analgesic.[57] Ticlopidine was first marketed in 1978, but it was plagued with serious adverse hematological effects. Thus, the search for an improved but equally effective antiplatelet agent began, even before the mechanism of action of ticlopidine was fully understood. After the testing of ~1000 derivatives, 10 years' of development, and large clinical studies, clopidogrel was introduced in 1998.[57] Clopidogrel, found to be an adenosine diphosphate antagonist, interacts with the P2Y12 receptor on the platelet surface to prevent platelet aggregation. There are case reports of the use of clopidogrel in pregnancy.[58] Although the medication is generally not considered teratogenic, it is unknown whether it crosses the placenta or has any impact on fetal or neonatal bleeding. Increased maternal bleeding has been described. When used, it should be discontinued 7 days before delivery or procedures. There are no data on its presence in breast milk.

Novel Antiplatelet Agents

During the last 20 years, new antiplatelet agents have been developed. These include additional adenosine diphosphate antagonists such as prasugrel, ticagrelor, and cangrelor. Like clopidogrel, prasugrel is also a thienopyridine P2Y12 receptor antagonist and also an oral medication, but has a 30 to 60 minute onset of action as opposed to a 2 to 4 hour onset of action. Ticagrelor is also an oral medication, but unlike clopidogrel and prasugrel, is not a thienopyridine and is reversible. Ticagrelor has a faster onset of action of 30 minutes or less and has a shorter half-life (8 to 12 h) compared with prasugrel or clopidogrel. Cangrelor is an IV P2Y12

receptor antagonist that allows for rapid, potent, and reversible inhibition of platelet aggregation (platelet function returns in <60 min), with an anti-ischemic benefit and no increase in major bleeding.[59] Cangrelor can be used when there is the potential for imminent surgery. Other than a single case report of the use of prasugrel in pregnancy,[60] there are no data on the use of these new antiplatelet agents in pregnancy or lactation.

Other IV antiplatelet agents include the platelet Gp IIb/IIIa receptor inhibitors abciximab, eptifibatide, and tirofiban. These antiplatelet agents are mostly used in the percutaneous coronary intervention setting where rapid onset of action is desired. Despite their novelty, the use of Gp IIb/IIIa receptor inhibitors has decreased in recent years due to bleeding concerns and the availability of the new, more potent oral P2Y12 inhibitors.[59]

Management of Anticoagulants and Antiplatelet Agents in the Acute Care Setting—Reversal and Other Peripartum Considerations

Whenever a patient is pregnant, there is the risk of bleeding with ectopic pregnancy, miscarriage or delivery, which can be particularly challenging to manage when the patient is anticoagulated or on antiplatelet therapy. When delivery or surgery is anticipated, ideally anticoagulation and antiplatelet therapy have been stopped, and the patient is not at a greater risk of bleeding than anyone else. That is not always the case; however, when a patient is actively bleeding or an emergent procedure or delivery is required. Then, there is a decision to be made as to whether the patient requires more than supportive therapy such as anticoagulation reversal or platelet transfusion. Important questions to be asked when anticoagulation reversal or platelet transfusion are contemplated are (1) can bleeding be controlled with supportive therapy alone? (2) Should a procedure or delivery proceed under anticoagulation or platelet inhibition? or (3) Can a procedure or delivery be delayed? or (4) Is there a reasonable expectation that the patient is truly anticoagulated or has impaired platelet function? If the patient is actively bleeding or a procedure or delivery cannot be delayed and the patient is truly anticoagulated or has impaired platelet function, then it is reasonable to proceed with anticoagulant reversal or platelet transfusion. Anticoagulant reversal or platelet transfusion, however, may not alter the risk of fetal or neonatal bleeding.

At the present time, there are no medications to reverse the effects of platelet suppression by antiplatelet agents. Time (or platelet transfusion) is required for the return of platelet function. With clopidogrel, full return of platelet function is not observed until 10 days after stopping the drug.[61] Guidelines recommend waiting 5 days before procedures.[62] With prasugrel, 7 days are recommended. With ticagrelor, whose mechanism of action is reversible, guidelines recommend only waiting 3 days before procedures.[61] Whereas this shorter interval is an advantage of ticagrelor, the reversible nature of the molecule is problematic. If a procedure needs to be performed emergently during this 3-day window, the ticagrelor will bind and deactivate transfused platelets as well. For this reason, a neutralizing monoclonal antibody fragment that binds ticagrelor is being developed as a ticagrelor reversal agent.[63] With cangrelor, whose mechanism is also reversible, but has more rapid onset and offset than ticagrelor, return of platelet function can be achieved by stopping the medication with recovery of platelet function within 20 minutes.

The reversal agents for the traditional anticoagulants are protamine sulfate in

the case of heparins and vitamin K and vitamin K–dependent clotting factors in the case of warfarin. For patients on warfarin who require reversal, 4-factor prothrombin complex concentrate containing factors II, VII, IX, and X is recommended for rapid results along with vitamin K 5 to 10 mg administered by slow IV injection to achieve a sustained response.[64] Protamine sulfate is an arginine-rich basic cationic protein derived from salmon sperm, which binds to and neutralizes heparin.[65] Protamine administration is not without risk. It may produce life-threatening side effects such as systemic hypotension, catastrophic pulmonary vasoconstriction, right heart failure, and anaphylaxis.[66] Nonetheless, protamine is the reversal agent of choice for UFH. As a reversal agent for LMWH, protamine has been shown to be only partially effective in both a rat model[67] and in clinical practice.[68]

Reversal of the novel anticoagulants is potentially more challenging. There is no reversal agent for fondaparinux.[69] In a study of ex vivo blood samples, activated prothrombin complex concentrate was more effective than recombinant factor VII in restoring thrombin generating capacity in subjects who had receive fondaparinux.[70] Specific reversal agents have been developed for the direct oral anticoagulants. The FDA-approved reversal agent for dabigatran is idarucizumab, a monoclonal antibody fragment that binds free and thrombin-bound dabigatran and neutralizes its activity.[71] The FDA-approved reversal agent for apixaban and rivaroxaban is andexanet alfa, a modified recombinant factor Xa that serves as a decoy to bind and sequester factor Xa inhibitors.[72] Andexanet alfa can also be used off-label to reverse edoxaban.[73] If these specific reversal agents are unavailable, prothrombin complex concentrates can be used to try to reverse the DOACs.[73] For very new factor XI inhibitors, there are no reversal agents. For the IV direct thrombin inhibitors that are used as an alternative to heparin in the acute care setting, there are no reversal agents or antidotes, but hemostasis can be achieved by stopping the infusions and initiating supportive measures. The biological half-life of bivalirudin is 25 to 30 minutes[74] and the biological half-life of argatroban is 45 minutes.[69]

Summary

Antithrombotic agents have become an essential tool in the prevention and treatment of thromboembolism during pregnancy and the postpartum period. Rates of thromboembolism are rising, in part, due to the rising prevalence of obesity and cardiovascular disorders in women of reproductive age. Thromboembolism prophylaxis and treatment is common among pregnant patients admitted to intensive care units. This increased frequency of use of antithrombotic agents in pregnancy merits a working knowledge of their mechanisms of action, potential for maternal and fetal side effects, and options for reversal among both obstetric and other healthcare providers practicing obstetric medicine (eg, critical care, anesthesia, cardiology, hematology, and primary care). Anticoagulation with injectable heparins—both unfractionated and low molecular weight—remains the mainstay of prevention and treatment for venous thromboembolism. Aspirin remains first-line therapy for prevention and treatment of arterial thromboembolism in pregnancy. Decisions to prescribe or continue antithrombotic agents other than heparin or aspirin should be made in consultation with a specialist in maternal-fetal medicine along with specialists in either cardiology or hematology.

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