Motherisk Update

Low-molecular-weight heparins during pregnancy

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ABSTRACT

QUESTION A few years ago I suffered from pulmonary emboli. My physician recommended I use dalteparin during this pregnancy although, during my previous pregnancy, I had received subcutaneous heparin injections three times daily. Is dalteparin the same as heparin?

ANSWER Based on the best available evidence from mostly small prospective case series, retrospective reports, and placental perfusion studies, low-molecular-weight heparins (LMWHs), such as dalteparin, are a safe and convenient alternative to heparin during pregnancy for both mothers and fetuses.

RÉSUMÉ

QUESTION J'ai subi, il y a quelques années, une embolie pulmonaire. Mon médecin m'a recommandé d'utiliser de la daltéparine durant ma présente grossesse alors qu'au cours de la précédente, on m'administrait des injections sous-cutanées d'héparine trois fois par jour. La daltéparine est-elle le même médicament que l'héparine?

RÉPONSE En se fondant sur les meilleures données scientifiques disponibles, tirées principalement d'études de séries de cas prospectives, de rapports rétrospectifs et d'études de la perfusion placentaire, les héparines à bas poids moléculaire (HBM) comme la daltéparine sont une alternative sûre et pratique à l'héparine pendant la grossesse, tant pour la mère que pour le fœtus.

Low-molecular-weight heparins have shorter polysaccharide chains and lower molecular weights than unfractionated heparin. Low-molecular-weight heparins are widely used, mainly for thromboprophylaxis. These agents are dalteparin (Fragmin), enoxaparin (Lovenox), certoparin, and a few other less popular preparations. The pharmacokinetic and pharmacodynamic characteristics of LMWHs are substantially different from those of unfractionated heparin.

In clinical practice, LMWHs are much easier and more convenient for patients and physicians to use compared with unfractionated heparin. This is due to their long half-life and few side effects. There is also no need for frequent monitoring of partial thromboplastin time.

Indications during pregnancy

There are several indications for anticoagulation treatment during pregnancy. Pregnancy and the postpartum period are especially thrombogenic. Whenever a condition requiring anticoagulation (eg, a current or recent thromboembolic event) would be treated in non-pregnant patients, it should usually be treated in pregnant patients also.

One exception is thromboprophylaxis for patients with heart-valve prostheses. Several reports, including one from the United States Food and Drug Administration,[1] recommend not using LMWH for these patients during pregnancy. Only heparin should be used (warfarin is teratogenic). Why LMWHs are less effective for patients with this condition is yet to be determined.

← FOR PRESCRIBING INFORMATION SEE PAGE 282

Motherisk Update

Pregnancy-specific indications

Antiphospholipid syndrome (APS) is associated with adverse pregnancy outcomes. A few controlled trials suggest that a combination of heparin and acetylsalicylic acid improves pregnancy outcomes in women with APS.[2,3]

In recent years, many reports have found an association between various thrombophilias and adverse pregnancy outcomes, such as preeclampsia, abruptio placentae, intrauterine growth restriction, recurrent abortions, and fetal death.[4-7] Only very limited hard data support use of LMWH for women with previous adverse pregnancy outcomes and thrombophilias. Nevertheless, offering these women anticoagulation therapy is relatively common. A recent article[8] has suggested that, for women with previous pregnancy loss and thrombophilia (namely factor V Leiden and prothrombin mutation), administration of LMWH rather than ASA improves pregnancy outcome. This new report might further increase use of LMWHs for women who have had previous adverse pregnancy outcomes.

Dosage and monitoring

In various reports, doses of dalteparin ranged from 2500 to 22 000 units in one or two subcutaneous (SC) injections daily. For enoxaparin, doses ranged from 20 mg/d to 120 mg/d divided into one or two SC injections daily.

There is no way of comparing dosage equivalences among the various LMWHs unit by unit, by pharmacokinetics, or by bioactivity. Testing anti-Xa levels will allow physicians to monitor LMWH levels 3 to 4 hours after administration. The importance and optimal frequency of monitoring anti-Xa levels during treatment with LMWH are still debatable.

Side effects

The most common side effects of heparin are bleeding, osteoporosis, and heparin-induced thrombocytopenia. The LMWHs have weaker interactions with platelets and inhibit bone formation less than unfractionated heparin. They also have higher bioavailability after SC administration, have a longer half-life, and are less bound to plasma proteins. All these factors make LMWHs less likely than heparin to cause side effects. Much less osteoporosis is seen with LMWH treatment. One recent study showed no difference in bone density until after pregnancy between women who had and had not been treated with LMWHs.[9,10] Heparin-induced thrombocytopenia is very rare with use of LMWH.

A common side effect reported is skin irritation at the injection site. This should not result in cessation of treatment.

Transfer to fetus and milk

An in vitro experimental study by Motherisk showed that LMWHs did not cross the placenta.[11] A clinical report, where LMWH was injected shortly before a late pregnancy termination, showed that anti-Xa was detected in the women but not in the fetuses, indicating no LMWH crossed the placenta.[12] In retrospective studies, no specific adverse fetal effects or teratogenicity were detected.[13] It should be noted that LMWHs are classified by the Food and Drug Administration as pregnancy category B (no evidence of adverse effects on humans). The concentration of LMWH in maternal milk was very

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Motherisk questions are prepared by the Motherisk Team at the Hospital for Sick Children in Toronto, Ont. Dr Many practises at the Tel Aviv Medical Center, Tel Aviv University, in Israel and is a member of the Motherisk Program. Dr Koren is Director of the Motherisk Program. Dr Koren, a Senior Scientist at the Canadian Institutes for Health Research, is supported by the Research Leadership for Better Pharmacotherapy during Pregnancy and Lactation and, in part, by a grant from the Canadian Institutes for Health Research. He also holds the Ivey Chair in Molecular Toxicology at the University of Western Ontario in London.

Do you have questions about the safety of drugs, chemicals, radiation, or infections in women who are pregnant or breastfeeding? We invite you to submit them to the Motherisk Program by fax at (416) 813-7562; they will be addressed in future Motherisk Updates.

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low, more than 10 times lower than in maternal serum, and thus had no clinical significance.[12] Women treated with LMWHs can safely breastfeed.

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