Aetiology and treatment of venous thromboembolism

Bank, I.

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High Rate of Skin Complications Due to Low-molecular Weight Heparins in Pregnant Women

Ivan Bank¹, Eduard J. Libourel², Saskia Middeldorp¹, Jan van der Meer² and Harry R. Büllert¹

¹Department of Vascular Medicine, Academic Medical Center, University of Amsterdam and ²Division of Haemostasis, Thrombosis and Rheology, Department of Haematology, University Hospital Groningen, University of Groningen, The Netherlands.

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Abstract
Low-molecular weight heparins (LMWH) are widely used in patients in whom anticoagulant therapy is indicated and skin complications are considered to be rare.

Of 66 consecutive pregnant or postpartum women seen, 29% developed skin complications while receiving LMWH. Almost one-fourth had to switch to another preparation because of these side effects, which mainly constituted of delayed hypersensitivity reactions and itching. Former use of LMWH and protein C deficiency predisposed to skin complications. In case of severe skin complications necessitating discontinuation, another LMWH is tolerated by approximately 70% of the patients.

Because LMWH remain the drug of first choice in pregnant women, both physician and patient have to be aware of these adverse effects.
Introduction
Low-molecular weight heparins (LMWH) are widely used in patients in whom anticoagulant therapy is indicated. Side effects include bleeding, heparin induced thrombocytopenia, and hypersensitivity reactions. Skin complications due to LMWH use are considered to be rare, but their incidence is likely to be underreported. They vary from an urticarial rash (type I immediate hypersensitivity reaction), to erythematous lesions (delayed type IV hypersensitivity reaction) and, exceptionally, skin necrosis.
LMWH are considered safe and effective in pregnant and lactating women. In systematic reviews of LMWH use during pregnancy or the postpartum period, the reported incidences of generalised skin reactions were low, i.e. 0.3% - 0.6%. We report here a remarkably higher rate of skin complications.

Methods
The efficacy and safety of treatment with LMWH during pregnancy and the postpartum period in consecutive women is evaluated in an ongoing prospective, observational study in two university hospitals. Indications included thromboprophylaxis in women with an increased risk for pregnancy-related VTE, treatment of VTE, and prophylaxis in women with mechanical heart valves. During scheduled follow-up visits, data on pregnancy and drug-related complications were collected. All patients were instructed to contact the study center in case of complications. LMWH were prescribed in body weight adjusted therapeutic dosages (75 anti-Xa IU/kg per day) or in prophylactic dosages (less than 75 anti-Xa IU/kg per day), depending on the indication. Laboratory measurements included among others platelet counts and anti-Xa levels. For calculating the incidence of complications. Only the first episode was counted and subsequent episodes were censored. Relative risks and their corresponding 95% confidence intervals (CI) were calculated using SPSS software (version 9.0).

Results
Until the present interim analysis 66 pregnant or postpartum women were treated with LMWH. Thirty-nine women received LMWH during the entire pregnancy and postpartum period, 13 during pregnancy only, and 14 in the postpartum period only. None of the women had a history of allergy to unfractionated heparin or LMWH. Besides folic acid, women were not using other drugs. Skin complications
occurred in 19 (29%) of the 66 women during LMWH use (Table 1), all except one during pregnancy. These consisted of itching (n=13, 20%), local redness (n=15, 23%), subcutaneous infiltrates localised at the injection sites (n=7, 11%) and pain during injection (n=2, 3%). Two women (3%) developed a generalised erythematous rash with well circumscribed lesions of various size at the injection areas, elbows, thighs and armpits. No other side effects of LMWH, especially no bleeding, thrombocytopenia, skin necrosis, angioedema or anaphylaxis were reported. There were also no signs of cholestasis.

Skin complications began 7 to 9.5 (median 26) days after start of LMWH, and disappeared spontaneously or after switch to another LMWH after 1 to 59 (median 10) days. Although therapy had to be changed in 15 women (23%), it was not necessary in four women because of the mild course of symptoms.

Five of the 15 women (33%) in whom the initial LMWH had been discontinued developed new skin complications or had persistent complaints while receiving a different LMWH as second choice (Table 1). In 3 of these 5 women, signs and complaints resolved after replacement of the second LMWH by Danaparoid; in

<p>| Types of LMWH used as first, second and third choice and skin complications. |
|---------------------------------|----------------|-----------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>LMWH of first choice</th>
<th>Any skin complication to LMWH of first choice</th>
<th>First switch to another LMWH</th>
<th>Second choice LMWH</th>
<th>Any skin complication to LMWH of second choice</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nadroparin 19,000 anti-Xa IU mlַ</td>
<td>24</td>
<td>11 (10%)</td>
<td>7 (29%)</td>
<td>2</td>
</tr>
<tr>
<td>Nadroparin 9,500 anti-Xa IU mlַ</td>
<td>39</td>
<td>6 (13%)</td>
<td>6 (15%)</td>
<td>2</td>
</tr>
<tr>
<td>Enoxaparin 10,000 anti-Xa IU mlַ</td>
<td>1</td>
<td>1 (100%)</td>
<td>1 (100%)</td>
<td>5</td>
</tr>
<tr>
<td>Dalteparin 25,000 anti-Xa IU mlַ</td>
<td>1</td>
<td>1 (100%)</td>
<td>1 (100%)</td>
<td>2</td>
</tr>
<tr>
<td>Tinzaparin 14,000 anti-Xa IU mlַ</td>
<td>1</td>
<td>1 (100%)</td>
<td>1 (100%)</td>
<td>2</td>
</tr>
<tr>
<td>Danaparoid 7,500 anti-Xa IU mlַ</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Total</td>
<td>66</td>
<td>19 (29%)</td>
<td>15 (23%)</td>
<td>15</td>
</tr>
</tbody>
</table>

* in one of these women using Danaparoid as third LMWH symptoms persisted (see text). ַ All given in therapeutic dosages. ַ 77 % was given as a therapeutic dosage
one woman (receiving Tinzaparin and Nadroparin (9,500 anti-Xa IU/ml) as first and second choice, respectively) symptoms persisted during Danaparoid and labour was induced in the 37th week of gestation for this reason; the remaining patient (receiving Nadroparin (19,000 anti-Xa IU/ml) and Nadroparin (9,500 anti-Xa IU/ml) as first and second choice, respectively) switched to vitamin K antagonists from the 16th to 36th week of gestation and subsequently tolerated an alternative LMWH (Tinzaparin) during the rest of her pregnancy. Risk factors for development of skin complications were a history of former use of LMWH (RR 3.5, (95%CI 1.1-11.1)) and inherited protein C deficiency (RR 3.3 (1.8-6.1)).

Discussion
We preferentially prescribed Nadroparin which makes it difficult to extrapolate our results to all LMWH. However, given the known and observed cross-reactivity we conclude that skin complications occur far more frequently during long-term use in pregnant women than reported during short-term use in non-pregnant individuals. Furthermore, skin complications were a reason for alteration of therapy in almost one-quarter of the pregnant women using LMWH for prophylaxis or treatment of thrombosis. Because of the characteristic time relation between start of LMWH and onset of skin complications, and the absence of signs of skin necrosis, our patients are most likely to have moderate delayed type IV skin reactions.

The clinical course was self-limiting in most of the women after switching to another LMWH or a vitamin K antagonist, and no antihistaminics or corticosteroids were necessary. However, about one-third of the women who had switched also had skin complications on another LMWH, indicating cross-reactivity between preparations.

An alternative explanation for our observations could be pruritic urticarial papules and plaques of pregnancy (PUPPP). However, this common feature usually occurs during the last weeks of pregnancy, and eruptions often become manifest within striae, which was different from the clinical picture in our patients. Although subcutaneous tests are considered to be the gold standard in case of delayed hypersensitivity type IV skin reactions, there is no consensus about the optimal diagnostic strategy, and we preferred a pragmatic approach in the management of skin complications. It is of interest to note that pregnant women on the once-a-day injection
formulation of nadroparin (19,000 anti-Xa IU/ml) appeared to have an increased risk of skin complications when compared to those using the lower concentration of the same preparation twice daily (observed difference: 30.4%, (7.5–53.4)). Since these formulations contain the same substances, this observation cannot yet be understood.

In the absence of alternative and safe anticoagulants during pregnancy, LMWH remain the treatment of choice, but physicians should be aware of skin complications, and should instruct patients properly. A pragmatic approach to switch to another LMWH when skin complications occur seems appropriate, since the majority of the patients will tolerate the other LMWH.

References