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 thrombocytopenia 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)

Introduction

Pulmonary embolism (PE) remains the leading cause of direct maternal death in the United Kingdom[1] 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 administration[8]; 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.

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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.

valves were excluded because these have recently been reviewed elsewhere[17] 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 hypertension[49]; 2 studies of 18 pregnancies in 16 patients[83] and 4 pregnancies[86] 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								0 (0)			
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											0 (0)
Enoxaprin	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 $< 100 \times 10^9$ 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 $< 100 \times 10^9$ 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 $< 100 \times 10^9$ 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 theoretical[9] and practical[11] 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.

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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.