

Low-molecular-weight heparins for thromboprophylaxis and treatment of venous thromboembolism in pregnancy: a systematic review of safety and efficacy

Ian A. Greer and Catherine Nelson-Piercy

To assess the safety and efficacy of low-molecular-weight heparins (LMWHs) for thromboprophylaxis and treatment of venous thromboembolism (VTE) in pregnancy, a systematic review of studies to the end of 2003 was undertaken. Data on VTE recurrence and side effects were extracted and cumulative incidences of VTE and adverse effects calculated. Of 81 reports identified, 64 reporting 2777 pregnancies were included. In 15 studies (174 patients) the indication for LMWH was treatment of acute VTE, and in 61 studies

(2603 pregnancies) it was thromboprophylaxis or adverse pregnancy outcome. There were no maternal deaths. VTE and arterial thrombosis (associated with antiphospholipid syndrome) were reported in 0.86% (95% confidence interval [CI], 0.55%-1.28%) and 0.50% (95% CI, 0.28%-0.84%) of pregnancies, respectively. Significant bleeding, generally associated with primary obstetric causes, occurred in 1.98% (95% CI, 1.50%-2.57%), allergic skin reactions in 1.80% (95% CI, 1.34%-2.37%), heparin-induced thrombocyto-

penia in 0%, thrombocytopenia (unrelated to LMWH) in 0.11% (95% CI, 0.02%-0.32%), and osteoporotic fracture in 0.04% (95% CI, < 0.01%-0.20%) of pregnancies. Overall, live births were reported in 94.7% of pregnancies, including 85.4% in those receiving LMWH for recurrent pregnancy loss. LMWH is both safe and effective to prevent or treat VTE in pregnancy. (*Blood*. 2005;106:401-407)

© 2005 by The American Society of Hematology

Introduction

Pulmonary embolism (PE) remains the leading cause of direct maternal death in the United Kingdom¹ and venous thromboembolism (VTE) in pregnancy is an important cause of morbidity, not only in pregnancy but also in the long term.² Effective primary prevention and acute management of VTE in pregnancy are therefore important to reduce maternal mortality and morbidity. Coumarins cross the placenta and their use in pregnancy is associated with significant fetal and maternal risks, related particularly to teratogenesis and hemorrhage.³ For many years, unfractionated heparin (UFH) was the standard anticoagulant used in pregnancy.⁴ Low-molecular-weight heparins (LMWHs) have replaced UFH for the prevention and management of acute VTE without pregnancy.^{5,6} In the United Kingdom, Europe, and Australasia, LMWHs are now also widely used for the prevention and treatment of VTE in pregnancy.^{7,8} The advantages of LMWHs over UFH include an enhanced ratio of anti-Xa (antithrombotic) to anti-IIa (anticoagulant), resulting in a reduced risk of bleeding; stable and predictable pharmacokinetics with increased bioavailability and half-life, allowing less frequent fixed or weight-based dosing without the need for monitoring; subcutaneous administration⁸; and less activation of platelets, with less binding to platelet factor 4 substantially reducing the risk of heparin-induced thrombocytopenia (HIT).^{9,10} A major concern with the widespread use of UFH in pregnancy has been the 2% risk of symptomatic heparin-induced osteoporotic fracture in pregnancy.⁹ LMWHs are associated with a lower risk of this devastating complication.¹¹⁻¹³

Peer-reviewed international guidelines endorse the use of LMWH for both the treatment^{11,14} and prevention^{11,15} of VTE. However, no LMWH has been licensed for use in pregnancy, and

data regarding efficacy and safety come mostly from small case series. A systematic review of LMWH use in pregnancy, published in 1999, included 486 cases and suggested that LMWHs were a safe alternative to UFH in pregnancy.¹³ The use of LMWH has become more widespread, both for VTE treatment and thromboprophylaxis, and more recently for the prevention of adverse pregnancy outcome.¹⁶

As more LMWHs are introduced, the range of applications increases, and confidence grows with their use in pregnancy, it is vital that the safety of such treatment is confirmed. The aim of the present study was to perform a systematic review of all the published studies of LMWH use in pregnancy to provide contemporary data on the efficacy of LMWHs, as evidenced by the incidence of recurrent or new VTE, and the safety of LMWHs, measured by the incidence of severe bleeding, allergic skin reactions, HIT, and osteoporosis.

Methods

A systematic review of LMWH use in pregnancy was undertaken by searching the electronic databases EMBASE, PubMed, and the Cochrane Library up to the end of December 2003. The search terms were pregnancy, pregnant, trimester, gestation, or "child birth," and LMWH, "low molecular weight heparin," "low molecular weight heparins," enoxaparin, dalteparin, Fragmin, fondaparinux, tinzaparin, nadroparin, ardeparin, reviparin, bemiparin, or Lovenox. This electronic search was supplemented by manual searches of reference lists and recent reviews. The methodologic quality of the studies was assessed. Case reports were included provided there was not duplicate publication. Cases of women with artificial heart

From the University of Glasgow, Glasgow, United Kingdom; and Guy's and St Thomas' Hospitals Trust and Queen Charlotte's Hospital, London, United Kingdom.

Submitted February 14, 2005; accepted March 1, 2005. Prepublished online as *Blood* First Edition Paper, April 5, 2005; DOI 10.1182/blood-2005-02-0626.

Supported by an unrestricted educational grant from Sanofi-Aventis.

Reprints: Ian Greer, Department of Obstetrics and Gynaecology, University of Glasgow, Glasgow Royal Infirmary, 10 Alexandra Parade, Glasgow, G31 2ER, United Kingdom; e-mail: i.a.greer@clinmed.gla.ac.uk.

© 2005 by The American Society of Hematology

valves were excluded because these have recently been reviewed elsewhere¹⁷ and because many of these patients received a combination of coumarins, UFH, and LMWH. Subjects included in reports who did not receive LMWH were excluded.

The remaining reports were subdivided into those where LMWH was primarily used for treatment of VTE, for thromboprophylaxis, or to prevent recurrent pregnancy loss (RPL) or other adverse pregnancy outcome. Care was taken to avoid the duplicate recording of cases reported in more than one publication. Where VTE was initially treated with UFH followed by treatment doses of LMWH, the indication was assigned as treatment, but where VTE was initially treated with UFH followed by prophylactic doses of LMWH, the indication was assigned as thromboprophylaxis.

Data on VTE recurrence or occurrence, LMWH dosage regime, and potential side effects were extracted into prepiloted forms. Thrombotic events were categorized into deep vein thrombosis (DVT), PE, other VTE, or arterial thrombotic events. Hemorrhagic complications were divided into antenatal bleeding, postpartum hemorrhage (PPH; blood loss exceeding 500 mL), and wound hematomas. Data on allergic skin reactions and thrombocytopenia (defined as a platelet count $< 100 \times 10^9/L$) were also collated. Data on pregnancy outcome were collected when provided. This was not a primary outcome measure of the present study, because pregnancy outcome in studies where LMWH was used to prevent adverse outcome, with or without thrombophilia, is the subject of another publication.¹⁸

Data from selected studies were pooled and the overall proportion of events and 95% confidence intervals (CIs) were calculated using the exact Clopper-Pearson test. Data on different LMWHs were compared using the χ^2 test.

Results

In total, 81 reports of LMWH use in pregnancy were identified, with a total of 2931 patients.¹⁹⁻⁹⁹ From these, we excluded 11 studies of 43 patients with artificial heart valves^{20,23,36,47,52,54,55,65,72,74,91}; 1 case report of primary pulmonary hypertension⁴⁹; 2 studies of 18 pregnancies in 16 patients⁸³ and 4 pregnancies⁸⁶ reported elsewhere; and 3 studies for methodologic reasons because insufficient information regarding LMWH use was given.^{64,81,94} In total, 64 studies reporting 2777 pregnancies were included in the analysis. These were subdivided depending on the principal indication for LMWH use (Table 1). In 6 studies^{21,22,82,90,92,95} of 720 pregnancies, the indication for LMWH use was not clearly specified, and in 4 studies^{35,53,70,75} there was a mixture of patients receiving LMWH for treatment and thromboprophylaxis. Within the 2603 patients in the nontreatment/thromboprophylaxis groups, 2176 received antenatal LMWH and 427 received LMWH only peripartum or postpartum. Some studies reported more than one prophylactic indication among the patients studied.

The specific LMWHs used in the pregnancies are shown in Table 2. The most common LMWH was enoxaparin, followed by dalteparin and nadroparin.

Table 1. Principal indication for LMWH use

Indication for LMWH	No. of studies	No. of pregnancies
Treatment of VTE	15	174
Thromboprophylaxis	30	1321
Thromboprophylaxis following VTE in index pregnancy	5	27
Prevention of RPL	15	447
Prevention of preeclampsia/IUGR	5	88
Unspecified prophylaxis	6	720
Total number of studies included in analysis	64*	2777

IUGR indicates intrauterine growth restriction.

*The total number of studies (76) is greater than the total included for analysis (64) because 12 studies clearly indicated multiple indications for LMWH use in different patients.

Table 2. Specific LMWH used in studies of treatment and thromboprophylaxis

LMWH	Total no. of pregnancies	Treatment, no.	Thromboprophylaxis, no.
Enoxaparin	1247	105	1142
Dalteparin	789	49	740
Nadroparin	530	20	510
Certoparin	108	0	108
Riviparin	42	0	42
Tinzaparin	3	0	3
Unspecified	58	0	58
Total	2777	174	2603

LMWH for treatment of VTE

In 15 studies (including 6 case reports) reporting data on 174 patients, LMWH was used for treatment.^{19,31,32,35,48,51,53,58,68,70,73,75,76,85,89} Of these patients, 105 women were treated with enoxaparin, 49 with dalteparin, and 20 with nadroparin. In 28 cases, VTE was initially treated with UFH between 2 days and 2 weeks after diagnosis. The LMWH was administered twice daily in 153 cases. Complications are summarized in Table 3. Recurrent VTE was reported in 2 (1.15%; 95% CI, 0.14%-4.09%) women (1 patient with DVT receiving 10 000 IU dalteparin once daily, and 1 patient with DVT receiving enoxaparin 1 mg/kg twice daily). There were no maternal deaths. Significant bleeding (> 500 mL) occurred in 3 women (1.72%; 95% CI, 0.36%-5.00%); in 2 of these women, the LMWH could have contributed to the extent of bleeding from primarily obstetric causes at the time of delivery, whereas the other woman had epistaxis. Minor allergic reactions occurred in 2 (1.15%; 95% CI, 0.14%-4.09%) women, and thrombocytopenia (unrelated to LMWH) occurred in 1 (0.57%; 95% CI, 0.02%-3.20%) woman. There were no cases of HIT or osteoporosis.

LMWH for thromboprophylaxis

In 30 studies, reporting 1348 pregnancies, LMWH was used at thromboprophylactic doses. Of these, LMWH was used for thromboprophylaxis in 1321 pregnancies.^{24-26,28,33-35,38-41,44-46,53,56,57,59,61,63,66,67,69,70,75,77,78,84,98,99} LMWH was administered because patients had thromboembolic risk factors (eg, previous VTE or thrombophilia). In 27 pregnancies, thromboprophylactic doses of LMWH were administered following initial treatment of VTE with UFH.

LMWH for prevention of adverse pregnancy outcome

There were 15 studies (447 pregnancies)^{27,29,30,37,42,43,60,62,66,79,80,87,88,93,97} in which the principal indication was prevention of RPL and 5 studies (88 pregnancies)^{50,69-71,96} in which LMWH was used to prevent preeclampsia, fetal growth restriction, or another adverse pregnancy outcome. The studies were heterogeneous with regard to whether coexistent thrombophilia was present. Where thrombophilia had been documented, the most common thrombophilic marker was antiphospholipid antibodies (247 pregnancies).

Complications in the group receiving LMWH for thromboprophylaxis, adverse pregnancy outcome, or unspecified indications

Complications are summarized in Table 3. In this group of patients there were no maternal deaths. VTE was reported in 22 women (0.84%; 95% CI, 0.53%-1.28%), 6 of whom had had previous VTE. There were 14 (0.54%; 95% CI, 0.29%-0.90%)

Table 3. Complications reported with LMWH use in pregnancy for different indications and different LMWHs

Indication and LMWH used	Total, no.	DVT, no. (%)	PE, no. (%)	Other or unspecified VTE, no. (%)	Arterial thrombosis, no. (%)	Severe antenatal bleeding, no. (%)	PPH exceeding 500 mL, no. (%)	Wound hematoma, no. (%)	Allergy, no. (%)	Low platelet count, no. (%)	Osteoporosis, no. (%)
Treatment											
Enoxaparin	105	1 (0.95)	0 (0)	0 (0)	0 (0)	1 (0.95)	1 (0.95)	0 (0)	2 (1.90)	1 (0.95)	0 (0)
Dalteparin	49	1 (2.04)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2.04)	0 (0)	0 (0)	0 (0)	0 (0)
Nadroparin	20	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Subtotal	174	2 (1.15)	0 (0)	0 (0)	0 (0)	1 (0.57)	2 (1.15)	0 (0)	2 (1.15)	1 (0.57)	0 (0)
Thromboprophylaxis											
Enoxaparin	855	7 (0.8)	3* (0.35)	0 (0)	9 (1.05)	4 (0.47)	10 (1.17)	0 (0)	1 (0.12)	2 (0.24)	0 (0)
Dalteparin	385	1† (0.26)	0 (0)	2 (0.52)	4 (1.04)	2 (0.52)	14‡ (3.6)	0 (0)	14 (3.63)	0 (0)	1 (0.26)
Nadroparin	33	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Certoparin	108	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Unspecified	55	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Thromboprophylaxis for RPL											
Enoxaparin	235	0 (0)	0 (0)	1 (0.43)	1 (0.43)	1 (0.43)	0 (0)	0 (0)	3 (1.30)	0 (0)	0 (0)
Dalteparin	110	2 (1.82)	1 (0.91)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Other	99	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Unspecified	3	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Unspecified											
Dalteparin	245	4 (1.63)	1 (0.41)	0 (0)	0 (0)	4 (1.63)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Nadroparin	420	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	18 (4.29)	0 (0)	0 (0)
Other/unspecified	55	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	17§ (30.9)	12 (21.8)	0 (0)	0 (0)
Subtotal	2603	14 (0.54)	5 (0.19)	3 (0.12)	14 (0.54)	11 (0.42)	24 (0.92)	17 (0.65)	48¶ (1.84)	2 (0.08)	1 (0.04)
Total	2777	16 (0.58)	5 (0.18)	3 (0.11)	14 (0.50)	12 (0.43)	26 (0.94)	17 (0.61)	50 (1.80)	3 (0.11)	1 (0.04)

No patients reported HIT.

*One PE occurred in a patient receiving a 20-mg/kg dose of enoxaparin.

†In a patient receiving a 2500-IU dose of dalteparin.

‡Nine had dextran.

§All less than 2 hours before cesarean.

¶Three patients had a general allergic reaction.

cases of DVT, 5 (0.19%; 95% CI, 0.06%-0.45%) PEs, and 3 (0.12%; 95% CI, 0.02%-0.34%) other venous thrombotic events. Arterial thrombotic events occurred in 14 pregnancies (0.54%; 95% CI, 0.29%-0.90%; all transient ischemic attacks occurred in women with antiphospholipid syndrome). Significant maternal bleeding occurred in 52 pregnancies (2.0%; 95% CI, 1.50%-2.61%), of which 11 (0.42%; 95% CI, 0.21%-0.75%) were classified as antenatal bleeding, 24 (0.92%; 95% CI, 0.59%-1.37%) were associated with primary obstetric causes at the time of delivery, and 17 (0.65%; 95% CI, 0.38%-1.04%) were associated with wound hematoma. Two patients (0.08%; 95% CI, 0.01%-0.28%) developed thrombocytopenia (platelet count < 100 × 10⁹ cells/L), but this was not induced by heparin or related to thrombosis. Allergic skin reactions occurred in 48 pregnancies (1.84%; 95% CI, 1.36%-2.44%), of which 3 were generalized, and there was a single case (0.04%; 95% CI, < 0.01%-0.21%) of osteoporotic fracture in a woman receiving dalteparin.

Use of regional anesthesia/analgesia

Only 14 studies on 440 pregnancies included any comment on the numbers of patients who received epidural or spinal analgesia or anesthesia without complications. There were no reported cases of epidural hematoma or hemorrhagic or neurologic complications. It was not possible, in most reports, to ascertain the temporal relationship to the LMWH injections, the form of regional technique used, or the dose of LMWH used in the patients receiving regional anesthesia or analgesia.

Pregnancy outcome

Pregnancy and neonatal outcome were not among the primary outcomes of this study and were not reported in all studies. Successful pregnancy outcome was defined as a live birth and excluded neonatal death. Data were insufficient to report on other pregnancy outcomes such as preeclampsia. Pregnancy outcome was reported in 2215 pregnancies treated with LMWH, with 94.7% successful outcomes. These were subdivided as follows: 370 pregnancies with LMWH given for RPL, with 85.4% successful outcomes, and 1845 pregnancies with LMWH given for thromboprophylaxis or the treatment of VTE, with 96.6% successful outcomes.

Overall complication rates for LMWH use in pregnancy

The rates of complications between the different LMWHs are reported in Table 3. Allergic skin reactions were reported significantly more commonly for nadroparin (18 of 530, 3.4%) and dalteparin (14 of 789, 1.8%) than for enoxaparin (6 of 1247, 0.48%). (Using the χ^2 test, $P = .061$ for nadroparin versus dalteparin, $P < .001$ for nadroparin versus enoxaparin, and $P = .004$ for dalteparin versus enoxaparin.)

Considering all studies of all LMWHs for any indication in pregnancy (Table 4), the rate of VTE was 24 of 2777 (0.86%; 95% CI, 0.55%-1.28%) and the rate of arterial thrombosis was 14 of 2777 (0.50%; 95% CI, 0.28%-0.84%), giving an overall rate of thrombosis of 38 of 2777 (1.37%; 95% CI, 0.97%-1.87%). The rates of significant bleeding were 12 of 2777 (0.43%; 95% CI, 0.22%-0.75%) for antenatal bleeding, 26 of 2777 (0.94%; 95% CI,

Table 4. Complications reported with LMWH use in pregnancy for all indications and all LMWHs

Complication	Rate, % (95% CI)
Thrombosis	1.37 (0.97-1.87)
Venous thromboembolism	0.86 (0.55-1.28)
Arterial thrombosis	0.50 (0.28-0.84)
Bleeding	1.98 (1.50-2.57)
Antenatal bleeding	0.43 (0.22-0.75)
PPH more than 500 mL	0.94 (0.61-1.37)
Wound hematoma	0.61 (0.36-0.98)
Allergy	1.80 (1.34-2.37)
Thrombocytopenia	
Platelets	0.11 (0.02-0.32)
HIT	0.00 (0.00-0.11)
Osteoporosis	0.04 (< 0.01-0.20)

0.61%-1.37%) for PPH, and 17 of 2777 (0.61%, 95% CI, 0.36%-0.98%) for wound hematoma, giving an overall rate of significant bleeding of 55 of 2777 (1.98%; 95% CI, 1.50%-2.57%). The reported rate of allergic skin reactions was 50 of 2777 (1.80%; 95% CI, 1.34%-2.37%). There were no reported cases of HIT, although thrombocytopenia (platelet count < 100×10^9 cells/L) was reported in 3 (0.11%; 95% CI, 0.02%-0.32%) cases. There was one case (0.04%; 95% CI < 0.01%-0.20%) of osteoporotic fracture.

Discussion

These data demonstrate a risk of recurrence VTE of 1.15% when treatment doses of LMWH were used to treat VTE in pregnancy. This compares favorably with recurrence rates of 5% to 8% reported in trials carried out in nonpregnant patients treated with LMWH or UFH followed by coumarin therapy who are followed up for 3 to 6 months,^{100,101} and it confirms that LMWHs are effective in the treatment of acute VTE in pregnancy. In addition, when LMWH was used in lower doses for thromboprophylaxis in women with acute VTE (following initial treatment with UFH), previous VTE, or in the presence of known thrombophilia and/or additional risk factors, VTE developed in only 0.84% of pregnancies and arterial events associated with antiphospholipid syndrome occurred in only 0.54% pregnancies, giving an overall rate of 1.38% for thrombosis. These data demonstrate that LMWHs provide effective thromboprophylaxis in pregnancy. Although not directly comparable, the risk of recurrent antenatal VTE was 2.4% in one well-documented study of women with a single previous VTE subsequently managed during pregnancy without any specific thromboprophylaxis.¹⁰²

One of the advantages of LMWH over UFH is the reduced risk of bleeding.⁹ This is of particular relevance in obstetric practice where PPH remains the most common cause of severe obstetric morbidity.¹⁰³ It is reassuring, therefore, to note that LMWHs are not associated with an increased risk of severe bleeding peripartum. The observed rate of major bleeding (1.98%) compares favorably with the rate of massive hemorrhage (0.7%) from one prospective study without the use of LMWH (in which massive hemorrhage was defined as blood loss > 1500 mL).¹⁰³ In most cases of PPH, there was a primary obstetric cause for the bleeding, such as uterine atony or vaginal lacerations, although the blood loss may have been increased by the concomitant use of LMWH.

The observed rate of allergic skin reactions (1.80%) is higher than that reported by Sanson et al (0.6%) in a study of 486 patients.¹³ The data shown in Table 3 suggest that allergic skin

reactions were significantly more common with the use of dalteparin and nadroparin than with enoxaparin. However, there was no consistency between studies regarding the reporting of allergic reactions, and not all reports listed skin complications as an a priori outcome. In addition, one paper specifically focused on skin complications and studied nadroparin.²¹ Thus, although we have found a significant difference in the incidence of skin complications, this should be interpreted with caution.

It is known that the risk of HIT is substantially lower with LMWH use compared with UFH.^{9,10} Nonetheless, it is reassuring that in 2777 pregnancies with LMWH use, no cases of HIT associated with thrombosis were reported. It is likely that there were many more than the 3 cases of thrombocytopenia (defined as platelet count < 100×10^9 cells/L), because gestational thrombocytopenia may occur in up to 7% of normal pregnancies,¹⁰⁴ as well as in pregnancy complications such as preeclampsia; however, authors may not have reported these episodes of thrombocytopenia if they were not attributed to the use of LMWH. Although these data are reassuring, HIT has been reported with LMWH use in pregnancy; however, this was in a patient with known HIT prior to pregnancy, with recurrent thrombocytopenia but no thrombotic complication following the use of dalteparin in pregnancy.¹⁰⁵ We are aware of at least one unreported, but well-documented, additional case with low platelet counts and thrombosis but no antibody information (M. Rodger, oral communication, November 2004). In addition, in one case included within this systematic review, a patient with a skin reaction to LMWH was also found to have a positive platelet aggregation assay for HIT but no thrombocytopenia or thrombosis.⁹⁹ The low rate of HIT in this study is consistent with the recent recommendation of the American College of Chest Physicians (ACCP) that there is no need to monitor platelet count in pregnant patients treated exclusively with LMWH.¹⁰⁶

These data also substantiate the results of theoretical⁹ and practical¹¹ studies showing a much reduced risk of LMWH compared with UFH for heparin-induced osteoporosis. The overall risk of this complication was 0.04%, derived from a single well-documented case of postpartum osteoporotic vertebral fracture in a woman who had received a high dose (15 000 IU daily) of dalteparin for a total of 36 weeks.⁴⁵ However, 3 cases of osteoporotic fractures in association with tinzaparin use in pregnancy in one center have been reported recently, suggesting that complacency in this area would be premature.¹⁰⁷ Whether this finding is causally related to tinzaparin therapy, and whether this risk applies to other LMWHs, is unclear and further consideration of this complication is warranted.

A major limitation of the present study is that many of the studies included in the analysis were retrospective and, therefore, data concerning complications of LMWH were reliant on patient or clinician recall or were extracted from obstetric databases rather than a systematic prospective collection. Another limitation relates to the heterogeneity of the patients included. Thus, the risks of thrombosis and of adverse events were extremely variable both within and between studies. We have made some allowance for this by classifying the exposed pregnancies depending on the indication for LMWH use, but the patient populations, particularly in the thromboprophylactic group, remained extremely diverse.

It is not possible to comment on the effect of LMWHs on rates of fetal and neonatal loss in the absence of properly conducted randomized controlled trials. Many of the women in these studies were at risk of RPL and late fetal loss and neonatal death from prematurity because of the presence of congenital or acquired

thrombophilia as well as a previous history of adverse pregnancy outcome. However, in general terms, the results reported here would be consistent with a beneficial effect of LMWH on rates of pregnancy loss. The successful pregnancy rate reported in this analysis of women receiving LMWH for previous adverse pregnancy outcomes, such as recurrent fetal loss, was over 80%. This rate is consistent with that found in randomized trials of antithrombotic therapy (UFH or LMWH) in women with previous pregnancy loss associated with antiphospholipid syndrome or inheritable thrombophilia, where such intervention resulted in a significant and substantial improvement in pregnancy outcome.^{16,108}

In conclusion, in this study, the largest systematic review of LMWH use in pregnancy, it has been confirmed that LMWH is safe

and effective for treating and preventing thrombosis in pregnancy. It is important that clinicians continue to justify the use of LMWH in pregnancy for other indications such as the prevention of adverse pregnancy outcome.¹⁶ We welcome further randomized controlled studies exploring the use of LMWH for these indications.

Acknowledgment

We gratefully acknowledge the statistical help of Paul Seed, Division of Reproductive Health, Endocrinology and Development (King's College London), Maternal and Fetal Research Unit, St Thomas' Hospital, London, United Kingdom.

References

- Confidential Enquiries into Maternal Deaths in the United Kingdom. The fifth report: why mothers die 1997-1999. London, United Kingdom; RCOG Press: 2001.
- McColl MD, Ellison J, Greer IA, Tait RC, Walker ID. Prevalence of the post-thrombotic syndrome in young women with previous venous thromboembolism. *Br J Haematol*. 2000;108:272-274.
- Bates SM, Ginsberg JS. Anticoagulants in pregnancy: fetal effects. *Baillieres Clin Obstet Gynaecol*. 1997;11:479-488.
- Greer IA, De Swiet M. Thrombosis prophylaxis in obstetrics and gynaecology. *Br J Obstet Gynaecol*. 1993;100:37-40.
- Scottish Intercollegiate Guidelines Network (SIGN). Guideline 62: prophylaxis of venous thromboembolism. Edinburgh, United Kingdom; SIGN: 2002.
- Scottish Intercollegiate Guidelines Network (SIGN). Guideline 36: antithrombotic therapy. Edinburgh, United Kingdom; SIGN: 1999.
- Hague WM, North RA, Gallus AS, et al, a Working Group on behalf of the Obstetric Medicine Group of Australasia. Anticoagulation in pregnancy and the puerperium. *Med J Aust*. 2001;175:258-263.
- Greer IA. Thrombosis in pregnancy: maternal and fetal issues. *Lancet*. 1999;353:1258-1265.
- Nelson-Piercy C. Hazards of heparin: allergy, heparin-induced thrombocytopenia and osteoporosis. *Baillieres Clin Obstet Gynaecol*. 1997;11:489-509.
- Warkentin TE, Levine MN, Hirsh J, et al. Heparin-induced thrombocytopenia in patients treated with low-molecular-weight heparin or unfractionated heparin. *N Engl J Med*. 1995;332:1330-1335.
- Bates S, Greer IA, Hirsh J, Ginsberg JS. Use of antithrombotic agents during pregnancy. *Chest*. 2004;126:627S-644S.
- Monreal M. Long-term treatment of venous thromboembolism with low-molecular-weight heparin. *Curr Opin Pulm Med*. 2000;6:326-329.
- Sanson BJ, Lensing AW, Prins MH, et al. Safety of low-molecular-weight heparin in pregnancy: a systematic review. *Thromb Haemost*. 1999;81:668-672.
- Royal College of Obstetricians and Gynaecologists (RCOG). Clinical green top guidelines, guideline 28: thromboembolic disease in pregnancy and the puerperium. RCOG, 2001. <http://www.rcog.org.uk/guidelines.asp?PageID=106&GuidelineID=20>. Accessed October 27, 2004.
- Royal College of Obstetricians and Gynaecologists (RCOG). Clinical green top guidelines, guideline 37: thromboprophylaxis during pregnancy, labour and after vaginal delivery. RCOG, 2004. <http://www.rcog.org.uk/guidelines.asp?PageID=106&GuidelineID=62>. Accessed October 27, 2004.
- Gris JC, Mercier E, Quere I, et al. Low-molecular-weight heparin versus low-dose aspirin in women with one fetal loss and a constitutional thrombophilic disorder. *Blood*. 2004;103:3695-3699.
- Oran B, Lee-Paritz A, Ansell J. Low molecular weight heparin for the prophylaxis of thromboembolism in women with prosthetic mechanical heart valves during pregnancy. *Thromb Haemost*. 2004;92:747-751.
- Kujovich JL. Thrombophilia and pregnancy complications. *Am J Obstet Gynecol*. 2004;191:412-424.
- Anand SS, Brimble S, Ginsberg JS. Management of iliofemoral thrombosis in a pregnant patient with heparin resistance. *Arch Intern Med*. 1997;157:815-816.
- Amout MS, Kazma H, Khalil A, et al. Is there a safe anticoagulation protocol for pregnant women with prosthetic valves? *Clin Exp Obstet Gynecol*. 1998;25:101-104.
- 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 Hemost*. 2003;1:859-861.
- Bar J, Cohen-Sacher B, Hod M, Blickstein D, Lahav J, Merlob P. Low-molecular-weight heparin for thrombophilia in pregnant women. *Int J Gynaecol Obstet*. 2000;69:209-213.
- Berndt N, Khan I, Gallo R. A complication in anticoagulation using low-molecular weight heparin in a patient with a mechanical valve prosthesis: a case report. *J Heart Valve Dis*. 2000;9:844-846.
- Blomback M, Bremme K, Hellgren M, Siegbahn A, Lindberg H. Thromboprophylaxis with low molecular mass heparin, 'Fragmin' (dalteparin), during pregnancy: a longitudinal safety study. *Blood Coagul Fibrinolysis*. 1998;9:1-9.
- Boda Z, Laszlo P, Rejto L, et al. Low molecular weight heparin as thromboprophylaxis in familial thrombophilia during the whole period of pregnancy [letter]. *Thromb Haemost*. 1996;76:128.
- Bonnar J, Norris LA, Greene R. Low molecular weight heparin for thromboprophylaxis during caesarean section. *Thromb Res*. 1999;96:317-322.
- Brenner B, Hoffman R, Blumenfeld Z, Weiner Z, Younis JS. Gestational outcome in thrombophilic women with recurrent pregnancy loss treated by enoxaparin. *Thromb Haemost*. 2000;83:693-697.
- Burrows RF, Gan ET, Gallus AS, Wallace EM, Burrows EA. A randomised double-blind placebo controlled trial of low molecular weight heparin as prophylaxis in preventing venous thrombotic events after caesarean section: a pilot study. *BJOG*. 2001;108:835-839.
- Carp H, Dolitzky M, Inbal A. Thromboprophylaxis improves the live birth rate in women with consecutive recurrent miscarriages and hereditary thrombophilia. *J Thromb Haemost*. 2003;1:433-438.
- Crowther MA, Spitzer K, Julian J, et al. Pharmacokinetic profile of a low-molecular weight heparin (reviparin) in pregnant patients: a prospective cohort study. *Thromb Res*. 2000;98:133-138.
- Daskalakis G, Antsaklis A, Papageorgiou I, Michalakis S. Thrombosis prophylaxis after treatment during pregnancy. *Eur J Obstet Gynecol Reprod Biol*. 1997;74:165-167.
- de Boer K, Heyboer H, ten Cate JW, Borm JJ, van Ginkel CJ. Low molecular weight heparin treatment in a pregnant woman with allergy to standard heparins and heparinoid [letter]. *Thromb Haemost*. 1989;61:148.
- Dullitzki M, Pautzer R, Langevitz P, Pras M, Many A, Schiff E. Low-molecular-weight heparin during pregnancy and delivery: preliminary experience with 41 pregnancies. *Obstet Gynecol*. 1996;87:380-383.
- Ebina Y, Yamada H, Kato EH, Yamamoto R, Sakuragi N, Fujimoto S. Thromboprophylaxis with low molecular weight heparin in thrombophilia-complicated pregnancy. *J Obstet Gynaecol Res*. 2002;28:251-257.
- Ellison J, Walker ID, Greer IA. Antenatal use of enoxaparin for prevention and treatment of thromboembolism in pregnancy. *BJOG*. 2000;107:1116-1121.
- Ellison J, Thomson AJ, Walker ID, Greer IA. Use of enoxaparin in a pregnant woman with a mechanical heart valve prosthesis. *BJOG*. 2001;108:757-759.
- Farquharson RG, Quenby S, Greaves M. Antiphospholipid syndrome in pregnancy: a randomized, controlled trial of treatment. *Obstet Gynecol*. 2002;100:408-413.
- Finkelstein Y, Aloni D, Kimia A, Sommer R, Sirota L. Deep venous thrombosis in a preterm newborn of a mother with activated protein C resistance. *Clin Pediatr (Phila)*. 1998;37:373-376.
- Funai EF, Klein SA, Lockwood CJ. Successful pregnancy outcome in a patient with both congenital hypofibrinogenemia and protein S deficiency. *Obstet Gynecol*. 1997;89:858.
- Gibson JL, Ekevall K, Walker I, Greer IA. Puerperal thromboprophylaxis: comparison of the anti-Xa activity of enoxaparin and unfractionated heparin. *Br J Obstet Gynaecol*. 1998;105:795-797.
- Gillis S, Shushan A, Eldor A. Use of low molecular weight heparin for prophylaxis and treatment of thromboembolism in pregnancy. *Int J Gynaecol Obstet*. 1992;39:297-301.
- Granger KA, Farquharson RG. Obstetric outcome in antiphospholipid syndrome. *Lupus*. 1997;6:509-513.
- Gris JC, Neveu S, Tailland ML, Courtieu C, Mares P, Schved JF. Use of a low-molecular weight heparin (enoxaparin) or of a phenformin-like substance (moroxydine chloride) in primary early recurrent aborters with an impaired fibrinolytic capacity. *Thromb Haemost*. 1995;73:362-367.

44. Hamersley S, Landy H. Low-molecular-weight heparin is associated with less peripartum blood loss than unfractionated heparin [abstract]. *Am J Obstet Gynecol.* 1998;178(suppl 1):66S.
45. Hunt BJ, Doughty HA, Majumdar G, et al. Thromboprophylaxis with low molecular weight heparin (Fragmin) in high risk pregnancies. *Thromb Haemost.* 1997;77:39-43.
46. Hunt BJ, Gattens M, Khamashta M, Nelson-Piercy C, Almeida A. Thromboprophylaxis with unmonitored intermediate-dose low molecular weight heparin in pregnancies with a previous arterial or venous thrombotic event. *Blood Coagul Fibrinolysis.* 2003;14:735-739.
47. Izaguirre R, De La Pena A, Ramirez A, Cortina E, Huerta M, Salazar E. Anti-Xa activity with low-molecular-weight heparin, enoxaparin, during pregnancy in women with mechanical heart valves. *Proc West Pharmacol Soc.* 2002;45:127-128.
48. Jacobsen AF, Qvigstad E, Sandset PM. Low molecular weight heparin (dalteparin) for the treatment of venous thromboembolism in pregnancy. *BJOG.* 2003;110:139-144.
49. Kiss H, Egarter C, Asseryanis E, Putz D, Kneussl M. Primary pulmonary hypertension in pregnancy: a case report. *Am J Obstet Gynecol.* 1995;172:1052-1054.
50. Kupfermink MJ, Fait G, Many A, et al. Low-molecular-weight heparin for the prevention of obstetric complications in women with thrombophilias. *Hypertens Pregnancy.* 2001;20:35-44.
51. Laifer SA, Stillier RJ, Dunston-Boone G, Whetham JC. Low-molecular weight heparin for treatment of pulmonary embolism in a pregnant woman. *Thromb Haemost.* 1999;82:1361-1362.
52. Lee LH, Liauw PC, Ng AS. Low molecular weight heparin for thromboprophylaxis during pregnancy in 2 patients with mechanical mitral valve replacement. *Thromb Haemost.* 1996;76:628-630.
53. Lepercq J, Conard J, Borel-Derlon A, et al. Venous thromboembolism during pregnancy: a retrospective study of enoxaparin safety in 624 pregnancies. *BJOG.* 2001;108:1134-1140.
54. Lev-Ran O, Kramer A, Gurevitch J, Shapira I, Mohr R. Low-molecular-weight heparin for prosthetic heart valves: treatment failure. *Ann Thorac Surg.* 2000;69:264-265.
55. Leyh RG, Fischer S, Ruhparwar A, Haverich A. Anticoagulation for prosthetic heart valves during pregnancy: is low-molecular-weight heparin an alternative? *Eur J Cardiothorac Surg.* 2002;21:577-579.
56. Lima F, Khamashta MA, Buchanan NM, Kerslake S, Hunt BJ, Hughes GR. A study of sixty pregnancies in patients with the antiphospholipid syndrome. *Clin Exp Rheumatol.* 1996;14:131-136.
57. Lindqvist PG, Dahlback B. Bleeding complications associated with low molecular weight heparin prophylaxis during pregnancy. *Thromb Haemost.* 2000;84:140-141.
58. Macklon NS, Greer IA, Reid AW, Walker ID. Thrombocytopenia, antithrombin deficiency and extensive thromboembolism in pregnancy: treatment with low-molecular-weight heparin. *Blood Coagul Fibrinolysis.* 1995;6:672-675.
59. Manoharan A. Use of low molecular weight heparin during pregnancy. *J Clin Pathol.* 1994;47:94-95.
60. Many A, Pauzner R, Carp H, Langevitz P, Martinowitz U. Treatment of patients with antiphospholipid antibodies during pregnancy. *Am J Reprod Immunol.* 1992;28:216-218.
61. Melissari E, Parker CJ, Wilson NV, et al. Use of low molecular weight heparin in pregnancy. *Thromb Haemost.* 1992;68:652-656.
62. Miyashita Y, Waguri M, Nakanishi I, Suehara N, Fujita T. Successful pregnancy with low molecular weight heparin in two women with recurrent miscarriage of unknown etiology. *Am J Reprod Immunol.* 2003;49:90-92.
63. Nelson-Piercy C, Letsky EA, de Swiet M. Low-molecular-weight heparin for obstetric thromboprophylaxis: experience of sixty-nine pregnancies in sixty-one women at high risk. *Am J Obstet Gynecol.* 1997;176:1062-1068.
64. Ojukwu C, Jenkinson SD, Obeid D. Deep vein thrombosis in pregnancy and heparin hypersensitivity. *Br J Obstet Gynaecol.* 1996;103:934-936.
65. Oles D, Berryessa R, Campbell K, Bhatti MA. Emergency redo mitral valve replacement in a 27-year-old pregnant female with a clotted prosthetic mitral valve, preoperative fetal demise and postoperative ventricular assist device: a case report. *Perfusion.* 2001;16:159-164.
66. Pauzner R, Dulitzki M, Langevitz P, Livneh A, Kenett R, Many A. Low molecular weight heparin and warfarin in the treatment of patients with antiphospholipid syndrome during pregnancy. *Thromb Haemost.* 2001;86:1379-1384.
67. Pettila V, Kaaja R, Leinonen P, Ekblad U, Kataja M, Ikkala E. Thromboprophylaxis with low molecular weight heparin (dalteparin) in pregnancy. *Thromb Res.* 1999;96:275-282.
68. Priollet P, Roncato M, Aiach M, Housset E, Poissonnier MH, Chavanie J. Low-molecular-weight heparin in venous thrombosis during pregnancy. *Br J Haematol.* 1986;63:605-606.
69. Rasmussen C, Wadt J, Jacobsen B. Thromboembolic prophylaxis with low molecular weight heparin during pregnancy. *Int J Gynaecol Obstet.* 1994;47:121-125.
70. Rey E, Rivard GE. Prophylaxis and treatment of thromboembolic diseases during pregnancy with dalteparin. *Int J Gynaecol Obstet.* 2000;71:19-24.
71. Riyazi N, Leeda M, de Vries JI, Huijgens PC, van Geijn HP, Dekker GA. Low-molecular-weight heparin combined with aspirin in pregnant women with thrombophilia and a history of preeclampsia or fetal growth restriction: a preliminary study. *Eur J Obstet Gynecol Reprod Biol.* 1998;80:49-54.
72. Roberts N, Ross D, Flint SK, Arya R, Blott M. Thromboembolism in pregnant women with mechanical prosthetic heart valves anticoagulated with low molecular weight heparin. *BJOG.* 2001;108:327-329.
73. Rodie VA, Thomson AJ, Stewart FM, Quinn AJ, Walker ID, Greer IA. Low molecular weight heparin for the treatment of venous thromboembolism in pregnancy: a case series. *BJOG.* 2002;109:1020-1024.
74. Rowan JA, McCowan LM, Raudkivi PJ, North RA. Enoxaparin treatment in women with mechanical heart valves during pregnancy. *Am J Obstet Gynecol.* 2001;185:633-637.
75. Rowan JA, McLintock C, Taylor RS, North RA. Prophylactic and therapeutic enoxaparin during pregnancy: indications, outcomes and monitoring. *Aust N Z J Obstet Gynaecol.* 2003;43:123-128.
76. Rowlands S, Lahoud R, Hertzberg M, Nicholl M. Thromboembolism treated with low molecular weight heparin in a pregnancy complicated by major placenta praevia: a case report. *J Obstet Gynaecol Res.* 1997;23:205-208.
77. Schambeck CM, Eberl E, Geisen U, Grossmann R, Keller F. The impact of dalteparin (Fragmin) on thrombin generation in pregnant women with venous thromboembolism: significance of the factor V Leiden mutation. *Thromb Haemost.* 2001;85:782-786.
78. Schneider DM, von Tempelhoff GF, Heilmann L. Retrospective evaluation of the safety and efficacy of low-molecular-weight heparin as thromboprophylaxis during pregnancy. *Am J Obstet Gynecol.* 1997;177:1567-1568.
79. Sephton V, Farquharson RG, Topping J, et al. A longitudinal study of maternal dose response to low molecular weight heparin in pregnancy. *Obstet Gynecol.* 2003;101:1307-1311.
80. Shefras J, Farquharson RG. Bone density studies in pregnant women receiving heparin. *Eur J Obstet Gynecol Reprod Biol.* 1996;65:171-174.
81. Sivakumaran M, Ghosh K, Munks R, Gelsthorpe K, Tan L, Wood JK. Delayed cutaneous reaction to unfractionated heparin, low molecular weight heparin and danaparoid. *Br J Haematol.* 1994;86:893-896.
82. Sorensen HT, Johnsen SP, Larsen H, Pedersen L, Nielsen GL, Moller M. Birth outcomes in pregnant women treated with low-molecular-weight heparin. *Acta Obstet Gynecol Scand.* 2000;79:655-659.
83. Sturridge F, de Swiet M, Letsky E. The use of low molecular weight heparin for thromboprophylaxis in pregnancy. *Br J Obstet Gynaecol.* 1994;101:69-71.
84. Subtil D, Deruelle P, Trillot N, Jude B. Preclinical phase of polycythemia vera in pregnancy. *Obstet Gynecol.* 2001;98(pt 2):945-947.
85. Tam WH, Wong KS, Yuen PM, Leung TN, Li CY. Low-molecular-weight heparin and thromboembolism in pregnancy. *Lancet.* 1999;353:932.
86. Thomson AJ, Walker ID, Greer IA. Low-molecular-weight heparin for immediate management of thromboembolic disease in pregnancy [letter]. *Lancet.* 1998;352:1904.
87. Triolo G, Ferrante A, Ciccia F, et al. Randomized study of subcutaneous low molecular weight heparin plus aspirin versus intravenous immunoglobulin in the treatment of recurrent fetal loss associated with antiphospholipid antibodies. *Arthritis Rheum.* 2003;48:728-731.
88. Tzafettas J, Mamopoulos A, Anapliotis A, et al. Thromboprophylaxis throughout pregnancy in women with previous history of recurrent miscarriages of unknown aetiology. *Clin Exp Obstet Gynecol.* 2002;29:267-270.
89. Ulander VM, Stenqvist P, Kaaja R. Treatment of deep venous thrombosis with low-molecular-weight heparin during pregnancy. *Thromb Res.* 2002;106:13-17.
90. van Wijk FH, Wolf H, Piek JM, Buller HR. Administration of low molecular weight heparin within two hours before caesarean section increases the risk of wound haematoma. *BJOG.* 2002;109:955-957.
91. Vural KM, Ozatik MA, Uncu H, et al. Pregnancy after mechanical mitral valve replacement. *J Heart Valve Dis.* 2003;12:370-376.
92. Wahlberg TB, Kher A. Low molecular weight heparin as thromboprophylaxis in pregnancy. A retrospective analysis from 14 European clinics. *Haemostasis.* 1994;24:55-56.
93. Younis JS, Ohel G, Brenner B, Haddad S, Lanir N, Ben Ami M. The effect of thromboprophylaxis on pregnancy outcome in patients with recurrent pregnancy loss associated with factor V Leiden mutation. *BJOG.* 2000;107:415-419.
94. Lamon D, Chang CK, Hruska L, Kerlakian G, Smith JM. Superior vena cava thrombosis after in vitro fertilization: case report and review of the literature. *Ann Vasc Surg.* 2000;14:283-285.
95. Casele HL, Laifer SA. Prospective evaluation of bone density in pregnant women receiving the low molecular weight heparin enoxaparin sodium. *J Matern Fetal Med.* 2000;9:122-125.
96. Spaanderman ME, Aardenburg R, Ekhardt TH, et al. Non-pregnant circulatory volume status predicts subsequent pregnancy outcome in normotensive thrombophilic formerly preeclamptic women. *Eur J Obstet Gynecol Reprod Biol.* 2001;95:218-221.
97. Backos M, Rai R, Thomas E, Murphy M, Dore C, Regan L. Bone density changes in pregnant women treated with heparin: a prospective, longitudinal study. *Hum Reprod.* 1999;14:2876-2880.
98. Magdelaine A, Verdy E, Coulet F, et al. Deep vein thrombosis during enoxaparin prophylaxis

treatment in a young pregnant woman homozygous for factor V Leiden and heterozygous for the G127 → a mutation in the thrombomodulin gene. *Blood Coagul Fibrinolysis*. 2000;11:761-765.

99. Myers B, Westby J, Strong J. Prophylactic use of danaparoid in high-risk pregnancy with heparin-induced thrombocytopenia-positive skin reaction. *Blood Coagul Fibrinolysis*. 2003;14:485-487.

100. Hirsh J, Warkentin TE, Shaughnessy SG, et al. Heparin and low-molecular weight heparin: mechanism of action, pharmacokinetics, dosing, monitoring, efficacy, and safety. *Chest*. 2001; 119(suppl 1):64S-94S.

101. Yusen RD, Gage BF. Outpatient treatment of acute thromboembolic disease. *Clin Chest Med*. 2003;24:49-61.

102. Brill-Edwards P, Ginsberg JS, Gent M, et al, Recurrence of Clot in This Pregnancy Study Group. Safety of withholding heparin in pregnant women with a history of venous thromboembolism. *N Engl J Med*. 2000;343:1439-1444.

103. Waterstone M, Bewley S, Wolfe C. Incidence and predictors of severe obstetric morbidity: case-control study. *BMJ*. 2001;322:1089-1093.

104. Burrows RF, Kelton JG. Thrombocytopenia at delivery: a prospective survey of 6715 deliveries. *Am J Obstet Gynecol*. 1990;162:731-734.

105. Huhle G, Geberth M, Hoffmann U, Heene DL, Harenberg J. Management of heparin-associated thrombocytopenia in pregnancy with subcutaneous r-hirudin. *Gynecol Obstet Invest*. 2000;49:67-69.

106. Warkentin TE, Greinacher A. Heparin-induced thrombocytopenia: recognition, treatment, and prevention: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest*. 2004;126(3 suppl):311S-337S.

107. Byrd LM, Johnston TA, Shlach C, Hay CRM. Osteoporotic fracture and low molecular weight heparin [abstract]. *J Obstet Gynaecol*. 2004;24(suppl 1):S11.

108. Rai R, Cohen H, Dave M, Regan L. Randomised controlled trial of aspirin and aspirin plus heparin in pregnant women with recurrent miscarriage associated with phospholipid antibodies (or antiphospholipid antibodies). *BMJ*. 1997;314:253-257.

Erratum

In the article by Müller et al entitled “Transmembrane CEACAM1 affects integrin-dependent signaling and regulates extracellular matrix protein-specific morphology and migration of endothelial cells,” which appeared in the May 15, 2005, issue of *Blood* (Volume 105:3925-3934), the wild-type LN panel in Figure 6Ai is incorrect. The correct Figure 6A appears below.

