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Use of Heparin in Women With Early and Late Miscarriages With and Without Thrombophilia

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Objective: In women with a history of recurrent miscarriage, the risk of miscarriage in a subsequent pregnancy is about 30% to 40%. In patients with thrombophilia, the risk is even higher. Placental thrombosis has been found in women with unexplained recurrent miscarriage independent of thrombophilia. In addition, proinflammatory changes, for example, altered Th1 to Th2 cytokine ratio and complement activation, have been repeatedly demonstrated in these women. Because of the fact that heparin has both anticoagulative and anti-inflammatory effects, the current study evaluated the efficacy of low-molecular-weight heparin (LMWH) in unexplained abortions. Study Design: A total of 164 women with unexplained early and late miscarriages presented in our hemostaseological clinic for thrombophilia screening. For these 164 women, 82 subsequent pregnancies in 79 patients were treated with subcutaneous LMWH independently of thrombophilia. In 54/82 unselected pregnancies, 100 mg aspirin was administered in addition to LMWH. Two patients were excluded due to termination of pregnancy. Results: Overall, 83.8% (67/80) of pregnancies resulted in live births. In 22/79 women (27.8%), thrombophilia markers were positive. Most noteworthy, patients with thrombophilia markers had live births at a similar frequency as patients without those parameters. No severe side effects of LMWH were seen. Conclusions: Our data support the notion that LMWH is efficacious in patients with recurrent abortions and thrombophilia. We demonstrated the same effect of LMWH in women with unexplained abortions without thrombophilia. The potential mechanism of action of LMWH in early and late abortions warrants further study. Keywords: heparin; abortions; fetal loss; thrombophilia

Introduction

The term recurrent fetal loss is used in women with 3 or more consecutive losses affecting 1% to 3% of couples or 2 or more losses affecting up to 5% of couples. Endocrinological abnormalities, anatomical alterations of the uterus, chromosomal aberrations, and infections frequently play a causative role. However, in many of these patients the cause of the abortions remains unclear. More recently, immunological abnormalities and thrombophilic dispositions have been suggested as risk factors in unexplained abortions. The current literature provides evidence for a link between the recurrent miscarriage and the following thrombophilic markers: activated protein C (APC) resistance with and without factor V (FV) Leiden mutation, prothrombin 20210G/20210A mutation, antithrombin deficiency, protein C and S deficiency, and hyperhomocysteinemia.1-12 Furthermore, a few studies reported on factor XII deficiency,
increased factor XI activity, protein Z deficiency, factor V HR2 haplotype, and fibrinolytic disturbances. A suspected association of homozygous methylenetetrahydrofolate reductase (MTHFR) mutation C677T and recurrent miscarriage could not be confirmed by independent studies.

The probability of a live birth in a subsequent pregnancy has been documented to be approximately 60% to 70% in women with recurrent early miscarriages. Thus, one third of women will have an additional abortion. Apart from the overall population, in women with thrombophilia and recurrent miscarriage, the chance of having a live birth is about 40%. Thus, more than half of these women will experience a further abortion.

First therapeutic trials with low-molecular-weight heparin (LMWH) in the pregnancy of women with thrombophilic defects and recurrent miscarriage demonstrated significantly enhanced live birth rates under LMWH treatment. In a subgroup of these patients, an association of recurrent miscarriage and antiphospholipid antibodies (APAs) is well established. These antibodies apparently play a causative role in recurrent fetal loss having a combined thrombophilic and inflammatory effect. In these patients, the efficient therapy with LMWH and low-dose aspirin has become standard of care. Recently, it has been shown that the mechanism of heparin in this condition is inhibition of complement activation. Further, anti-inflammatory effects of heparin were demonstrated to be due to preventing leukocyte activation by blocking P- and L-selectins.

Pathological studies of placenta from women with thrombophilia and miscarriages/adverse pregnancy outcome demonstrated infarctions and thrombosis resulting in placental insufficiency. However, these findings can also frequently be detected in placenta from women with abortions without thrombophilia. In these cases, undetectable thrombophilic defects or other causes (eg, immunological), which involve activation of the clotting system, could play a causative role. However, in some women with and without thrombophilia, no placental infarctions or thrombosis can be seen. These observations suggest a combined influence of the coagulation and immune system in recurrent fetal loss. Thus, we hypothesized that the use of LMWH in unexplained pregnancy loss can be beneficial using both the anticoagulative and the anti-inflammatory capacity of this drug. Therefore, this study assessed the role of LMWH therapy in patients with unexplained early and late miscarriages, allowing an evaluation of its efficacy in patients with and without thrombophilia.

### Materials and Methods

#### Patients

A total of 164 consecutive women presented with a history of unexplained miscarriages in our hemostaseological clinic between January 2001 and February 2004. These patients have been referred by their gynecologists to evaluate thrombophilic defects after endocrinological and anatomical alterations, infections, and chromosomal abnormalities of the woman and her partner had been excluded.

Among these 164 patients, 85 did not become pregnant or were lost to follow-up. The remaining 79 women were treated in 82 subsequent spontaneous pregnancies with LMWH subcutaneously. The women’s age was 20 to 43 years (median 32.7 ± 6.0 years). They had experienced a minimum of 2 consecutive early abortions (≤13 weeks) or 1 late abortion (>13 weeks) (median 4.0 ± 2.2 abortions). Forty-five women did not have a successful pregnancy before (primary aborters; Table 1).

Two patients had to be excluded from evaluation of the pregnancy outcome due to termination of pregnancy (1 case with fetal triploidy). So we evaluated the outcome of 80 pregnancies in 77 patients regarding the number of live births, premature deliveries (<37 weeks), and the number of early (≤13 weeks) and late (>13 weeks) miscarriages. We compared our live birth rate to that of untreated pregnancies of similar patient populations from a literature review.

#### Treatment Schedule

Treatment with LMWH in the current pregnancy was administered whether or not a thrombophilic
state was documented in these women. All patients enrolled in this study had a history of at least 2 early abortions or 1 late abortion. Contraindications for heparin were strictly considered but none of the screened patients needed to be excluded. Patients included did not take progesterone.

Low-molecular-weight heparin therapy started with diagnosis of a pregnancy by the gynecologist in patients with early miscarriages (mean 5.4 weeks of gestation, range 4-10 weeks). In 14 patients with only late abortions therapy started with mean 12.3 weeks (range 5-21 weeks). There were no pregnancy losses before the start of heparin therapy. Low-molecular-weight heparin was continued at least until week 37 of gestation. In patients with thrombophilia, the LMWH treatment was continued to 6 to 12 weeks postpartum for thromboprophylactic reasons.

Seventy-nine of 82 pregnancies were treated with dalteparin. The regular daily dose was 5000 U dalteparin subcutaneously. In 2 patients, we decided to give 5000 U dalteparin twice and 3 times daily because of a combination of FV Leiden mutation and prothrombin 20210G/20210A mutation. In another patient, the daily dalteparin dosage was modified using dosages between 2500 and 7500 U. In 2 further cases, enoxaparin was used (20 and 40 mg daily, respectively). One woman received 2850 U nadroparin once daily. Fifty-four unselected pregnancies of the overall 82 (65.9%) pregnancies were treated with LMWH in combination with aspirin 100 mg daily. To evaluate the effect of coadministration of aspirin, we analyzed the patients with and without aspirin separately.

Logistic regression was used to reveal statistical significance of the influence of thrombophilia, additional aspirin treatment, and maternal age on the outcome of LMWH-treated women.

Laboratory Analyses

All patients were analyzed for their thrombophilic risk profile, including anticardiolipin antibodies of immunoglobulin G (IgG) and IgM class, lupus inhibitor, APC resistance, activity of protein S and protein C, antithrombin activity, and random plasma homocysteine on a routine laboratory basis. Patients were regarded as APA positive if a moderate or strong positive test for anticardiolipin antibodies or lupus inhibitor, respectively, was confirmed after a time interval of at least 6 weeks and if the patients had at least 3 previous abortions.

In addition, the presence of the following gene mutations and polymorphisms, respectively, was tested: FV Leiden 1691G/1691A, prothrombin 20210G/20210A, and MTHFR 677C/677T. Genomic DNA was prepared from whole blood by the GenoM-6 (Genovision Vienna, Austria) according to the manufacturer’s instructions. Polymerase chain reaction (PCR) using an amplification refractory mutation system (ARMS)-based screening assay was performed as published.

After initiating LMWH therapy, complete blood counts (CBC) including thrombocytes were checked twice weekly for 3 weeks to exclude heparin-induced thrombocytopenia (HIT) type II. Afterwards, CBC was checked every 4 weeks.

Doppler studies were performed by the referring gynecologist, but the available information was incomplete.

Results

Frequency of Thrombophilic Risk Parameters in Women With Recurrent Fetal Losses

Of 79 patients 22 (27.8%) were tested positive for at least 1 of the thrombophilic parameters for which an association with recurrent abortions is known (APAs, FV Leiden mutation, APC resistance, prothrombin polymorphism 20210G/20210A, hyperhomocysteinemia). Protein C, protein S, or antithrombin deficiency did not occur within our patient population. Notably, 3 patients (3.8%) showed a combination of 2 thrombophilic parameters: 2 patients with heterozygous FV Leiden mutation and heterozygous prothrombin polymorphism and another patient with APAs and hyperhomocysteinemia. The remaining 19 patients had a single thrombophilic risk factor (Table 2).

Pregnancy Outcome in Women With Previous Miscarriages and Subsequent LMWH Treatment

Because of induced abortion in 2 cases as described above, 80 pregnancies in 77 women were assigned for analysis of pregnancy outcome.

Of 80 pregnancies, 67 (83.8%) resulted in live births. Among those, 62/67 women (92.5%) delivered at term (≥37 weeks). Of 80 pregnancies treated with LMWH, 13 (16.2%) resulted in

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abortions (11 early miscarriages, 2 miscarriages after 15 weeks of gestation).

In 45 women with primary abortions (all 129 previous pregnancies were aborted), subsequent LMWH treatment led to live births in 39 of 46 pregnancies (84.8%) and to abortions in 7 of 46 pregnancies (15.2%). If patients with only 2 early miscarriages were excluded (n = 13), the live birth rate under LMWH was 83.6% (56/67).

In 26 patients with a history of late miscarriages, LMWH treatment of the current pregnancy resulted in live births in 78.6% (22/28 pregnancies) and in miscarriages in 21.4% (6/28 pregnancies).

Frequency of Live Births Under LMWH Is Independent of Thrombophilia

In pregnancies with positive thrombophilia screening (22 patients with 24 pregnancies), the live birth rate was 87.5% (21/24 pregnancies) versus 82.1% (46/56 pregnancies) in pregnancies without thrombophilia (Figure 1).

Among 3 patients with combined thrombophilic defects, 1 woman with a combined FV Leiden mutation and prothrombin polymorphism experienced an abortion but had a successful subsequent pregnancy under a higher LMWH dose; the remaining 2 patients delivered a healthy child (Table 3).

A potential confounding variable of the outcome is the simultaneous use of aspirin. Considering the outcome of the pregnancies treated with LMWH/aspirin and only LMWH separately, the calculated live birth rate was 84.9% (45/53) versus 81.5% (22/27) and, therefore, very similar. The outcome in the groups with and without thrombophilia dependent on the additional use of aspirin is presented in Table 4.

Logistic regression revealed no influence of additional aspirin treatment (odds ratio [OR] 0.74; 95% confidence interval [CI] 0.21-2.57), occurrence of thrombophilia (OR 0.69; 95% CI 0.17-2.80), and maternal age (OR 1.04; 95% CI 0.94-1.15) on the outcome of LMWH-treated pregnancies. Dalteparin as well as the other LMWH used were well tolerated. There were no cases of major bleedings and no cases of HIT II.

Discussion

Thrombophilia in Recurrent Pregnancy Loss

Recent studies reported an association of recurrent fetal loss and the following thrombophilic markers: FV Leiden mutation (OR for early abortions 2.01, OR for late abortions 7.83), APC resistance without FV Leiden mutation (OR 3-4), prothrombin mutation 20210G/20210A (OR for early abortions 2.56, OR for late abortions 2.3), hyperhomocysteinemia (OR 3-7).10,12 In this context, the current study identified an increased prevalence of FV Leiden mutation (especially associated with late abortions) and prothrombin polymorphism 20210G/20210A in patients with recurrent abortions. Notably,
hyperhomocysteinemia was significantly less frequent in our patients (3.8%) than previously reported (17%-27%). Evaluation of an association of antithrombin, protein C and protein S deficiency, and recurrent fetal loss is limited by the low prevalence of these disorders and was not found by the current study. The frequency of occurrence of the homozygous mutation in the MTHFR gene C677T was not different in our patients with recurrent abortions as compared to that among normal controls (4%-20%) in agreement with recent reviews.

Low-Molecular-Weight Heparin in Women With Recurrent Pregnancy Loss and Thrombophilia

The efficacy of LMWH and low-dose aspirin in antiphospholipid antibody associated fetal loss is well accepted. Untreated, the live birth rate in these patients is about 10%. It has been demonstrated that the live birth rate can be increased to about 80% using LMWH and low-dose aspirin. Although only 5 patients of our cohort were diagnosed with APA, 5 of their 6 pregnancies resulted in live births under LMWH and aspirin and are therefore consistent with previous data.

Table 3. Pregnancy Outcome in 3 Women With Combined Thrombophilic Defects

<table>
<thead>
<tr>
<th>Pat</th>
<th>Thrombophilic Markers</th>
<th>History of Previous Abortions</th>
<th>Daily Dalteparin/Aspirin Dosages</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>FV Leiden mutation + FII G20210</td>
<td>2 early, 1 late</td>
<td>1. 62 U/kg</td>
<td>1. Abortion at 9 weeks under LMWH</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2. 170-237 U/kg + aspirin 100 mg</td>
<td>2. live birth at 40 weeks</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3. 94-105 U/kg + aspirin 100 mg</td>
<td>Live birth at 38 weeks No complications</td>
</tr>
<tr>
<td>2</td>
<td>FV Leiden mutation + FII G20210</td>
<td>3 early</td>
<td>4. 60-70 U/kg + aspirin 100 mg</td>
<td>Live birth at 40 weeks No complications</td>
</tr>
<tr>
<td>3</td>
<td>Antiphospholipid antibodies positive + hyperhomocysteinemia</td>
<td>2 early, 1 late</td>
<td>5. 70-105 U/kg + aspirin 100 mg</td>
<td>Live birth at 40 weeks No complications</td>
</tr>
</tbody>
</table>

Table 4. Comparison of Pregnancy Outcome in Patients With and Without Thrombophilia Treated With LMWH/Aspirin versus LMWH Only

<table>
<thead>
<tr>
<th></th>
<th>Patients With Thrombophilia</th>
<th>Patients Without Thrombophilia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LMWH + Aspirin</td>
<td>LMWH</td>
</tr>
<tr>
<td>Total number of pregnancies</td>
<td>15</td>
<td>9</td>
</tr>
<tr>
<td>Number of live births</td>
<td>15 (100%)</td>
<td>6 (66.7%)</td>
</tr>
<tr>
<td>Number of miscarriages</td>
<td>0 (0%)</td>
<td>3 (33.3%)</td>
</tr>
</tbody>
</table>

NOTE: LMWH = low-molecular-weight heparin.

However, the optimal therapy for women with other thrombophilic states and recurrent abortions remains unclear. A limited number of smaller studies demonstrated an increased live birth rate under LMWH. Brenner et al treated 50 women with recurrent miscarriage and thrombophilia in 61 subsequent pregnancies with enoxaparin (40-120 mg/d). A total of 75% of pregnancies resulted in live births compared to 20% of previously untreated pregnancies in the same women. Carp et al demonstrated 70% live births under 40 mg/d enoxaparin in 37 women with thrombophilia and recurrent abortions compared to 44% live births in 48 untreated women. A multicenter prospective randomized trial (the LIVE-ENOX study) with patients with thrombophilia and abortions compared 40 and 80 mg/d enoxaparin and found them to be equally effective resulting in live births in 81% and 77% compared to only 28% live births in previously untreated pregnancies of these women. Sarto et al demonstrated a live birth rate of 85% in 35 women with recurrent abortions and thrombophilia under enoxaparin. Before thrombophilia was diagnosed, only 15% of 105 untreated pregnancies of these women resulted in live births.

In the current study, the live birth rate in our overall patient population was 83.8% without significant differences between patients with and without
thrombophilia (87.5% vs. 82.1%). No additional effect of low-dose aspirin could be observed. In comparison, 283 previously untreated pregnancies of the very same women had been successful (live birth) in 47 cases (16.6%), whereas the fetus had been aborted in 236 previous pregnancies of the cohort (83.4%). However, comparison with the patients’ history will bias the results. To obtain information on pregnancy outcomes of women similar to our study population but untreated with LMWH, we performed a literature review (Table 5). Many trials have shown consistent data demonstrating that the likelihood of a live birth after 3 unexplained early abortions is between 60% and 70%.21,22 After late abortions exclusively, the chances for a live birth are about 50%.21,22

In patients with thrombophilia and abortions, the probability of a live birth in a subsequent untreated pregnancy is somewhat lower (about 37%-44%).22,23 Interestingly, the overall live birth rate of 83.8% in our patients treated with LMWH is very similar as expected in a normal pregnancy population without abortions (87.2%).19 Note-worthy, especially in our patients with thrombophilia, the live birth rate (87.5%) under LMWH is significantly higher than what other authors have demonstrated in untreated thrombophilic women with recurrent abortions (37%-44%, Table 5).22,23

Table 5. Live Birth Rates in Our LMWH-Treated Patients Compared to Untreated Patients From a Literature Review

<table>
<thead>
<tr>
<th>Live Birth Rates</th>
<th>Our Patient Population, LMWH Treated</th>
<th>Literature Review Untreated Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women with unexplained abortions</td>
<td>83.8%</td>
<td>Rai et al,21 438 patients</td>
</tr>
<tr>
<td></td>
<td>63.5%</td>
<td>Rai et al,22 153 patients</td>
</tr>
<tr>
<td></td>
<td>69.3%</td>
<td>Stirrat,19 4 prospective trials</td>
</tr>
<tr>
<td></td>
<td>66.9%</td>
<td>Stirrat,19 4 retrospective trials</td>
</tr>
<tr>
<td>Women with abortions and thrombophilia</td>
<td>87.5%</td>
<td>Carp et al,23 48 patients</td>
</tr>
<tr>
<td></td>
<td>044.0%</td>
<td>Rai et al,22 25 patients</td>
</tr>
<tr>
<td></td>
<td>37.5%</td>
<td></td>
</tr>
</tbody>
</table>

NOTE: LMWH = low-molecular-weight heparin.

Low-Molecular-Weight Heparin in Women With Unexplained Pregnancy Loss Without Thrombophilia

Little is known about LMWH treatment of women with unexplained recurrent miscarriage and lack of thrombophilic markers. One study reported LMWH treatment of 2 pregnant women with 11 and 8 previous unexplained abortions after APA and inherited thrombophilias had been excluded. Low-molecular-weight heparin was administered by continuous intravenous infusion from diagnosis of a pregnancy until 34 weeks of gestation. Both women delivered healthy babies.45 Tzafettas et al29 treated 51 pregnant women with a history of unexplained recurrent miscarriage with nadroparin and low-dose aspirin. Thrombophilia screening was positive in 24 of the patients; in the remaining 27 patients, no cause of the abortions could be detected, including thrombophilic markers. The success rate (viable pregnancy >24 weeks) was equally effective (83.3% and 85.1%, respectively).26

In our study, there were also no significant differences in the outcome of pregnancies with and without thrombophilia. Forty-six of 56 pregnancies without thrombophilia ended with live births (82.1%) under LMWH, similar to the expected value in normals.19 Therefore, LMWH also seems to increase the live birth rate in women, in whom after exclusion of thrombophilia the cause of the abortions remains unclear.

Proposed Pathophysiologic Mechanisms and Heparin Effects in Nonthrombophilic Pregnancy Loss

In our patients with a negative thrombophilia screening, unknown thrombophilic parameters cannot be firmly excluded. Apart from thrombophilia, immunological abnormalities could be involved in the pathogenesis. In this regard, changes in Th1 to Th2 cytokine ratio with a predominance of proinflammatory cytokines like tumor necrosis factor α (TNF-α), interleukin 1 (IL-1), and interferon γ (IFN-γ) have been demonstrated in patients with unexplained recurrent fetal loss.46-49 Antiproliferative and anti-inflammatory effects of heparin are well
known in addition to its anticoagulatory mechanism. Several immunologically important mechanisms of action of heparin have been shown. Heparin binds to P- and L-selectins (CD62 molecules) on the surface of trophoblast cells, granulocytes, monocytes, and lymphocytes and may interfere with cell adhesion. Since P- and L-selectins activate leukocytes and thrombocytes, heparin inhibits this effect resulting in a diminished release of proinflammatory cytokines. After intravenous administration of heparin, a massive release of hepatocyte growth factor (HGF) was also reported, which probably inhibits TNF-α and therefore may represent another anti-inflammatory cytokine pathway induced by heparin. Clark et al demonstrated that after Th1 cytokine stimulation (TNF-α, IFN-γ) a prothrombinase is increasingly secreted by endothelial cells in trophoblast and decidua, which leads to the formation of microthrombi and abortions. It was shown that heparin was able to prevent abortions in mice. In addition, cytokines can lower the progesterone level and therefore can lead to abortions. Other authors demonstrated an increase of proinflammatory cytokines, for example, TNF-α, and an increase of abortion rates under stress.

In addition, activation of the complement cascade has been shown to play a central role in recurrent abortions. Tichenor et al demonstrated an activated complement system in 30% of women with recurrent miscarriage after 7 weeks of gestation. Activation of the complement system directly leads to cell lysis via the membrane attack complex (MAC) and to migration and activation of leukocytes and therefore supports the inflammation process. Inhibition of complement seems to be an absolute requirement for normal pregnancy. Complement regulatory proteins like decay accelerating factor (DAF) and membrane cofactor protein (MCP) play an important role in complement inhibition. They are strongly expressed in human placentae. In animal experiments, Xu et al demonstrated the role of the complement regulatory protein Crry (complement receptor 1–related protein), which occurs in trophoblast cells and maternal decidua in mice. All Crry negative mice showed complement deposition in the placenta at the fetomaternal interface and aborted the fetus. Abortion was directly related to complement activation since all fetuses survived if the mice were also C3 deficient (C3–/–Crry–/–).

A role of complement activation has also been shown in APA syndrome, which is followed by a rapid increase of TNF-α as a possible effector. Girardi et al convincingly demonstrated the inhibition of complement activation by heparin in vivo and in vitro. After injection of APAs, unfractionated heparin and LMWH prevented the activation of complement as well as abortion in pregnant mice. Interestingly, the effect of heparin was also observed with a low dose not detectable by the PTT. Most noteworthy, neither fondaparinux nor hirudin inhibited complement activation and prevented pregnancy loss. Therefore, the mechanism of action of LMWH in APA may be independent of its anticoagulatory effects.

Our data support the hypothesis that LMWH is an efficacious therapy not only for recurrent miscarriage associated with thrombophilia but also in hitherto unexplained cases. In these situations, both anticoagulatory as well as anti-inflammatory effects of LMWH (inhibition of complement activation and of cytokine release) may be of critical importance.

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