Evaluation of an Optimal Dose of Low-Molecular-Weight Heparin for Thromboprophylaxis in Pregnant Women at Risk of Thrombosis Using Coagulation Activation Markers

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Key Words

Thromboprophylaxis ·
Low-molecular-weight heparin · Pregnancy ·
Coagulation activation markers ·
Thrombin-antithrombin · D-dimers

Abstract

There is no consensus on the dose of low-molecular-weight (LMW) heparin for thromboprophylaxis in pregnant women at increased risk of thrombosis. Based upon monitoring with anti-factor Xa activity, the studies showed conflicting results suggesting either fixed dosages throughout the pregnancy or dosages adapted to the gestational age. We tested whether monitoring thromboprophylaxis with D-dimers and thrombin-antithrombin complexes (TAT) would provide additional information on the optimal dose of LMW

heparin. Women (165 women and 202 pregnancies) with hereditary or acquired thrombophilia or a history of thrombosis were considered to receive prophylactic LMW heparin therapy. All women received initially 5,000 IU/day of dalteparin s.c. All further dosages were determined solely on the basis of TAT and/or D-dimer values which were determined every 2–3 weeks. As soon as one of these values increased above the normal range, the dose of LMW heparin was adjusted. In 84.6% of all pregnancies, TAT and/or D-dimer values increased above the normal range once or more during the pregnancy. Consequently, the dose of LMW heparin had to be adjusted at least once over the course of the pregnancy. The mean daily dose of LMW heparin increased from 5,000 to 11,200 U between the 6th and 40th week of gestation. Adverse effects included one ma-

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for bleeding and six local complications, but no thromboembolic event. In conclusion, increasing doses of LMW heparin are needed to keep TAT and D-dimers within the normal range during pregnancy. Hence, to suppress thrombin generation, apparently, the dosage of LMW heparin should be adjusted to the gestational age rather than using fixed doses throughout the pregnancy. However, it remains to be further established whether elevated TAT and D-dimers truly reflect a prothrombotic state during pregnancy.

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Introduction

Although unfractionated heparin is still widely considered as the anticoagulant of first choice for obstetrical thromboprophylaxis, there is increasing evidence that low-molecular-weight (LMW) heparin provides a safe anticoagulation in pregnancy [1]. However, the adequate dose of LMW heparin is still under debate. While some studies have indicated that, based upon anti-factor Xa levels, thromboprophylaxis with a fixed dose of LMW heparin throughout the pregnancy seemed to be effective [2–4], other studies have shown that, also based upon anti-factor Xa levels, the dose of LMW heparin should be permanently adjusted to the gestational age probably due to increasing heparin requirements [5–7].

In the late 80s and early 90s, there was considerable interest in the clinical evaluation of coagulation activation markers such as thrombin-antithrombin complexes (TAT), D-dimers, or prothrombin fragment (F1 + 2). In particular, it was thought that the determination of these markers would help to assess the individual risk of thrombosis more accurately. Several studies have indeed shown that patients with a clearly increased risk of venous or arterial thromboembolic events (e.g.

cancer, atrial fibrillation or surgery) had often elevated levels of TAT, F1 + 2, and D-dimers [8–10]. Consequently, elevation of activation markers has been suggested to represent a hypercoagulable state and might justify the onset of thromboprophylaxis. However, meanwhile it has become clear that activation markers are poor predictors of thromboembolism since the specificity is rather low. The only widely accepted usefulness of D-dimers (more than TAT) is their negative predictive value in the diagnosis of deep venous thrombosis. In addition, several reports presented evidence that activation markers may be a helpful tool to judge the effectiveness of anticoagulant treatment and to optimize heparin therapy, although this strategy has not been adopted in daily routine [11–14].

In 1992, we performed a preliminary study to investigate whether the use of TAT and D-dimers would help to find an optimal dosage of unfractionated heparin [15]. The data showed that monitoring prophylaxis with unfractionated heparin based on TAT and D-dimers was feasible and safe. In addition, it became evident that the heparin requirements changed over the course of the pregnancy. When compared to conventional-dose regimens, doses were generally lower in the first half of the pregnancy but gradually increased to equal or even higher doses in the second half. Based on these initial observations, we wanted to evaluate whether monitoring thromboprophylaxis with D-dimers and TAT would provide additional information on the optimal dose of LMW heparin and would help to clarify the discrepant results of studies using anti-factor Xa activity for monitoring. This report now presents the experience of 202 high-risk pregnancies treated with LMW heparin monitored solely by TAT and D-dimer values.

Patients and Methods

Women

Pregnant women were considered to be at increased risk of thrombosis if one of the following criteria was found: (1) hereditary thrombophilia with a history of thromboembolism including activated protein C resistance, antithrombin deficiency, protein C deficiency, or protein S deficiency; (2) acquired thrombophilia with a history of thromboembolism including antiphospholipid antibody syndrome, cancer, obesity and severe varicose veins; (3) personal history of idiopathic (without a risk factor), multiple (>2 thrombotic episodes) or pregnancy-related thromboembolism, or (4) a strong family history of thromboembolism (>2 family members). All thromboembolic episodes were objectively identified by either venography, ultrasonography, or perfusion-ventilation lung scans. Exclusion criteria were: mechanical prosthetic valves, anticoagulation with coumarins, bleeding disorders, multifetal gestations, abortions, and nonthrombotic obstetrical complications. Between 1993 and 1999, 165 women (202 pregnancies) were included in the protocol, while 8 women were excluded. The mean age was 28.3 years (range 15–41). The clinical characteristics of the 165 women are summarized in table 1.

Diagnosis of Thrombophilia

In all women, testing of thrombophilia was performed before or after pregnancy. Activated protein C resistance was determined using the Coatest APC resistance assay (Chromogenix, Mölndal, Sweden). From 1995 on, the new test generation was used where the patient's plasma was mixed with factor-V-deficient plasma at a ratio of 1:4. To diagnose antithrombin deficiency, protein C deficiency, and protein S deficiency, both a functional and an immunological assay were performed. Functional antithrombin, protein C, and protein S were determined using chromogenic substrate assays from Chromogenix, Dade-Behring (Marburg, Germany), and Stago (Paris, France), respectively. Immunological antithrombin and protein C levels were determined by immunoelectrophoresis. Protein S (total and free protein S) was measured immunologically by a commercial ELISA kit from Stago. To screen for antiphospholipid antibodies, plasma was tested for lupus anticoagulant activity with an aPTT-based coagulation assay (Dade-Behring) and/or serum was tested for anticardiolipin IgG/IgM and antiphosphatidylserine IgG/IgM using an ELISA as described previously [16].

Table 1. Clinical characteristics of the study women

	Women	Pregnancies
Hereditary thrombophilia with history of thrombosis		
Activated protein C resistance	37	41
Protein C deficiency	5	7
Protein S deficiency	2	2
Antithrombin deficiency	1	1
Acquired thrombophilia		
Antiphospholipid antibody syndrome	3	4
Other (cancer, obesity, severe varicose veins)	7	10
Personal history of thrombosis		
Previous idiopathic thrombosis (no risk factors)	23	23
Previous multiple thrombosis (>2 thromboembolic events)	41	57
Previous thrombosis during a pregnancy	10	10
Family history of thrombosis (>2 family members)	36	47
Total	165	202

Women were considered to be at increased risk of thrombosis, if they fulfilled one of these criteria. Between 1993 and the end of 1999, 165 women and 202 pregnancies were included. Eight women were excluded.

Activation Markers

During pregnancy, activation markers were determined every 2–3 weeks. To ensure correct blood sampling and rapid handling, blood was only drawn in our laboratory. To avoid *in vitro* generation of activation markers, blood was collected into syringes containing 3.8% trisodium citrate, 2% EDTA, and a cocktail of protease inhibitors including 3.6 mg/ml theophyllin, 2,000 U/ml aprotinin, and 50 mg/ml D-Phe-Pro-Arg-chloromethylketone (PPACK). After centrifugation, plasma samples were immediately frozen at -70°C and then tested within 24 h. TAT and D-dimers were determined using commercial ELISA kits from Stago (Enzygnost TAT and Asserachrom D-dimer). The cutoff values (means + 2 SD) were determined in a previous study with healthy women [15], where the TAT and D-dimer values increased from 3 to 9.5 ng/ml and from 500 to 1,000 ng/ml, respectively, between weeks 6 and 40.

Heparin Treatment

Based upon the experiences of first pilot studies in the early 90s showing that a dose of LMW heparin of 4,000–5,000 U/day may be adequate for thromboprophylaxis in pregnancy [4, 17], all women received an initial dose of LMW heparin of $1 \times 5,000$ U/day s.c. dalteparin (Low Liquemin[®], Roche, Basel, Switzerland or Fragmin[®], Pharmacia, Uppsala, Sweden) independent of the body weight and clinical diagnosis. In all women, treatment was started between the 6th and 15th gestational week. Then, during the entire pregnancy, TAT and D-dimer values were determined every 2–3 weeks. As long as these two markers remained within the normal range, the daily dose of 5,000 U of LMW heparin remained unchanged. However, if a subsequent TAT and/or D-dimer value increased above the cutoff, the daily dose of LMW heparin was further increased by 2,500 U. If subsequent measurements of TAT and D-dimer values had decreased to normal-range values, the previously increased dose of LMW heparin remained unchanged. If there was no decrease of the markers to normal range values (or even a further increase, the daily dose of LMW heparin was further increased by 2,500 U until normal values were reached. The upper limit of the daily dose was set to 20,000 U/day. Injections of 5,000 or 7,500 U were usually given in the evenings, while doses $\geq 10,000$ U were given as two injections.

Statistical Analysis

Statistical significance of the difference in the mean daily dose of LMW heparin among the different groups was calculated by the χ^2 test. Confidence intervals (CI) of 95% were used.

Results

Course of TAT and D-Dimers

Although both TAT and D-dimer values increased at least once above the cutoff in most individuals, mean values of all pregnancies stayed within the normal range as it was the aim of the heparin therapy (fig. 1). It is notable that the D-dimers always remained well beneath the cutoff throughout the pregnancy (close to the mean values of normal pregnancies), whereas the TAT values were found mostly close to or slightly above the cutoff. Likewise, TAT values were much more frequently above the cutoff than D-dimers. In particular, TAT and D-dimer values which were at least once above the cutoff during pregnancy were found in 171 (84.6%) and 30 women (14.9%), respectively. An increase in D-dimers was always accompanied by increased TAT values. Details about the number of pregnancies with markers above the cutoff are given in table 2. Although there was a tendency to more frequent elevations in TAT and/or D-dimer values in the third trimester, there was no significant difference in the elevations of these two markers among the periods.

Dosage of LMW Heparin

Due to the number of increased TAT values above the cutoff, the dose of LMW heparin had to be adjusted in 84.6% of the pregnancies. The initial daily dose of 5,000 U LMW heparin could be maintained only in 31 pregnancies throughout gestation. In the majority of cases (47%), the dose had to be changed twice, resulting in a daily dose of 10,000 U towards the end of the pregnancy. A maximum final dose of 17,500 U per day was given only to 3 women. When the doses of all 202 pregnancies were summarized (fig. 2), the mean daily doses of LMW heparin were found to increase from 5,000 U at the 6th ges-

Fig. 1. TAT and D-dimer values of all 202 pregnancies between 6 and 40 weeks of gestation. The solid line represents the cutoff value (mean + 2 SD of normal pregnancies).

tational week to 11,200 U at the 40th gestational week. On average, the median dose of LMW heparin of all pregnancies was 7,560 U.

Doses of LMW Heparin and Clinical Characteristics

It was of particular interest to evaluate whether the doses of LMW heparin would be different depending upon the clinical characteristics of the women. When expressed as mean daily dose of the entire pregnancy, none of the different groups received significantly

more or less LMW heparin. The range of all groups was between $7,350 \pm 2,800$ and $7,700 \pm 3,200$ U/day (mean $\pm$ SD). For example, while women with protein C deficiency and a history of thrombosis required about 7,450 U/day, women with only a family history of thrombosis received also about 7,250 U/day. Since the doses were calculated solely on the basis of TAT and D-dimer values, these values did also not differ among the different groups (data not shown).

Fig. 2. Daily doses of LMW heparin of all pregnancies between 6 and 40 weeks of gestation. The total number of treatment weeks was 4,448. The solid line (M) shows the mean dose of all doses determined between 6 and 40 weeks of gestation. The solid bars represent the mean $\pm$ SD of all 202 pregnancies.

Table 2. Number of pregnancies with TAT/D-dimer values above cutoff levels

	TAT		D-dimers	
	n	%	n	%
Marker never above cutoff	31	15.4	172	85.1
Marker 1 $\times$ above cutoff	40	19.8	28	13.9
Marker 2 $\times$ above cutoff	95	47.0	1	0.5
Marker 3 $\times$ above cutoff	24	11.9	1	0.5
Marker 4 $\times$ above cutoff	9	4.5	0	0
Marker 5 $\times$ above cutoff	3	1.5	0	0
Total	202	100	202	100

Each time when a TAT or D-dimer value increased above the cutoff, the daily dose of LMW heparin was increased by 2,500 U. For example, in patients where a marker increased three times above the cutoff value, the final daily dose of LMW heparin was consequently 12,500 U (starting dose of 5,000 U plus 3 $\times$ 2,500 U). The cutoff values are defined in the ‘Material and Methods’.

Complications
In the 202 pregnancies, we observed a total of seven complications most probably related to the therapy with LMW heparin. Based on the number of 5,448 treatment weeks with LMW heparin, there was about one complica-

tion every 778 treatment week. Six of these seven complications occurred at the injection sites including indurations, hematomas, and allergic reactions. In 3 cases, the therapy with LMW heparin had to be stopped prematurely because of severe vaginal bleeding (1 case)

and severe allergic reactions (2 cases). Importantly, there were no thromboembolic complications. Other rare LMW-heparin-related complications such thrombocytopenia or elevation in liver enzymes did not occur.

Discussion

There is increasing evidence that LMW heparins can be used safely during pregnancy [1]. However, it is so far not clear whether LMW heparins should be given at fixed doses throughout the pregnancy (if yes at which dose?) or adjusted to the gestational age. The idea to adjust the dose to the gestational age comes from previous observations with women under therapeutic doses of unfractionated heparin showing that many of them required significantly increasing doses towards the end of the pregnancy to maintain a therapeutic aPTT level [18]. This phenomenon has been ascribed to increases in the plasma volume, renal and placental clearance of heparin and to the increasing concentration of circulating heparin-neutralizing proteins such as platelet factor 4, von Willebrand factor, and others [19].

Since LMW heparins are not or only minimally neutralized in vivo resulting in a much better bioavailability, it was assumed that dose adjustments would not be necessary during pregnancy. Indeed, there are several reports demonstrating that a fixed daily dose of 4,000–5,800 U prevented thromboembolism effectively [2–4]. Moreover, Nelson-Piercy et al. [2] showed that the gestational age did not influence the levels of LMW heparin assessed by anti-factor Xa activity. Likewise, Blomback et al. [20] reported that, using a daily dose of 5,000 U of dalteparin, 14 of 22 women (64%) remained within the target range of 0.2–0.4 IU/ml anti-factor Xa activity throughout the pregnancy. There are, however, other studies showing that the great ma-

jority of women at increased risk of thrombosis required up to 10,000 U/day of LMW heparin to maintain the anti-factor Xa activity within the target range [5, 6].

The effect of heparin, however, can be assessed either by its anticoagulant (or specifically anti-factor Xa) effect in vitro or through its in vivo effect on the reduction of the generation of thrombin (TAT) and fibrin (D-dimers) [11–14]. We hypothesized that, independent of the heparin level, only complete suppression of these markers would reflect an effective anticoagulation. In this study, we have now found that in more than 80% of the 202 pregnancies the TAT or D-dimer values increased above the normal range despite daily administration of 5,000 U/day or more of LMW heparin. The fact that the number of elevations of TAT and D-dimer values above the cutoff decreased by using higher doses of LMW heparin clearly indicates that there is a correlation between the plasma concentration of heparin and the generation of thrombin and fibrin. Since D-dimers increased less frequently above the cutoff than TAT values, it seems that activation of coagulation in pregnancy is limited primarily to the generation of thrombin rather than that of fibrin. Alternatively, the moderate increase in D-dimers may also indicate a poor fibrinolysis due to the increase in plasminogen-activator inhibitors. It is well known that coagulation activation markers increase continuously with the course of the pregnancy [21, 22]. The reason, however, is not clear. It has been speculated that coagulation markers may be released into the circulation from the intervillous space of the placenta. If this is true, the increase in markers would consequently reflect the growth of the placenta. However, it is also conceivable that thrombin may increasingly be generated intravascularly (perhaps due to stasis in the veins of the pelvis and lower limbs) indicating a hypercoagulable state.

To completely suppress the generation of thrombin, increasing doses of LMW heparin had to be administered over the course of the pregnancy. While starting with a dose of 5,000 U/day, the mean dose was more than 11,000 U at the 39th and 40th gestational week. This increase is very similar to that found in the study by Hunt et al. [6], where the dosage of LMW heparin has been calculated by anti-factor Xa activity. When expressed as mean dose/trimester, this increase from 5,000 to 11,200 U would translate into a dose of about 5,500, 7,700 and 9,100 U in the first, second, and third trimester, respectively. Surprisingly, among the different clinical groups, we did not find any differences in the number of increased TAT or D-dimer values and, consequently, the heparin doses. In all groups, there were individuals with frequent and rare elevations in the markers. Thus, thrombin generation seems to be more dependent on the individual itself than on the type of thrombophilia.

Despite the relatively high doses of dalteparin towards the end of the pregnancy, only in 1 case of 202 pregnancies, dalteparin treatment had to be stopped prematurely due to severe vaginal bleeding. Thus, the frequency of major bleeding complications was less than 0.5% in our study, whereas in other studies

using LMW heparin at these dosages the incidence of bleeding was about 1.3% on average, although the treatment periods were only a few days compared to several weeks in our patients [23].

Based on the observation that, despite an initial dose of 5,000 U of dalteparin, the TAT and D-dimer values increased gradually over the course of the pregnancy, this study provides evidence that the dose of LMW heparin should be adjusted to the gestational age rather than to use fixed doses throughout the pregnancy. However, since it is not clear whether an elevation in coagulation markers represents a hypercoagulable state predicting the occurrence of thrombotic events and since the regular determination of coagulation markers is expensive and cumbersome for the patient and the laboratory, we strongly discourage its use in daily routine. Only prospective, randomized studies using lower and/or fixed doses of LMW heparin will help to find the optimal dose of LMW heparin in pregnancy.

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