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Incidence of hypersensitivity skin reactions in patients on full-dose low-molecular-weight heparins during pregnancy

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ABSTRACT

Background: Low-molecular-weight heparins (LMWH) are the most commonly used anticoagulants for the treatment and prophylaxis of venous thromboembolism in pregnancy. Hypersensitivity skin reactions associated with the use of LMWH are frequently seen, but are probably underreported.

Objective: To evaluate the incidence of hypersensitivity skin reactions due to the use of LMWH in pregnancy, and the subsequent management of anticoagulation.

Patients/methods: From 1999 to 2009, we followed consecutive women who used therapeutic anticoagulation for venous indications. Women visited a combined obstetric/coagulation clinic and were seen by a thrombosis specialist every two months until six weeks postpartum. All women were started on nadroparin.

Results: We included 135 pregnancies in 88 women. Overall, in 52 of 135 pregnancies (39%), women switched at least once to another anticoagulant because of the development of hypersensitivity skin reactions. Switching to another preparation of LMWH was effective in 77% of the cases. In 23% of the cases skin reactions recurred and another switch had to be made.

Conclusion: In almost half of the pregnancies, women had to switch at least once to another anticoagulant preparation due to the development of hypersensitivity skin reactions on LMWH. In most cases, skin reactions did not recur on the second preparation of LMWH used.

KEYWORDS

Anticoagulation, hypersensitivity skin reactions, LMWH, pregnancy, venous thromboembolism

INTRODUCTION

For pregnant women with either a current venous thromboembolism (VTE) or a high risk of recurrent VTE, low-molecular-weight heparins (LMWH) are the most commonly used anticoagulant. However, hypersensitivity skin reactions are a recognised complication in pregnant patients who use LMWH. Moreover, when this heparin intolerance occurs, alternative choices for anticoagulation are limited and hypersensitivity skin reactions might recur when another preparation of LMWH is used.[1]

A vitamin K antagonist (VKA) could be an alternative anticoagulant, but this drug crosses the placenta and its use in pregnancy is associated with significant foetal risks, particularly teratogenesis and foetal haemorrhage.[2,3] In pregnancy VKAs might also be associated with mild neurological dysfunctions in children of school age.[4] Fondaparinux is another alternative anticoagulant treatment, but data on the use in pregnancy are limited.[5]

Rates of mild hypersensitivity skin reactions due to LMWH use in the general population range from 2-7.5%.[6,7] Risk factors for the development of hypersensitivity skin reactions are female sex, obesity and long duration of heparin therapy.[7] It has been hypothesised that the hormonal status may be of influence in the pathogenesis of the delayed hypersensitivity skin reaction to LMWH.[8] Pregnancy also seems to increase the incidence of these skin reactions, ranging from 0.6-40%.[1,9-14] These reactions may present as erythematous, well-circumscribed lesions without necrosis, usually secondary to a delayed type IV hypersensitivity reaction. An urticarial rash (type I immediate hypersensitivity reaction), skin necrosis and heparin-induced thrombocytopenia have also been reported, although these types of reactions are rare.[8]

A few studies report on the incidence of hypersensitivity skin reactions to LMWH in pregnant women, but these studies had other primary outcomes and therefore hypersensitivity skin reactions are probably underreported.[9-11,13]

We performed a cohort study in our hospital to assess the safety of the use of a full dose of LMWH in pregnancy. Here, we report the prevalence of hypersensitivity skin reactions of LMWH usage during pregnancy and the subsequent management of anticoagulation.

PATIENTS AND METHODS

Patients

This is a single-centre cohort study, including 88 consecutive women who received a therapeutic dosage of LMWH during pregnancy and the puerperium. All women visited the University Medical Centre Groningen and were followed between 1999 and 2009. We included 135 ongoing pregnancies of these 88 women. Early foetal losses (<22 weeks of gestation) were not included, due to lack of information on these pregnancies. Indications for anticoagulation were a history of idiopathic, provoked or previous pregnancy-related venous thromboembolism, a VTE in the current pregnancy, recurrent foetal loss or asymptomatic severe thrombophilic defects (protein C, S or antithrombin deficiency).

Women visited a combined obstetric/coagulation clinic and were seen by a thrombosis specialist every two months until six weeks postpartum. Information on hypersensitivity skin reactions, episodes of VTE, bleeding, external risk factors for thrombosis, obstetric history, anticoagulant treatment, delivery and pregnancy outcome were collected using a standardised questionnaire and by reviewing medical records. Additional data were added retrospectively. National legislation and the ethical committee of our institution approve this type of study without the need for review of the protocol.

Treatment protocol

Women either had a prophylactic indication and were started on LMWH in early pregnancy, as soon as a pregnancy test was positive, or were treated for VTE in the current pregnancy. They were all treated with a body weight adjusted therapeutic dosage during pregnancy and until six weeks postpartum. Women with a current VTE during pregnancy were treated for six months, but at least until six weeks postpartum. Women started with a once daily dosage of LMWH, and from the 37th week of pregnancy all women switched to a twice daily dose to minimise the bleeding risk during delivery. Women were instructed about self-injection by a research nurse and received an information letter; most women actually injected themselves, but a few were injected by home-care nurses. Anti-Xa levels were not routinely measured and doses of LMWH were not adjusted for increasing bodyweight or increasing renal clearance.

Switch protocol

In the first pregnancy, all women started on nadroparin in a weight-adjusted therapeutic dosage (175 anti-Xa IU kg^{-1} day^{-1}). If a woman developed hypersensitivity skin reactions, she was switched to tinzaparin in a weight-adjusted therapeutic dosage. If the hypersensitivity skin reactions recurred again, the woman was switched to a VKA (only during the second trimester), dalteparin, danaparoid or fondaparinux. In subsequent pregnancies women started with the preparation that was used without complications during their previous pregnancy.

Definitions

The definitions were are follows:

- Red pruritic injection infiltrates: itchy, erythematous, well-circumscribed lesions without necrosis, subcutaneous, usually secondary to a delayed type IV hypersensitivity reaction.
- Generalised rash: rash not restricted to the site of injection.
- Mild symptoms: symptoms of skin reactions, (including haematomas, pruritic injection infiltrates and non-pruritic injection infiltrates) not severe enough to switch treatment (dependent on patient and doctor's preferences).

Statistical analysis

Descriptive statistics were used. The statistical analysis was performed in PASW version 18.0 (IBM SPSS, Chicago, Illinois, United States).

RESULTS

Eighty-eight women had 135 pregnancies between 1999 and 2009. Twelve of these women (=12 pregnancies) were also included in a study by Bank *et al.*[1] Median maternal age was 30 years (range 20-43). Indications for anticoagulation were previous VTE in 98 (73%) pregnancies, a current VTE in four (3%) pregnancies, an asymptomatic thrombophilic defect in 23 (17%) pregnancies and recurrent foetal loss in six (4%) pregnancies. In four (3%) pregnancies the therapeutic dosage of LMWH was given for other reasons (strong positive family history for VTE). In 66 (49%) of the pregnancies women were nulliparous. None of the patients had a history of thrombocytopenia or an allergy to LMWH. Baseline characteristics are displayed in *table 1*.

Table 1. *Baseline characteristics of study population*

Women, n	**88**
Pregnancies, n	135
Maternal age (median, range)	30 (20-43)
Parity: - Nulli- - Multi-	 66 (49%) 69 (51%)
Gestational age at delivery in weeks (median, range)	39.4 (27.5-42.3)
Birth weight in grams (median, range)	3372 (750-4890)
Indication for anticoagulation during pregnancy:	
- VTE in current pregnancy, n (%)	4 (3%)
- Previous VTE, n (%)	98 (73%)
- Asymptomatic thrombophilia, n (%)	23 (17%)
- Recurrent foetal loss, n (%)	6 (4%)
- Other (strong positive family history for VTE)	4 (3%)
Pregnancy outcome:	
- Live born	129
- Congenital birth defects	4
- Stillborn	1
- Late foetal loss (>22 weeks)	3
- Termination due to severe foetal anomalies	2

Pregnancy outcomes

The 135 pregnancies, including one twin pregnancy, resulted in 129 live infants. Median gestational age of live infants was 39.4 weeks, ranging from 27.5-42.3 weeks. Median birth weight was 3372 gram, ranging from 750-4890 gram. Three late foetal losses (23-27 weeks) were observed. In one of these three pregnancies, a VKA was used during the second trimester. In addition, one infant was stillborn due to placental abruption at 31 weeks and two pregnancies were terminated, for severe foetal anomalies (trisomy 18 and severe cardiac defect). Four live born infants had congenital defects: a cleft palate, clubfeet and a (genetic form of) retinoblastoma: no VKAs were used in these pregnancies. One male infant was born with an epispadia; in this pregnancy VKAs were used during the second trimester. Results are also displayed in *table 1*.

Anticoagulation used

Overall, in 52 out of 135 pregnancies (39%), women switched at least once to another treatment because of the development of hypersensitivity skin reactions. In 44 pregnancies (34%) women switched to another LMWH, thereafter in 77% (n=34) no other switch in treatment was required. In two pregnancies (2%) women switched twice to a different LMWH and in eight pregnancies (6%) women switched to VKA in the second trimester, due to the recurrence of hypersensitivity skin reactions. In 19 pregnancies (14%) women switched to a VKA for other reasons, such as aversion to injections or patients' preferences. In sixty-two pregnancies (46%) women continued using LMWH during their whole pregnancy and puerperium without hypersensitivity skin reactions, or with only mild reactions not severe enough to switch (*figure 1*).

Four women used danaparoid; one of these women developed a generalised rash, while one woman developed mild symptoms but continued using danaparoid.

Fondaparinux was used in 15 pregnancies (11%) because of hypersensitivity skin reactions to at least one type of LMWH in the current or previous pregnancy. No skin reactions were observed with the use of fondaparinux. These results were described elsewhere.[5]

Taking into account only the first pregnancies (n=88), all women started on nadroparin. Overall, in 37 (42%) first pregnancies, women were switched at least once to another anticoagulation treatment for hypersensitivity skin reactions. In the subsequent pregnancies, this incidence was lower: in only 13 pregnancies (28%) women were switched to another anticoagulation treatment for hypersensitivity skin reactions.

Type of skin reactions

LMWH were used in a total of 131 pregnancies. Pruritic erythematous infiltrates on the site of injection due to the use of LMWH were observed in 38% (n=50) of pregnancies. Mild symptoms which did not require a switch in treatment occurred in another 25% (n=33) of the pregnancies. Results are displayed in *table 2*.

A more generalised rash was observed in 2% (n=2) of the pregnancies. One woman developed a rash on nadroparin; no complications were observed with the subsequent use of dalteparin. Another woman developed a generalised rash on nadroparin, dalteparin and even on danaparoid. Finally, the delivery was initiated and in the next pregnancy she received VKA and fondaparinux without complications.

DISCUSSION

In this study, we evaluated the use of a therapeutic dosage of LMWH during pregnancy. Overall, in 39% of the pregnancies, women had to switch at least once to another LMWH, acenocoumarol, danaparoid or fondaparinux due

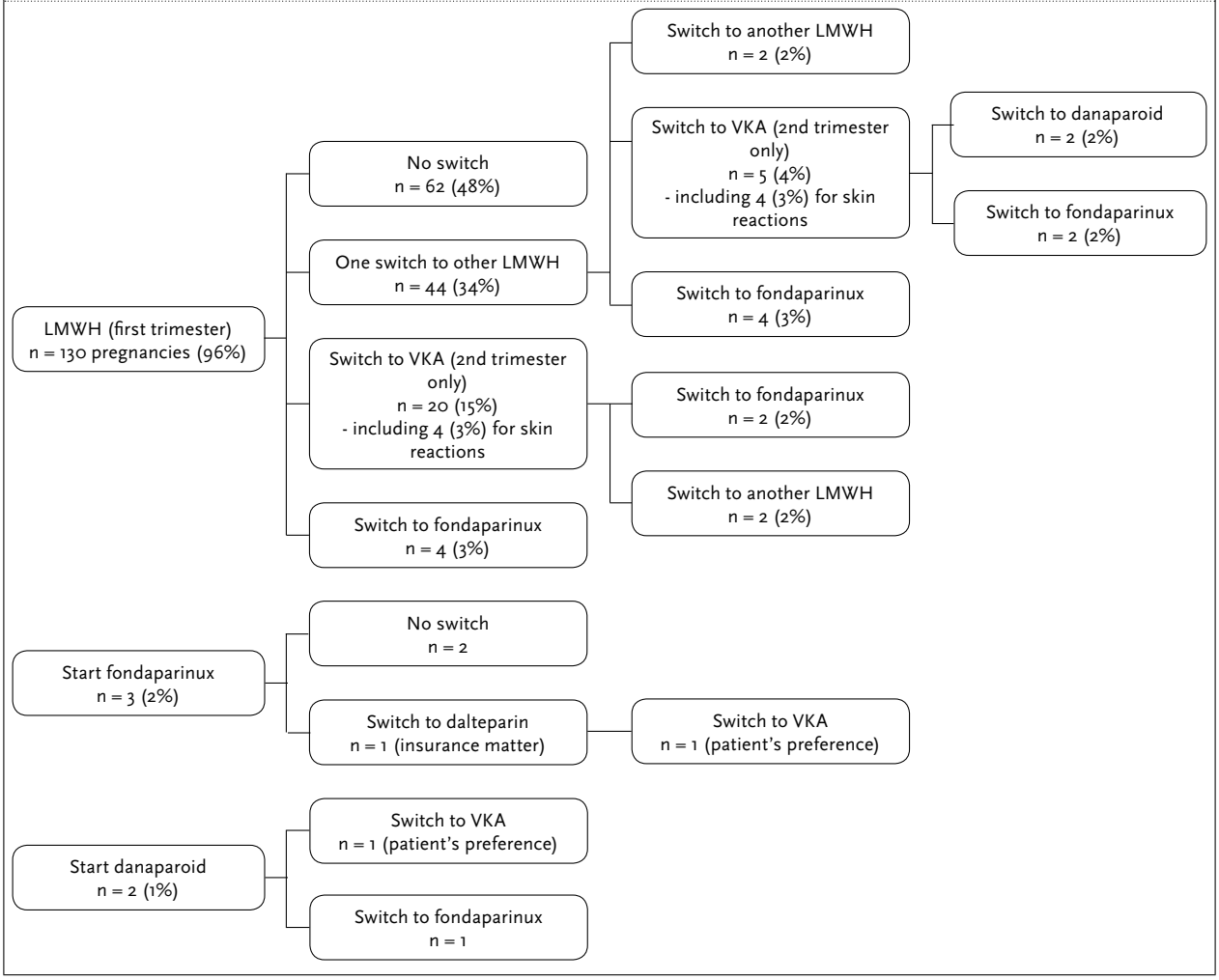
Table 2. *Reported side effects of LMWH*

	Pregnancies with exposure to LMWH (n= 131)
No side effects, n(%)	46 (35%)
Pruritic injection infiltrates, n(%)	50 (38%)
Rash (generalised), n(%)	2 (2%)
Mild symptoms, n (%)	33 (25%)

to the development of hypersensitivity skin reactions. In the first pregnancies with a full-dose anticoagulation (n=88) the rate was even higher: 42% switched at least once to another anticoagulation treatment. Switching to another preparation of LMWH seems to have a good effect, because in 77% of these pregnancies no second switch was needed.

Compared with other studies with skin lesions as primary outcome, our rate exceeds the highest reported rate of 29% by Bank *et al.*[1] They reported a prospective, observational study, including 66 pregnant women. They found a skin complication rate of 29%; these skin complications consisted of itching (20%), local redness (23%), subcutaneous infiltrates at the injection site (11%), pain during injection (3%) and a generalised rash (3%). To maintain a consecutive cohort, data of 12 pregnancies included in the study by Bank *et al.*[1] were also included in our study, but excluding these pregnancies did not change our results. Other studies that assessed the usage of LMWH during pregnancy had mostly bleeding or thrombotic complications as a primary outcome. Two reviews evaluated the complication rate of LMWH and also reported skin reactions as a secondary outcome in pregnancy. First, Sanson *et al.*[9] performed a review of 21 studies, including 486 pregnancies. They found only three cases (0.6%) of diffuse skin reactions, which led to cessation or change of treatment. Second, in a review by Greer and Nelson-Piercy,[11] 64 reports were included with in total 2777 pregnancies. They found that 1.8% of women using LMWH in pregnancy developed allergic skin reactions. We think that the high rate of skin complications we report here is real. A study by Kaandorp *et al.*[13] compared the effect of aspirin plus heparin or aspirin alone in women with recurrent miscarriage, as a secondary outcome they report that 40% of the women in the heparin group complained of swelling and local redness at the injection site. Wütschert *et al.*[8] also suggested in a review that the incidence of hypersensitivity skin reactions on LMWH might be underreported. In our hospital women were followed with a focus on adverse events, which may be an explanation for the higher incidence of reported hypersensitivity skin reactions. However, the

Figure 1. *Switches of anticoagulation treatment during pregnancy*



true percentage of hypersensitivity skin reactions in this cohort seems to be even higher, because some women did develop mild skin reactions, but did not switch to another treatment.

Different types of hypersensitivity skin reactions are described.[8,12] Most common is the delayed type IV hypersensitivity reaction; other reactions include type I immediate hypersensitivity reactions, skin necrosis and heparin-induced thrombocytopenia.[8] In our study the delayed type IV reaction was also most commonly observed.

Fondaparinux was used in 15 pregnancies in our study. No hypersensitivity skin reactions were observed, but the use of this drug is limited by the fact that it crosses the placenta.[15] The use of fondaparinux in this study population was already described elsewhere.[5]

Schindewolf *et al.*[7] described an increased risk for developing hypersensitivity skin reactions for a body mass index greater than 25, duration of heparin therapy longer than nine days and female sex. They reported an overall incidence of 7.5%, but they included only a few pregnant women. In our cohort, patients by definition had at least two of these risk factors. Unfortunately, we had no information about the BMI, so we could not analyse this relation.

A limitation of our study was the diagnosis of the skin reactions. The interpretation and the decision to switch to another anticoagulant was based on a clinical diagnosis made by different doctors, and was not objectified by skin tests. On the other hand, there is also no consensus in the literature about how to test skin allergy to LMWH.[8] A recent review by Schindewolf *et al.*[12] recommended switching to another LMWH without prior skin tests, especially in pregnant women. They advise to switch to a different heparin preparation, thus performing a subcutaneous provocation of fair sensitivity.

Because the optimal dosage of thromboprophylaxis in women with an increased risk of VTE during pregnancy and puerperium is not established, we chose to give a therapeutic dosage of LMWH to all pregnant women with an indication for thromboprophylaxis.

In our study a tendency towards more hypersensitivity skin reactions on nadroparin can be observed. Schindewolf *et al.*[14] suggested in a review that nadroparin probably had a more allergenic epitope in the nadroparin molecule than other heparins. There is a bias by indication; all women were started on nadroparin and other preparations were only used when a woman had already shown hypersensitivity skin reactions to nadroparin. Switching treatment seems to have a good effect, but we cannot exclude that longer duration of exposure to LMWH might also decrease the development of hypersensitivity skin reactions.

Our findings should lead to an altered view of hypersensitivity skin reactions during pregnancy. Physicians should be aware that patients receiving LMWH have a high risk of developing a delayed type IV hypersensitivity reaction. Therefore, we recommend monitoring pregnancies with anticoagulant treatment to recognise skin reactions.

In conclusion, we report here a 39% rate of hypersensitivity skin reactions in women on LMWH during pregnancy. These reactions can primarily be managed by changing therapy to another preparation of LMWH, which is successful in 77% of the patients. In a subgroup of women, it is necessary to ultimately switch to VKA or fondaparinux.

REFERENCES

1. Bank I, Libourel EJ, Middeldorp S, Van Der Meer J, Buller HR. High rate of skin complications due to low-molecular-weight heparins in pregnant women. J Thromb Haemost. 2003;1:859-61.
2. Mehndiratta S, Suneja A, Gupta B, Bhatt S. Fetotoxicity of warfarin anticoagulation. Arch Gynecol Obstet. 2010;282:335-7.
3. Wainwright H, Beighton P. Warfarin embryopathy: fetal manifestations. Virchows Arch. 2010;457:735-9.
4. Wesseling J, Van Driel D, Smrkovsky M, et al. Neurological outcome in school-age children after in utero exposure to coumarins. Early Hum Dev. 2001;63:83-95.
5. Knol HM, Schultinge L, Erwich JJ, Meijer K. Fondaparinux as an alternative anticoagulant therapy during pregnancy. J Thromb Haemost. 2010;8:1876-9.
6. Ludwig RJ, Schindewolf M, Utikal J, Lindhoff-Last E, Boehncke WH. Management of cutaneous type IV hypersensitivity reactions induced by heparin. Thromb Haemost. 2006;96:611-7.
7. Schindewolf M, Schwaner S, Wolter M, et al. Incidence and causes of heparin-induced skin lesions. CMAJ. 2009;181:477-81.
8. Wutschert R, Piletta P, Bounameaux H. Adverse skin reactions to low molecular weight heparins: frequency, management and prevention. Drug Saf. 1999;20:515-25.
9. Sanson BJ, Lensing AW, Prins MH, et al. Safety of low-molecular-weight heparin in pregnancy: a systematic review. Thromb Haemost. 1999;81:668-72.
10. Santoro R, Iannaccaro P, Prejan S, Muleo G. Efficacy and safety of the long-term administration of low-molecular-weight heparins in pregnancy. Blood Coag Fibrinol. 2009;20:240-3.
11. Greer IA, Nelson-Piercy C. Low-molecular-weight heparins for thromboprophylaxis and treatment of venous thromboembolism in pregnancy: a systematic review of safety and efficacy. Blood. 2005;106:401-7.
12. Schindewolf M, Lindhoff-Last E, Ludwig RJ, Boehncke WH. Heparin-induced skin lesions. Lancet. 2012;380:1867-79.
13. Kaandorp SP, Goddijn M, van der Post JA, et al. Aspirin plus heparin or aspirin alone in women with recurrent miscarriage. N Engl J Med. 2010;362:1586-96.
14. Schindewolf M, Gobst C, Kroll H, et al. High incidence of heparin-induced allergic delayed-type hypersensitivity reactions in pregnancy. J Allergy Clin Immunol. 2013;132:131-9.
15. Dempfle CE. Minor transplacental passage of fondaparinux in vivo. N Engl J Med. 2004;350:1914-5.