Low molecular weight heparin versus no treatment in women with previous severe pregnancy complications and placent al findings without thrombophilia

Michael Kupferminc, Eli Rimon, Ariel Many, Sharon Maslovitz, Joseph B. Lessing and Ronni Gamzu

Low molecular weight heparin (LMWH) treatment has been recommended for pregnant women with previous adverse pregnancy and who were diagnosed as having a thrombophilia. We now examined the effect of LMWH on pregnant women without thrombophilias who had severe pregnancy complications and placent al vasculopathy in an earlier pregnancy. Seventy-two women with a history of severe pre eclampsia, fetal growth restriction (FGR) less than fifth percentile, severe placental abruption and/or stillbirth after 20 weeks, whose thrombophilia workup was negative, were enrolled. Placent al vasculopathy was defined as villous infarcts, fibrinoid necrosis of decidual vessels, fetal vessel thrombosis, evidence of placent al abruption and perivillous fibrin deposition. The study group consisted of 32 pregnant women who were treated with LMWH and 40 pregnant women who were not treated with LMWH (control group) in their ensuing pregnancy in our institution between 2003 and 2007. The incidences of severe preeclampsia, FGR, placental abruption and stillbirth in the previous pregnancies were similar for both groups. The incidences of severe preeclampsia and placental abruption in the study group in the index pregnancy were significantly lower than the control group (3.13 versus 20%, \( P = 0.03 \); and 0 versus 15%, \( P = 0.03 \), respectively). The respective incidence of FGR was 6.25 versus 22.5%, and of overall adverse outcome was 9.4 versus 60% (\( P = 0.001 \)). Treatment with LMWH may reduce the rate of the recurrence of severe pregnancy complications and significant placent al vasculopathy in women without thrombophilias. *Blood Coagul Fibrinolysis* 22:123–126 © 2011 Wolters Kluwer Health | Lippincott Williams & Wilkins.

**Blood Coagulation and Fibrinolysis** 2011, 22:123–126

**Keywords:** fetal growth restriction, low molecular weight heparin, placental abruption, placent al vasculopathy, severe preeclampsia, stillbirth, thrombolias

Department of Obstetrics and Gynecology, Lis Maternity Hospital, Tel Aviv Sourasky Medical Center, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

Correspondence to Dr Michael Kupferminc, Department of Obstetrics and Gynecology, Lis Maternity Hospital, Tel Aviv Sourasky Medical Center, 6 Weizman Street, Tel Aviv 64239, Israel

Tel: +972 524 266955; fax: +972 3 6973164;

e-mail: tmcobgyn@tasmc.health.gov.il

Received 3 July 2010 Revised 9 November 2010
Accepted 20 November 2010

### Introduction

Severe pregnancy complications, including severe pre eclampsia, fetal growth restriction (FGR), placent al abruption and stillbirth are associated with thrombophilias [1–4]. These pregnancy complications are also associated with typical placent al vasculopathy, such as infarcts and thrombosis in women with and without thrombophilias [5–7]. Several studies have reported a high-recurrence rate of severe pregnancy complications among women with thrombophilias [8–11], as well as among women who were not tested for thrombophilias [12–14], and in women without thrombophilias [15]. Thrombophilias are associated with thrombosis, and there is a consensus that low molecular weight heparin (LMWH) reduces the incidence of recurrent thrombotic events. Several studies have also shown that LMWH may prevent the recurrence of pregnancy complications among women who are known to have thrombophilias, and the therapeutic administration of LMWH and heparin has become common practice during the subsequent pregnancies of these women in many countries [9–11,16–20].

One randomized study showed an advantage in administering LMWH in pregnant women who had experienced placent al-mediated complications in an earlier pregnancy, but whose workup for thrombophilias had been negative [15]. The issue of whether all women with a similar history should be treated with LMWH remains unresolved. Pregnancy complications, such as severe preeclampsia, FGR, placental abruption and stillbirth, share similar placent al vasculopathies as those seen in thrombosis and reduced placent al perfusion. These pregnancy complications are associated with abnormal placent al findings in women with and without thrombophilias [5–7]. Our hypothesis was that pregnancy complications associated with the presence of histopatholog ical features of the placent a may benefit from antithrombotic treatment by means of LMWH, and that this approach will improve pregnancy outcome in subsequent pregnancies. We designed this study to examine the efficacy of LMWH in preventing recurrence of severe pregnancy complications in pregnant women who had negative results for inherited and acquired thrombophilias in their earlier pregnancy.
Participants and methods

Study design

This retrospective study was approved by the local hospital ethics committee. It included women who delivered between 2003 and 2007 in our institution and had a history of severe preeclampsia, FGR less than fifth percentile, severe placental abruption and stillbirth after 20 weeks. They all were negative for inherited and acquired thrombophilias. Significant placental vasculopathy had been detected in each patient.

Severe preeclampsia was defined as blood pressure of at least 160/110 mmHg, proteinuria in excess of 5 g/24 h, platelet count less than 100,000 cells/mm$^3$ or the presence of hemolysis, elevated Serum aminotransferase concentrations and platelet count less than 100,000 cells/mm$^3$ (hemolysis, elevated liver enzymes, low platelets syndrome) or eclampsia. Placental abruption was diagnosed when abruption was associated with vaginal bleeding, concealed hemorrhage, uterine tenderness and either fetal distress or maternal shock or maternal coagulopathy. FGR was defined as birth weight of less than fifth percentile for gestational age. The exclusion criteria for women with FGR were the presence of congenital malformations or chromosomal abnormalities, recent maternal cytomegalovirus infection or a history of drug or alcohol abuse during pregnancy. Stillbirth was defined as fetal death after 20 weeks’ gestation. Exclusion criteria for women with stillbirths were abnormal karyotype of the stillborn or congenital anomalies detected by autopsy, recent cytomegalovirus infection, positive cultures for Listeria monocytogenes obtained from the fetus and placenta, and an abnormal oral glucose tolerance test. The workup for thrombophilias included the mutation of factor V Leiden, factor II and methylenetetrahydrofolate reductase, protein S, protein C and antithrombin III levels and the lupus anticoagulant and antiphospholipid antibodies. Thrombophilia assays were performed as described elsewhere [1]. All protein S assays were performed at least 3 months after delivery.

Placental vasculopathic findings for inclusion in this study included villous infarcts of at least 1 cm, multiple infarcts, fibrinoid necrosis of decidual vessels, fetal stem vessel thrombosis, spiral artery thrombosis and evidence of placental abruption and perivillous fibrin deposition. The presence of placental vasculopathy had been recorded in the medical records, but the women with severe complications and placental vasculopathy had not been offered treatment before June 2005. As of July 2005, we adopted the policy of offering LMWH treatment to pregnant women with a history of severe pregnancy complications, a negative workup for thrombophilias and significant placental vasculopathy.

Patients

A total of 72 women were enrolled in the study. The study group consisted of 32 women who had had severe preeclampsia, FGR less than fifth percentile, severe placental abruption and stillbirth after 20 weeks and the above-cited placental vasculopathy in a previous pregnancy. These women had been offered and elected to be treated during the index pregnancy with LMWH (enoxaparin sodium 1 mg/kg; Sanofi-Aventis, Paris, France), beginning from week 5–15 until 38 weeks of gestation or until delivery. The control group consisted of 40 women with a history of the same pregnancy complications and placental findings, but who delivered between 2003 and 2005 and were either not treated because of our earlier departmental policy that lacked the LMWH option or women who elected not to be treated when it was available. Exclusion criteria were the initiation of treatment after 15 weeks of gestation, treatment with low-dose aspirin, history of venous or arterial thrombosis, congenital or chromosomal anomalies, diagnosis of diabetes before pregnancy or any known vascular or connective tissue disorder. The outcomes of these two groups were compared.

Statistical analysis

The results of the two groups were compared by two-tailed Student’s $t$-tests, Fisher’s exact tests and Pearson’s $\chi^2$-tests. Significance was set at $P$-value less than 0.05. Statistical analyses were performed with the SPSS program for Windows, version 17 (SPSS, Chicago, Illinois, USA).

Results

There was no difference in maternal age between the study (31.8 ± 5.2 years) and control (31.9 ± 4.3 years) groups. The index delivery was the second one for 30 women (93.8%) and the third one for two women in the study group. The index delivery was the second one for 38 (95%) and the third one for two women in the control group.

There was no difference in the rate of each adverse outcome for the previous pregnancies between the two groups (Table 1). There was no difference in placental

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Adverse outcomes in the study and control groups before treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LMWH (study group, $n = 32$)</td>
</tr>
<tr>
<td>Severe preeclampsia</td>
<td>10 (31%)</td>
</tr>
<tr>
<td>FGR &lt; 5th percentile</td>
<td>9 (28%)</td>
</tr>
<tr>
<td>Stillbirth &gt; 20 weeks</td>
<td>6 (19%)</td>
</tr>
<tr>
<td>Placental abruption</td>
<td>7 (22%)</td>
</tr>
</tbody>
</table>

FGR, fetal growth restriction; LMWH, low molecular weight heparin.

Copyright © Lippincott Williams & Wilkins. Unauthorized reproduction of this article is prohibited.
vasculopathic findings in the two groups (Table 2). Notably, mixed findings of placental vasculopathy were detected in many patients.

The incidences of severe preeclampsia and placental abruption were significantly lower in the study group compared with the control group (Table 3). The incidence of FGR was also lower, but the difference did not reach a level of significance. The incidence of stillbirth was similar in both groups. The incidence of total adverse outcome was significantly lower in the study group ($P < 0.0001$, Table 3).

Twenty-eight (87%) of the study group women delivered at least 37 weeks of pregnancy compared with 17 women (42%) in the control group ($P < 0.001$, odds ratio 7.7, 95% confidence interval 2.2–26.1). The gestational age at delivery and the birth weight were significantly higher in the study group compared with the control group: 38.15 ± 1.24 versus 35.3 ± 3.38 weeks ($P < 0.001$) and 2970 ± 544 versus 2267 ± 797 g ($P < 0.001$), respectively. There were no side-effects associated with the use of enoxaparin.

**Discussion**

In the current study, we tested the hypothesis that pregnant women with previous pregnancy complications, with evidence of placental vasculopathy and with negative workup for thrombophilia might benefit from antithrombotic therapy. We treated women with LMWH on the basis of the presence of typical histological features of placental vasculopathy. Our results showed that the pregnant women who underwent treatment with LMWH had a significantly reduced incidence of severe preeclampsia and placental abruption compared with a control group of demographically comparable women who were not treated by LMWH. The incidence of total adverse outcome was significantly lower in the study group compared with the controls. Moreover, 87% of the women in the study group delivered at least 37 weeks of pregnancy compared with 42% in the control group in which there was a significant lower mean gestational age at delivery. The overall risk reduction rate associated with the use of LMWH was 82%, and there were no significant complications that could be attributed to treatment by means of LMWH.

LMWH has been shown to decrease the recurrence rate of adverse pregnancy outcome in women with inherited and acquired thrombophilies and pregnancy complications [8,9,16–19]. For example, Gris et al. [8] showed significant reduction in adverse outcome in women with known thrombophilies and fetal loss after they had been treated with LMWH compared with those treated with aspirin during their subsequent pregnancy [8]. In a pilot randomized controlled trial, Rey et al. [15] showed a significant decrease in the rate of placental-mediated complications that led to adverse outcome among women who were negative for thrombophilies and who received LMWH treatment. Antiplatelet drugs, such as aspirin, were also shown to slightly reduce the incidence of preeclampsia, FGR and stillbirth [21].

As women with preeclampsia, severe FGR, placental abruption and stillbirth share common placental findings [6,22], placental vasculopathy may be a common marker of a process of reduced perfusion and thrombosis.

The approach to administer LMWH treatment on the basis of placental findings that reflect placental vasculopathy is a novel one. Our departmental policy is to routinely screen women who had had severe preeclampsia, FGR less than fifth percentile, severe placental abruption and unexplained stillbirth for the presence of thrombophilies. We based our decision on the evidence that LMWH treatment in the subsequent pregnancy may reduce the rate of recurrence in the

### Table 2 Placental findings in the study and control groups

<table>
<thead>
<tr>
<th></th>
<th>LMWH (study group, $n = 32$)</th>
<th>No treatment (control group, $n = 40$)</th>
<th>$P$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Villous infarcts*</td>
<td>16 (50%)</td>
<td>22 (55%)</td>
<td>NS</td>
</tr>
<tr>
<td>Multiple infarcts*</td>
<td>8 (25%)</td>
<td>10 (25%)</td>
<td>NS</td>
</tr>
<tr>
<td>Fibrinoid necrosis*</td>
<td>6 (19%)</td>
<td>8 (20%)</td>
<td>NS</td>
</tr>
<tr>
<td>Vessel thrombosis*</td>
<td>7 (22%)</td>
<td>6 (15%)</td>
<td>NS</td>
</tr>
<tr>
<td>Placental abruption*</td>
<td>7 (22%)</td>
<td>9 (22.5%)</td>
<td>NS</td>
</tr>
<tr>
<td>Spiral artery thrombosis*</td>
<td>8 (25%)</td>
<td>7 (17.5%)</td>
<td>NS</td>
</tr>
<tr>
<td>Perivillous fibrin deposition*</td>
<td>6 (19%)</td>
<td>7 (17.5%)</td>
<td>NS</td>
</tr>
</tbody>
</table>

LMWH, low molecular weight heparin. *In many patients combined placental findings were found.

### Table 3 Adverse outcomes in the study and control groups after treatment

<table>
<thead>
<tr>
<th></th>
<th>LMWH (study group, $n = 32$)</th>
<th>No treatment (control group, $n = 40$)</th>
<th>RR (95% CI)</th>
<th>$P$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe preeclampsia</td>
<td>1 (3.13%)</td>
<td>8 (20%)</td>
<td>1.21 (1.025–1.43)</td>
<td>0.037</td>
</tr>
<tr>
<td>FGR ≤ 5th percentile</td>
<td>2 (6.25%)</td>
<td>9 (22.5%)</td>
<td>1.21 (1.001–1.46)</td>
<td>0.09</td>
</tr>
<tr>
<td>Stillbirth &gt; 20 weeks</td>
<td>0</td>
<td>1 (2.5%)</td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td>Placental abruption</td>
<td>0</td>
<td>6 (15%)</td>
<td>0.03</td>
<td></td>
</tr>
<tr>
<td>Total adverse outcome</td>
<td>3 (9.4%)</td>
<td>24 (60%)</td>
<td>2.26 (1.5–3.36)</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

CI, confidence interval; FGR, fetal growth restriction; LMWH, low molecular weight heparin; RR, relative risk.
ones found to be positive for thrombophilias [9,10,12].

Considering the results of the present work, we propose that another subset of women with severe complications may be candidates to benefit from antithrombotic therapy. Reducing the rate of the severe pre-eclampsia associated with maternal and fetal mortality and morbidity [23,24] certainly has important implications and justifies offering suitable women the option of undergoing treatment with LMWH. The same argument can be made for severe placental abortion, which is also associated with maternal and fetal mortality and morbidity. We believe that the reduction in the incidence of FGR being only of borderline significance in the study group was probably due to the small number of women.

We propose that our results justify offering a regimen of LMWH in women with severe preeclampsia, placental abortion, FGR less than fifth percentile and with significant placental vasculopathy. This step in the attempt to reduce the risk of recurrence of such complications is very important, given the high maternal and neonatal morbidities associated with severe pregnancy complications. We offer LMWH treatment to these women during their subsequent pregnancy, emphasizing that it has not been well established for this indication, but that it is well tolerated and free of major side-effects. It is our experience that most women who had had previous complications elect to be treated.

Our regimen is to treat these women with LMWH (enoxaparin) 1 mg/kg as we do in women with adverse pregnancy outcome and thrombophilias. We do not perform routine antifactor Xa for these women with adverse pregnancy outcome. We do use antifactor Xa, mostly in women with previous thrombotic complications such deep vein thrombosis and pulmonary embolism.

We are aware that our study has limitations. It is retrospective and the sizes of the study and control groups are small. A randomized trial in a high-volume institution should be carried out before any evidence-based clinical recommendations can be made.

In conclusion, we recommend that women with a history of severe pregnancy complications and significant placental vasculopathy should be offered treatment with LMWH in an attempt to reduce the rate of recurrence of these complications, in spite of their not having thrombophilias.

Acknowledgements

The authors would like to thank Esther Eshkol for editorial assistance.

References


