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Prevention and Management of Thromboembolism in Pregnancy When Heparins are Not an Option

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Abstract: Heparins, unfractionated heparin, and low molecular weight heparin, are the preferred anticoagulants in pregnancy. There are circumstances, however, in which an alternative to heparin should be considered. These circumstances include, the presence of heparin resistance, a heparin allergy manifesting as heparin-induced skin reactions or heparin-induced thrombocytopenia, and the presence of a mechanical heart valve. 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. In this article, these circumstances are reviewed and alternative anticoagulants are discussed.

Key words: warfarin, direct oral anticoagulants, direct thrombin inhibitor, antithrombin concentrate, fondaparinux, pregnancy

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Heparins, unfractionated heparin (UFH) and low molecular weight heparin (LMWH), are the preferred anticoagulants in pregnancy. Neither UFH nor LMWH crosses the placenta,[1] and both are considered safe for mother and fetus.[1] The mechanism for both UFH and LMWH is potentiation of antithrombin, a natural anticoagulant. Because of fewer side effects and a longer half-life, LMWHs are preferred to UFH.[2] There are circumstances, however, in which an alternative to heparin should be considered. These circumstances include:

- The availability of an equally safe, but less-expensive or nonparenteral anticoagulant.
- Heparin resistance.
- Heparin allergy manifesting as heparin-induced skin reactions or heparin-induced thrombocytopenia (HIT).

- The presence of a mechanical heart valve.

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. In this article, these circumstances are reviewed and alternative anticoagulants are discussed.

Availability of an Equally Safe, But Less-expensive or Nonparental Anticoagulant

At the present time, there is no cheaper, equally safe alternative to LMWH and there are no oral anticoagulants which are considered safe in pregnancy. Warfarin, a vitamin K antagonist, crosses the placenta and increases the risk of birth defects. Moreover, up to 30% of women who take warfarin during pregnancy have a miscarriage, and ~7% experience stillbirth.[3] Although there are exceptional circumstances, such as the presence of a mechanical heart valve, in which warfarin may be the preferred anticoagulant during pregnancy,[3] women are advised against vitamin K antagonists. Besides warfarin, there are 5 other oral anticoagulants (the direct oral anticoagulants) that have been approved by the United States Food and Drug Administration (FDA). They are dabigatran (a direct thrombin inhibitor), and rivaroxaban, apixaban, edoxaban, and betrixaban (all antifactor Xa inhibitors). They all cross the placenta and are all likely to be present in breast milk. Whether they increase the risk of birth defects, fetal bleeding, or neonatal bleeding is unknown, but at the present time, they should not be used during pregnancy or lactation.[4]

Heparin Resistance

The clinical scenario is that of a pregnant patient presenting with a new deep vein thrombosis or pulmonary embolism. The patient is started on UFH or LMWH and requires increasing doses in an attempt to achieve an antifactor Xa level or activated partial thromboplastin time in the therapeutic range. Even after receiving doses of up to twice the anticipated dose, the patient remains subtherapeutic.

Heparin resistance is defined as increasing requirements of heparin to maintain therapeutic anticoagulation. Patients who do not respond to even very high doses of heparin are assumed to have heparin resistance. In clinical practice, heparin resistance is most often encountered during cardiothoracic surgery—up to 20% of patients on cardiopulmonary bypass experience heparin resistance.[5] Heparin resistance is also seen with other instances of increased heparin clearance (which occurs in pregnancy with its increased volume of distribution) and with an elevation in heparin binding proteins (which also occurs in pregnancy) or with antithrombin deficiency. As antithrombin, one of the natural anticoagulants, is the substrate for heparin and is responsible for inactivating thrombin along with the activated clotting factors IX, X, XI, and XII, deficiency of antithrombin renders heparin ineffective.

Alternative anticoagulants that have been used in heparin resistance include bivalirudin, argatroban, and antithrombin concentrate. Bivalirudin has been used during cardiothoracic surgery in patients unresponsive to heparin.[6] Bivalirudin is a direct thrombin inhibitor and a semisynthetic derivative of hirudin, a modified component of leech saliva,[5] which was first used as an alternative to heparin in the management of acute coronary syndromes.[5] As a direct thrombin inhibitor, bivalirudin inactivates thrombin directly, rather than indirectly through antithrombin, as heparin does. Compared with heparins, bivalirudin, and other direct thrombin inhibitors have activity against cell-bound and clot-bound thrombin, not just free thrombin.[7] Consequently, bivalirudin and other direct thrombin inhibitors are not impacted by low

antithrombin levels and are not subject to heparin resistance.[5] As for its possible use in pregnancy, bivalirudin, with a molecular weight of 2180 Da,[8] is larger than the placental transfer threshold of 1000 Da,[9] 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.[8] Argatroban is another direct thrombin inhibitor which has been used in critically ill patients unresponsive to heparin.[10] Argatroban was first used in Japan and was approved by the FDA as an alternative anticoagulant for the treatment and prevention of thrombosis in HIT. Argatroban has also been used as an alternative anticoagulant in a variety of other clinical situations.[11] Similar to bivalirudin, argatroban is not subject to heparin resistance. Argatroban, however, is a relatively small molecule, with a molecular weight of 527 Da,[12] and, since the molecular weight is less than the placental transfer threshold of 1000 Da, is much more likely to cross the placenta. Animal studies reveal no evidence of fetal harm, but there are no data in humans,[12] except for a few case reports. Antithrombin concentrate has also been used in patients who are unresponsive to heparin. For heparin to function and inhibit thrombin, heparin must bind to both thrombin and antithrombin. Inherited or acquired deficiency of antithrombin can lead to heparin resistance. In patients unresponsive to heparin, antithrombin replacement can be administered as antithrombin concentrate or as a component of plasma, and has been used in a variety of clinical situations. Antithrombin is a large molecule, with a molecular weight of 58,000 Da,[13] and presumably does not cross the placenta. There are no reports of fetal harm. Antithrombin has been used in pregnancy to treat inherited antithrombin deficiency[14] and to treat heparin resistance.[15]

In the clinical scenario above, antithrombin deficiency must be suspected and if confirmed, replacement with antithrombin concentrate initiated.

Heparin Allergy Manifesting as Heparin-induced Skin Reactions or HIT

The clinical scenario of heparin-induced skin reactions is that of a pregnant patient being treated for current or prior venous thromboembolism (VTE), or treated for high-risk thrombophilia, who develops tender, pruritic, erythematous nodules at the site of subcutaneous injections. The rash may become widespread. Some of the nodules may progress to necrotic patches. The skin reactions may or may not persist no matter what type of heparin the patient receives (in the United States this includes 2 LMWHs-enoxaparin and dalteparin).

The clinical scenario of HIT is that of a pregnant patient being treated for current or prior VTE, or high-risk thrombophilia, who has falling platelet counts and possibly paradoxical thromboembolism after starting UFH or (rarely) LMWH.

Alternatively, the patient may require an alternative anticoagulant due to a prior history of either heparin-induced skin reactions or HIT.

HIT is a limb-threatening and/or life-threatening prothrombotic condition caused by an immune reaction to complexes containing heparin and an endogenous platelet protein, platelet factor 4. Although the immune reaction is common, affecting 8% to 17% of medical patients treated with UFH, 50% of patients undergoing cardiac surgery, and 2% to 8% of patients treated with LMWH or fondaparinux, clinical complications of thrombocytopenia and thrombosis are far less frequent, affecting only 0.2% to 3% of patients exposed to heparins.[16] The incidence of antibody formation in pregnant patients is unknown, but the incidence of thrombocytopenia and thrombosis is, fortunately, very rare. If HIT is going to develop, it usually manifests within days of heparin exposure with an absolute drop in platelet count or as a relative decrease in

TABLE 1. The 4Ts Heparin-induced Thrombocytopenia Scoring System[17]

4Ts	2 Points	1 Point	0 Points
Thrombocytopenia	Platelet count fall >50% and platelet nadir ≥20	Platelet count fall 30%-50% or platelet nadir 10-19	Platelet count fall <30% or platelet nadir <10
Timing of platelet count fall	Clear onset between days 5-10	Consistent with days 5-10 fall, but not clear	Platelet count fall <4 d
Thrombosis or other sequelae	New thrombosis, or skin necrosis	Progressive, recurrent or suspected thrombosis, Non-necrotic (erythematous) skin lesions	None
Other causes for thrombocytopenia	None apparent	Possible	Definite

platelet count of 30% to 50% from baseline counts.[16] Thrombotic complications occur concurrently and can affect any part of the circulation.[16] When suspected, the probability of HIT can be estimated by a scoring system. The most widely used is the 4Ts and is summarized in Table 1.[17] If the score is ≤3, HIT is very unlikely. Scores of 4 to 5 (intermediate) and ≥6 deserve further investigation. The presence of anti–platelet factor 4/heparin antibodies can confirm the diagnosis.

Treatment of HIT consists of discontinuation of all heparins as soon as the condition is suspected and initiation of anticoagulation with an alternative parenteral anticoagulant such as danaparoid (which is no longer available in the United States), bivalirudin (discussed above), argatroban (which likely crosses the placenta and is, therefore, less desirable), and fondaparinux (a synthetic pentasaccharide LMWH which does not cross-react with HIT antibodies and has little placental transfer).[16] Adverse pregnancy outcomes have not been reported with fondaparinux.[18] In a systematic review of HIT in pregnancy, only 12 cases of HIT were identified. Patients were initially managed with lepirudin (n = 4), argatroban (n = 3), danaparoid (n = 3), or fondaparinux (n = 2); and were ultimately bridged to a vitamin K antagonist or maintained on lepirudin (a recombinant hirudin, is no longer available in the United States). All patients had resolution of HIT. Complications included therapeutic abortion before valve replacement in a case of valve thrombosis (n = 1), preterm delivery (n = 2), and preeclampsia (n = 1).[19] Currently, the anticoagulant of choice for women with HIT or a history of HIT, where danaparoid is unavailable, is fondaparinux.

Heparin-induced skin reactions are most frequently due to allergic reactions or possibly HIT.[20] In a prospective study of 320 patients receiving subcutaneous heparin (LMWH in >90% of the patients and UFH in <10% of the patients),[21] 24 (7.5%) developed skin reactions. Some patients had small eczematous plaques at the injection sites, others had generalized, itchy erythematous plaques, and still others had widespread lesions. Delayed hypersensitivity reactions were confirmed by histology, allergy testing, or both in 23 of 24 of the patients. One of 24 was diagnosed with HIT. Among the 17 patients who underwent allergy testing, only 2 patients tested positive for other heparins, suggesting that an alternative heparin can be used. For patients with heparin-induced skin reactions, the authors recommend obtaining a punch biopsy and obtaining a platelet count. If HIT is excluded, an alternative heparin can be tried. If all heparins induce skin reactions, the anticoagulant of choice

TABLE 2. Mechanism, Molecular Weight, Route of Delivery, Placental Transfer, Use in Pregnancy, Safety in Pregnancy and Safety in Breastfeeding for Heparins and Alternative Anticoagulants

Anticoagulant	Mechanism	Molecular Weight in Da (g/mol)	Route of Delivery	Placental Transfer	Use in Pregnancy	Safety in Pregnancy	Safety in Breastfeeding
Unfractionated heparin	Potentiates antithrombin	15,000	IV, SC	No	Yes	Yes	Yes
LMWH	Potentiates antithrombin	4500	SC	No	Yes	Yes	Yes
Warfarin	Vitamin K antagonist	308	Oral	Yes	In exceptional circumstances	No	Yes
Dabigatran	Direct thrombin inhibitor	628	Oral	Yes	No	Unknown	Unknown
Rivaroxaban	Anti-Xa inhibitor	436	Oral	Yes	No	Unknown	Unknown
Apixaban	Anti-Xa inhibitor	459	Oral	Yes	No	Unknown	Unknown
Edoxban	Anti-Xa inhibitor	548	Oral	Yes	No	Unknown	Unknown
Betrixaban	Anti-Xa inhibitor	452	Oral	Yes	No	Unknown	Unknown
Bivalirubin	Direct thrombin inhibitor	2180	IV	Unknown	Not reported	Unknown	Unknown
Argatroban	Direct thrombin inhibitor	527	IV	Presumed	Reported	Unknown	Unknown
Antithrombin	Natural anticoagulant	58,000	IV	No	Yes	Yes	Yes
Danaparoid*	LMWH heparinoid*	5500	SC	No	Yes	Yes	Yes
Fondaparinux	Potentiates antithrombin	1727	SC	Little	In exceptional circumstances	Unknown	Yes

*Danaparoid: no longer available in the United States.

IV indicates intravenous; LMWH, less molecular weight heparin; SC, subcutaneous.

where danaparoid is unavailable, is fondaparinux.

In some patients who are not receiving anticoagulation for a current VTE, the balance of risks and benefits may favor no anticoagulation, or postpartum anticoagulation only, rather than an alternative to heparins. The mechanism, molecular weight, route of delivery, placental transfer, use in pregnancy, safety in pregnancy, and safety in breastfeeding for heparins and alternative anticoagulants are summarized in Table 2.

The Presence of a Mechanical Heart Valve

The clinical scenario is that of a woman with a mechanical heart valve who becomes pregnant.

Pregnancy in a woman with heart disease is potentially life threatening, but the risks are compounded in a woman with a mechanical heart valve. In 2015, data were published from the European Society of Cardiology Registry of Pregnancy and Cardiac Disease (ROPAC),[3] which included the largest and most current series of pregnant women with a prosthetic heart valve. Among the pregnant women with a prosthetic heart valve, 212 of 346 (61%) had a mechanical, as opposed to a tissue valve, and of the pregnant women with a mechanical valve 129 of 212 (61%) had a mitral mechanical valve. Among the women who did not have a prosthetic heart valve, maternal mortality was 0.2%, whereas among the 212 women who had a mechanical valve, maternal mortality was 1.4%, and among the 134 women with a tissue valve, maternal mortality was 1.5%. For women with a prosthetic heart valve, this represents about a 100-fold increase in mortality compared with healthy women. Although maternal mortality was not significantly different between women with a mechanical valve versus a tissue valve, the rate of other complications was significantly higher

among women with a mechanical valve. During pregnancy, 21% of women with a tissue valve had a serious adverse event, but 42% of women with a mechanical valve had a serious adverse event. The most common adverse events were hemorrhage and thrombosis. Mitral valve thrombosis, the most feared complication with mechanical heart valve, occurred in 4.7% of pregnancies and was associated with a 20% rate of mortality. Half of the cases of mitral valve thrombosis occurred in the first trimester, all while women were on a heparin. The use of warfarin and other vitamin K antagonists during the first trimester, however, was associated with an increased risk of miscarriage and fetal death.

The anticoagulant regimens that were used in developed countries and reported in the ROPAC registry are summarized in Table 3. For a woman with a mechanical heart valve who becomes pregnant no one anticoagulant regimen is superior to another.[3] Warfarin has been the preferred anticoagulant for the mother, but it is associated with an increased risk of fetal complications.[3] It increases the risk of miscarriage, birth defects, stillbirth, fetal bleeding, and, possibly, adverse neurological outcome.[22]

TABLE 3. Anticoagulation Regimens for Women With a Mechanical Heart Valve in the Registry of Pregnancy and Cardiac Disease Database[3]

Regimen			
First Trimester	Second and Third Trimesters <36 wk	≥ 36 wk	Using this Regimen in Developed Countries (%)
Heparin	Heparin	Heparin	32
Heparin	VKA	Heparin	40
VKA	VKA	Heparin	10
VKA	VKA	VKA	4
Other regimen			14

VKA indicates warfarin or other vitamin K antagonist.

Women with a mechanical heart valve who choose to pursue a pregnancy should be counseled about the maternal and fetal risks before pregnancy. Mechanical valves are more durable than tissue valves, but patients with tissue valves do not require the same intensity of anticoagulation. Consequently, patients with tissue valves experience less morbidity and less fetal loss than patients with mechanical valves, and this should be discussed with women even before valve replacement.[3] Women who choose to pursue a pregnancy despite the risks to themselves and their fetuses, should be counseled about the options for anticoagulation and the implications. Discussions should involve the patient, her family, and specialists from obstetrics, cardiology, and hematology. The patient should be aware that warfarin is the preferred agent for the mother, but that is associated with adverse fetal outcomes. She should be aware that fetal outcomes are improved with heparins, but UFH and LMWH are associated with an increased risk of valve thrombosis. Close monitoring of anticoagulation levels and the addition of low-dose aspirin may reduce the risk of valve thrombosis, but there are insufficient data to prove the benefit of these strategies. The strategy of avoiding warfarin during the critical period of organogenesis has been shown to reduce the risk of congenital anomalies, but does not reduce the risk of fetal hemorrhage, stillbirth, or other sequelae from exposure to warfarin during the second or third trimester. Whatever anticoagulation regimen is prescribed, a multidisciplinary approach is required.

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