Preeclampsia and pregnancy loss in women with a history of venous thromboembolism and prophylactic low-molecular-weight heparin (LMWH) during pregnancy

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Summary

Limited data are available regarding complications of pregnancy and pregnancy outcome under prophylaxis with low-molecular-weight heparin (LMWH) in women with a history of thromboembolism (TE). We retrospectively evaluated pregnancy complications in a cohort of 80 women. All had a history of TE (76 venous, two arterial and two venous and arterial) and received prophylactic LMWH during 86 pregnancies. The rate of pre-eclampsia and stillbirth in these women was compared to that of a control group of 313 women without a history of TE and LMWH. Prophylaxis was started at a median of 10 weeks of gestation and usually continued until six weeks post partum. In 94% of the cases the outcome of pregnancy was favourable with a live birth. Four pregnancies (4.7%) ended in miscarriage. Two (2.3%) pregnancies were complicated by a thromboembolic event (one deep leg vein thrombosis and PRIND, respectively). One patient developed HELLP-syndrome. Severe preeclampsia occurred in three (3.8%) and stillbirth in one (1.3%) of the patients (n=80), whereas this was the case in four (1.3%, odds ratio 3.01; 95% confidence interval (CI) 0.66–13.73, p=0.15) and 10 (3.2%, OR=0.38; 95% CI 0.05–3.04, p=0.72) control women. Mean birth weight and standard deviation of infants was 3,160 ± 930 g in patients and 3,300 ± 540 g in controls (p=0.11). We conclude that a favourable pregnancy outcome in women with a history of thromboembolism who use prophylactic LMWH during pregnancy can be expected. There was a trend towards a higher risk of preeclampsia, and these women should be carefully monitored for this complication.

Keywords

Low-molecular-weight heparin, history of VTE, pregnancy loss, preeclampsia

Introduction

Preeclampsia and pregnancy loss are considered to result from underperfusion of the placenta due to structural and occlusive changes including thrombosis in the placental vessels (1). Evidence has been presented that an increased risk for preeclampsia and pregnancy loss may be associated with thrombophilia (2–4). Women with a history of thrombosis can be considered obviously having “thrombophilia”, irrespective of whether an established thrombosis risk factor can be identified. While it is a well known fact that women with antiphospholipid antibodies often suffer pregnancy losses and have an increased risk for preeclampsia (5, 6), a direct association with other thrombophilic disorders such as factor V Leiden mutation, the prothrombin variation, antithrombin-deficiency, protein C and S deficiency is still discussed controversially (7, 8). Data regarding risk of pregnancy complications and adverse pregnancy outcome in women with a history of venous thromboembolism are hitherto very few (7, 9).

Low-molecular-weight heparin (LMWH) is in widespread use during pregnancy in women with a history of venous thromboembolism, in those with thrombophilia and also in women with a history of pregnancy loss and presence of thrombophilia. A large number of reports on the safety of LMWH have been published in the literature (10, 11). Recently a systematic review published by Greer et al. on safety and efficacy of LMWH in pregnant women has summarized data on 2,777 pregnancies (10). In this review a successful pregnancy outcome of 85% in
370 pregnancies treated with LMWH because of recurrent pregnancy loss was reported. Data on preeclampsia is missing. Results on this specific issue concerning pregnancy outcome and complications of pregnancy in women with a history of VTE with and without LMWH are very rare in the literature. There is only one study from our group (9); however, in this study no differentiation between patients with and without heparin was made. The majority of the articles report on patients with thrombophilia with and without a history of VTE (4, 7), regardless of the fact that adverse pregnancy outcome may differ widely in women with and without previous VTE. Since limited data are available regarding the incidence of fetal loss, preeclampsia and HELLP syndrome under prophylaxis with LMWH in women with a history of venous thromboembolism (VTE), it was the aim of our study to further investigate these associations.

Patients and methods

We retrospectively evaluated pregnancy complications in a cohort of 80 women of our outpatient department of Internal Medicine I, Division of Haematology and Haemostaseology between 1994 and 2004, who had a history of TE (venous n=76, arterial n=2, venous and arterial n=2) that had occurred at least three months before the beginning of pregnancy. In all patients TE was documented by objective methods (phlebography, duplex ultrasonography or computerized tomography). Each woman received prophylactic LMWH during pregnancy. There were no uniform decisions on the dosage of LMWH, the decision was made on an individual basis. Miscarriage was defined as intrauterine death before the 24th week of gestation or when the fetus weighed <500 gram. Stillbirth was defined as intrauterine death within or after the 24th week of gestation. For preeclampsia we used the definitions given by Davey and MacGillivray (12).

To make the rates of pregnancy complications (stillbirth and preeclampsia) comparable, we analysed a control cohort of 313 women without a history of VTE and without thrombosis prophylaxis [mean age ± standard deviation (SD) at inclusion 42 ± 12 years]. These women had in total 563 pregnancies and a median number of two (range 1–13) pregnancies per woman. These women were investigated or treated at the Department of Obstetrics and Gynaecology (outpatients and inpatients with routine gynaecological investigation, birth control counselling, or planned surgery because of non-malignant disease) and were invited to the standardized interview involving the complications of pregnancy. A history of superficial thrombophlebitis was not an exclusion criterion. Informed consent for collection of data was obtained from all women, and the history of their pregnancies was revealed in a standardized interview. No laboratory investigation was performed in controls. Women in the control cohort had not received thrombosis prophylaxis during pregnancy.

Plasma samples were obtained from patients after overnight fasting and centrifuged at 2,000 x g for 20 minutes. Coagulation tests for diagnosis of lupus anticoagulant were performed within three hours after blood sampling. For determination of natural coagulation inhibitors plasma was frozen at −20°C until analysis. Diagnosis of the lupus anticoagulant was made according to the criteria of the International Society on Thrombosis and Haemostasis (13) using two different screening tests (activated partial thromboplastin time and diluted Russel’s viper venom time) and confirmatory tests as previously described (14). Antithrombin and protein C activity were determined on an automatic analyzer, and free protein S antigen was determined by ELISA as previously described (9). Analysis of the factor V Leiden mutation and the prothrombin variation were performed by multiplex PCR following the general principle of mutagenically separated PCR (15). An individual heterozygous for both mutations was included as positive control in each experiment.

Statistical methods

Variables of interest are described by mean ± standard deviation (SD). Fisher’s exact test was applied to compare dichotomous variables between patients and controls and Mann-Whitney-test for metric variables, respectively. To compare the birth weight of infants between patients and controls, the mean birth weight was calculated as a summary measure of the infants of each mother. The t-test and Fisher’s exact test were used for comparison of the groups. A two-sided p-value of less than 0.05 was considered to indicate statistical significance. Because a woman’s pregnancies cannot be assumed to be independent of each other, the analyses are based on patients and not on pregnancies or births. Statistical
analyses were performed with the statistical package SPSS 12.01 for Windows®.

Results

Eighty women with a history of VTE were included in the analysis. Basic characteristics of patients and results from thrombophilia screening are given in Table 1. Thirty-nine women (48.8%) had developed idiopathic thromboembolism and 16 (20%) recurrent events. Thirty-six women had a history of PE (48%). Thirty-six women (48%) did not receive any anticoagulation when they became pregnant, 16 (20.5%) had LMWH and two (2.6%) oral anticoagulation. Mean age of women at first TE was 24.4 years, (standard deviation 5.8) and 30.1 years (standard deviation 4.6) at pregnancy. The median time interval between pregnancy and past VTE was 1,867 days (median value; 25th – 75th percentile: 837 – 3,131, range: 36 – 9,279 days).

Eighty-six pregnancies of these women were analyzed. Thrombosis prophylaxis was started at a median time of 10 weeks of gestation (range: 1 – 28). The applied dosage was between 4,000 and 5,000 units (U) once daily in 66 pregnancies, 2,500 U in two and between 6,000 and 10,000 U in 17 pregnancies. One woman received 1,500 U danaparoid sodium per day.

Forty-three women received dalteparin, 39 enoxaparin, two nadroparin and one reviparin. Additionally to LMWH, aspirin (100 mg) was given during eight pregnancies. Twenty-nine caesarean sections (35.4%) were performed (data not available in three women).

Eighty-one of the 86 pregnancies (94%) in women with a history of VTE or ischemic stroke ended with a live birth. Table 2 summarizes data on pregnancy complications and outcome. Two of 86 (2%) pregnancies were complicated by a vascular event: One woman with a twin pregnancy and a combination of hereditary thrombosis risk factors had DVT of the lower extremity. She had a history of spontaneous DVT and PE 11 years before. Another woman without known thrombosis risk factors and a history of ischemic stroke had a prolonged reversible ischemic neurologic deficit (PRIND) at 37 weeks of gestation. Four of 86 pregnancies ended with spontaneous abortion at 6, 9, 16 and 18 weeks of gestation, respectively, and one pregnancy with stillbirth at 27 weeks of gestation. Severe preeclampsia and HELLP syndrome complicated four pregnancies.

Significant maternal bleeding occurred in one woman who had a spontaneous abortion and bleeding at the 16th week of gestation (patient R.S. in Table 2). She had received dalteparin (5,000 U once daily) beginning at the 12th week of gestation.

The frequency of the occurrence of preeclampsia and stillbirth in patients in comparison to controls is depicted in Table 3. A higher number of women with a history of TE and LMWH during pregnancy had preeclampsia in comparison to controls; however, the difference was not statistically significant. The rate of stillbirth was not higher in patients than controls. The mean

Table 2: List of patients with a history of thromboembolism, with pregnancy complications and of those with adverse pregnancy outcome.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>History of TE</th>
<th>Thrombophilia</th>
<th>LMWH Anti-Xa U/day</th>
<th>Complication</th>
<th>Week of gestation</th>
<th>Outcome</th>
<th>End of pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>R.V.</td>
<td>27</td>
<td>DVT+PE</td>
<td>LA</td>
<td>1500+100 mg aspirin</td>
<td>–</td>
<td>–</td>
<td>abortion</td>
<td>6th week</td>
</tr>
<tr>
<td>R.S.</td>
<td>30</td>
<td>DVT</td>
<td>AT-def.</td>
<td>5000</td>
<td>–</td>
<td>–</td>
<td>abortion</td>
<td>16th week</td>
</tr>
<tr>
<td>H.L.</td>
<td>24</td>
<td>PE</td>
<td>FVL het.</td>
<td>5000</td>
<td>–</td>
<td>–</td>
<td>abortion</td>
<td>18th week</td>
</tr>
<tr>
<td>S.D.</td>
<td>34</td>
<td>DVT+PE</td>
<td>AT-def.</td>
<td>5000</td>
<td>–</td>
<td>–</td>
<td>stillbirth</td>
<td>27th week</td>
</tr>
<tr>
<td>S.L.</td>
<td>30</td>
<td>DVT+PE</td>
<td>FVL het. + F II var. het.</td>
<td>6000</td>
<td>DVT</td>
<td>28</td>
<td>2 viable infants**</td>
<td>34th week</td>
</tr>
<tr>
<td>A.A.</td>
<td>31</td>
<td>stroke</td>
<td>none</td>
<td>7500+100 mg aspirin</td>
<td>PRIND</td>
<td>37</td>
<td>1 viable infant</td>
<td>37th week</td>
</tr>
<tr>
<td>G.N.</td>
<td>29</td>
<td>DVT</td>
<td>LA</td>
<td>7500</td>
<td>preeclampsia</td>
<td>17</td>
<td>1 viable infant</td>
<td>27th week</td>
</tr>
<tr>
<td>H.F.</td>
<td>32</td>
<td>DVT</td>
<td>none</td>
<td>6000</td>
<td>preeclampsia</td>
<td>17</td>
<td>1 viable infant</td>
<td>29th week</td>
</tr>
<tr>
<td>D.K.</td>
<td>31</td>
<td>stroke</td>
<td>refusal of screening</td>
<td>5000+100 mg aspirin</td>
<td>preeclampsia</td>
<td>17</td>
<td>1 viable infant</td>
<td>35th week</td>
</tr>
<tr>
<td>P.K.</td>
<td>31</td>
<td>DVT</td>
<td>FVL het.</td>
<td>4000</td>
<td>HELLP</td>
<td>24</td>
<td>1 viable infant</td>
<td>30th week</td>
</tr>
</tbody>
</table>

*Danaparoid. **Twin pregnancy. AT-def., antithrombin deficiency; DVT, deep vein thrombosis (of the leg in each patient); FVL het., factor V Leiden heterozygous; F II var. het., prothrombin G20210A variation heterozygous; HELLP, hemolysis, elevated liver enzymes, low platelets; LA, lupus anticoagulant; PE, pulmonary embolism; PRIND, prolonged reversible ischemic neurologic deficit.

Table 3: Preeclampsia and stillbirth in patients and controls.

<table>
<thead>
<tr>
<th></th>
<th>Patients (n=80)</th>
<th>Controls (n=313)</th>
<th>Odds ratio and 95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preeclampsia, n (%)</td>
<td>3 (3.8)</td>
<td>4 (1.3)</td>
<td>3.01 (0.66–13.73)</td>
</tr>
<tr>
<td>Stillbirth, n (%)</td>
<td>1 (1.3)</td>
<td>10 (3.2)</td>
<td>0.38 (0.05–3.04)</td>
</tr>
</tbody>
</table>
duration of pregnancy ending with a live birth (data available in 75 patients) was comparable in patients (39 weeks ± 4 standard deviation [SD], range: 28 – 43) and control subjects (39 weeks ± 2 SD). Mean birth-weight of infants in controls (3,300 ± 540 g SD) was not significantly different from that of infants born to patients (3,160 ± 930 g SD). We evaluated how many infants born to patients and controls in the 38th, 39th and 40th week of gestation had a birth weight below the 10th percentile (16, 17). These were 5/19 infants (26%) from patients and 43/211 (20%) from controls. This difference was statistically not significant (p=0.58).

Discussion

In most of our women with a history of VTE, who had a subsequent pregnancy and were treated with LMWH, the outcome was favorable. There was one recurrence of VTE, and one woman suffered a PRIND. Preeclampsia occurred more frequently in women with a history of thromboembolism; however, the difference was not statistically significant. The number of pregnancy losses was low and definitely not higher than in the control women.

Data of several recent studies suggest that thrombophilia does not only predispose for thrombosis but also for preeclampsia (7, 18–20) and for stillbirth (2, 7, 21, 22). In women with preeclampsia, thrombophilia was more often found in comparison to those with normal pregnancies or the normal population (19, 23). Preston et al. (24) reported an increased risk of stillbirth in women with thrombophilia in a large study comprising 571 women. However, in the prospective EPCOT (25) study there was no significantly increased risk of fetal loss in women with thrombophilia. Preeclampsia was not evaluated in the EPCOT study.

An attempt to investigate the impact of a history of VTE on pregnancy outcome and complications was previously made by our group (9). The prevalence of pregnancy-induced hypertension was statistically higher in the patient group than in controls (OR = 4.13) and there was a trend for severe preeclampsia (OR = 2.43). There was no statistically significant difference with regard to miscarriage and stillbirth between patients and controls. Notably, in a number of women pregnancy had occurred before the thrombotic event and most women were not on heparin prophylaxis during their pregnancy. In the present study all patients had a history of thromboembolism and all had thrombosis prophylaxis with LMWH during pregnancy. They were compared to women without a history of VTE and without thrombosis prophylaxis, who were previously investigated (9). Similar to findings of our previous study, the frequency of preeclampsia was, albeit not significantly, higher in patients than in controls, while the rate of stillbirth was definitely not increased.

There is only one study that evaluates the impact of LMWH on pregnancy loss in women with thrombophilia (26). Women with a history of one fetal loss and known thrombophilia but without a history of VTE received either 40 mg/day of enoxaparin or aspirin. The results of the outcome of this study, namely a lower rate of pregnancy loss in women with LMWH, can not directly be transferred to the group of patients from our study, who had a history of thromboembolism without or with known thrombophilia. An approach to investigate different doses of LMWH prophylaxis in women with hereditary thrombophilia and pregnancy loss was initiated in a multicenter prospective study by Brenner et al. (27). Both doses (40 and 80 mg/day enoxaparin) showed a favourable outcome with live birth rates of 84% and 78%, respectively. Interestingly, the rates of preeclampsia (3.4% in women using 40 mg/day and 4.4% in those using 80 mg/day) were very similar to the rate found in our patients, although the inclusion criteria were different in the two studies. Whereas Brenner et al. included women with recurrent fetal loss, we evaluated women with a history of thromboembolism.

Recently, Greer et al. (10) showed promising results in the largest systematic review on LMWH use in pregnancy including 2,777 pregnancies. The recurrence rate of VTE was 1.15% in women who used treatment doses of LMWH. This compares well with our data of a recurrence rate of 2.3% (2/86). Notably, the recurrence rate in women who had previous thrombosis but no thrombosis prophylaxis during a subsequent pregnancy was 2.4% (3/125) in the prospective study by Brill-Edwards et al. (28) and 8/197 (4.1%) in the study from our group (29), which is close to the recurrence rate in patients with prophylaxis. In the guidelines of the American College of Chest Physicians (30) LMWH is suggested in women with idiopathic VTE with and without thrombophilia with a grade 2C level, there is no firm recommendation for this patient group.

A major limitation of our study is the retrospective evaluation of data from this cohort. However, to avoid a reporting bias we included each woman and each pregnancy that had occurred during the given time interval. Another limitation is that the median time of inclusion was 10 weeks of gestation. Therefore we were not able to evaluate the rate of early pregnancy loss. This problem of late recruitment was also present in the sole prospective study evaluating the risk of recurrent VTE in women without prophylaxis (28), the women in this study were included at a median duration of 15 weeks of gestation. In the present study we did not evaluate the risk of early pregnancy loss, because the observation began when patients were referred to us for thrombosis prophylaxis after diagnosis of pregnancy at a median time of 10 weeks of gestation, and thus we did not know how many women did not come for thrombosis prophylaxis, because an early abortion had occurred.

We conclude from our data that a favourable pregnancy outcome can be expected in women with a history of thromboembolism who use prophylactic LMWH during pregnancy. There was a trend towards a higher risk of preeclampsia in patients compared to controls, and, therefore, these women should be carefully monitored for this complication. The risk of late fetal loss was comparable to that in healthy women. These findings should be applied in counselling women with a history of thrombosis who wish to have children.

Acknowledgements

We wish to thank Daniela Dunkler for her statistical assistance and Silvia Koder and Laura Ovissi for their skilful technical support.
References