Enoxaparin for prevention of unexplained recurrent miscarriage: a multicenter randomized double-blind placebo-controlled trial

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Key Points

• The use of low-molecular-weight heparin did not improve live-birth rates in nonthrombophilic women with consecutive recurrent miscarriage.
• Prophylactic doses of low-molecular-weight heparin should no longer be prescribed in this clinical setting.

Introduction

Miscarriage, defined as a spontaneous loss of the conceptus before 20 weeks’ gestation, is clinically detected in approximately 10% to 15% of pregnancies and recurs in 5% of subsequent pregnancies.1 Recurrent miscarriage is often defined by ≥3 consecutive losses and affects 1% to 2% of women of fertile couples who become pregnant.2 However, many experts accept 2 consecutive losses as sufficient for the diagnosis of recurrent miscarriage because the recurrence rate is close to that after 3 losses.3 In addition, the prevalence of abnormal results for evidence-based diagnostic tests does not differ among women after 2 vs 3 losses.4 Moreover, distressed women are often referred for care after 2 vs 3 losses. Causes and recurrence rates differ according to the gestational age at miscarriage. Most women have recurrent early loss with a failure of development before 10 weeks, although clinical symptoms most often occur after 10 weeks’ gestation. Therefore, the traditional grouping of all pregnancy losses before 20 weeks has been revised.5

Standard investigations fail to reveal any apparent cause in >50% of the women.1,2 On the basis of a parallel drawn with the antiphospholipid syndrome, hypotheses on thrombotic mechanisms were raised in unexplained pregnancy loss. An association with some inherited thrombophilias was suggested.6-8

At the time our study was designed, a randomized open-label trial suggested a strong benefit of low-molecular-weight heparin (LMWH) vs aspirin to improve the live-birth rate in women with at least 1 previous loss after 10 weeks’ gestation and an inherited thrombophilia.9 This led to extensive use of LMWH as the standard of care in thrombophilic women with recurrent miscarriage. Moreover, despite the lack of such a recommendation in evidence-based guidelines, it had become common practice in many centers to provide empirical treatment with low-dose aspirin, prophylactic doses of LMWH, or both for women with unexplained recurrent miscarriage, in the absence of an inherited thrombophilia.

It is common practice in many centers to offer antithrombotic medications to women with unexplained recurrent miscarriage, in the presence or absence of inherited thrombophilia. Although no benefit of aspirin vs placebo has been clearly demonstrated, a double-blind placebo-controlled trial on the effect of low-molecular-weight heparin is lacking.10 A recent randomized, double-blind, placebo-controlled trial, enoxaparin (40 mg once daily) did not improve the chance of a live birth in nonthrombophilic women with unexplained recurrent miscarriage. This trial is registered at www.ClinicalTrials.gov as #NCT00740545 and the French National Health and Drug Safety Agency (EudraCT #2006-003350-18). (Blood. 2015;125(14):2200-2205)
Although our goal was to evaluate the efficacy of LMWH in women with recurrent miscarriage regardless of the presence of a known thrombophilia, such a trial would have been deemed unethical in thrombophilic women at that time. Moreover, because nonpharmacologic interventions such as psychological support potentially improve the birth rate among women with recurrent miscarriage, we strongly believed a double-blind randomized trial was particularly required to avoid bias.\(^{10}\)

Therefore, in 2006, we designed the PREFIX (Prevention of Unexplained Recurrent Abortion by Enoxaparin) study, a randomized, double-blind, placebo-controlled multicenter trial to investigate whether LMWH would improve the live-birth rate among nonthrombophilic women.

### Methods

The study protocol was approved by the local Ethics Committee and the Comité pour la Protection des Personnes of Brest University Hospital. All patients provided written informed consent.

### Study population

Between April 4, 2007 and October 31, 2012, women were enrolled in 13 French hospital centers (Bordeaux, Brest, Caen, Dijon, La Réunion, Lille, Lorient, Marseille, Montpellier, Paris, Pau, Rouen, Saint-Etienne). Before initiation, the study was advertised to all obstetricians working in each participating center’s catchment area who were asked to refer potentially eligible women.

Inclusion criteria for the participants were pregnancy, age 18 to 45 years, and history of unexplained recurrent miscarriage. The current pregnancy had to be confirmed by a clinician. Recurrent miscarriage was defined as \(\geq 2\) consecutive miscarriages before 15 weeks’ gestation, conception with the same partner, and no live births subsequent to the consecutive miscarriages. The definition of miscarriage required both documentation of pregnancy and clinical manifestations of miscarriage but did not include the loss of a biochemical pregnancy (a transient elevation of the level of human chorionic gonadotropin near menses). Unexplained recurrent miscarriage was diagnosed in cases of normal karyotypes of both partners, the absence of any anatomical abnormality likely to be responsible for miscarriage, the absence of antiphospholipid syndrome,\(^{11}\) the absence of factor V Leiden, prothrombin G20210A mutations, and the absence of Protein S, C, and antithrombin deficiencies.

Exclusion criteria were women with another indication for aspirin or antiocoagulant therapy (eg, high risk of venous thromboembolism during pregnancy, chronic antithrombotic therapy for a cardiovascular condition), contraindication to enoxaparin 40 mg injections as per French labeling (eg, anemia <10 g/dL, platelet count <150 \(\times\) 10\(^9\)/L, creatinine clearance <30 mL/min), or they were unwilling or unable to consent.

### Study design

Women were included very early in their pregnancy, ideally before 5 weeks’ gestation, after a positive pregnancy test. At the first visit, after confirming eligibility and obtaining consent, women were randomized using a central web-based randomization system (ClinInfo Inc., Lyon, France) and received education for self-injections. Blocked randomization (allocation ratio of 1:1, block size of 6) was stratified according to study center and to 3 levels of disease severity, based on combination of woman’s age and the number of previous miscarriages. This was done in line with a previous longitudinal study on prediction of success rates of subsequent pregnancy (Table 1).\(^{12}\)

<table>
<thead>
<tr>
<th>Table 1. Baseline characteristics of the patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enoxaparin</td>
</tr>
<tr>
<td>---</td>
</tr>
<tr>
<td>N</td>
</tr>
<tr>
<td>Age, y (mean [SD])</td>
</tr>
<tr>
<td>Body mass index, kg/m(^2) (mean ± SD)</td>
</tr>
<tr>
<td>Daily smoking ≥1 cigarette, n (%)</td>
</tr>
<tr>
<td>Systolic blood pressure(^*), mm Hg (mean [SD])</td>
</tr>
<tr>
<td>Previous venous thromboembolic event, n (%)</td>
</tr>
<tr>
<td>Gestation at inclusion, days (mean ± SD)</td>
</tr>
<tr>
<td>Number of previous miscarriage, n (median [range])</td>
</tr>
<tr>
<td>One or more loss ≥10 wk†, n (%)</td>
</tr>
<tr>
<td>Randomization strata, n (%)‡</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>3</td>
</tr>
</tbody>
</table>

\(^*\)At inclusion.

\(^†\)Two missing data in each intervention group.

\(^‡\)Strata 1: (2 previous miscarriages and age <35 y) or (3 previous miscarriages and age <30 y) or (4 or 5 previous miscarriages and age <25 y), Strata 2: (2 previous miscarriages and 35 ≤ age <40 y) or (3 previous miscarriages and 30 ≤ age <40 y) or (4 or 5 previous miscarriages and 25 ≤ age <35 y), Strata 3: (2 or 3 previous miscarriages and age ≥40 y) or (4 or 5 previous miscarriages and age ≥35 y).

subsequently once a day, initiated from the inclusion visit (or within 24 hours) and continued by self-injection until 35 weeks’ gestation.

Women were seen in clinic every month until completion of the pregnancy, and one time 2 months post-delivery, by a medical investigator. Pregnancy surveillance, platelet count monitoring, compliance, and side effects were addressed during this visit with the use of a structured form. Compliance was assessed by reviewing at each visit a “treatment adherence notebook,” in which women recorded the time and site of injection daily. Patients, doctors, and trial nurses were all unaware of the study group assignments.

Women also received standard care and pregnancy monitoring, including fetal ultrasonography, by their own obstetrician throughout the pregnancy. All women were advised to take a folic acid supplement.

### Outcome measures

The primary outcome measure was the rate of live and viable births. In case of preterm and/or low birth weight, we defined the viability by the decision to transfer the newborn to a neonatal intensive care unit.

Secondary outcomes included rates of miscarriage, rates of obstetric complications (intrauterine fetal death after 20 weeks’ gestation, preeclampsia, birth of a small-for-gestational-age neonate, placental abruption, and premature delivery), rates of maternal thrombocytopenia (defined as a platelet count <0.6 \(\times\) baseline platelet count or platelet count <100,000/mm\(^3\)), bleeding episodes, and skin reactions.

All data on the infant and delivery were collected during the last visit, most often performed around 2 months after delivery. Obstetric and pediatric medical reports were retrieved.

### Statistical analysis

Baseline characteristics of the study population were expressed as means and standard deviation, or number of patients and proportions, as appropriate. The primary outcome and the rates of different classifications of pregnancy loss were assessed in all women, according to the intention-to-treat principle. Differences in dichotomous outcomes among the 2 study groups were analyzed with the use of the \(x^2\) test or Fisher’s exact test as appropriate. Differences in live-birth rates were expressed as absolute differences and relative risks, with associated 95% confidence intervals, with the placebo group as the reference. A Student \(t\) test was used to compare continuous outcome measures.

The incidences of preeclampsia, placental abruption, preterm delivery, and small-for-gestational-age size were calculated for women who had an ongoing...
randomized. The inclusions) and 400 women (two-thirds of the planned inclusions) were lost to follow-up, but some did not complete the treatment as planned in the protocol (Figure 1). Two women immediately withdrew consent before the first injection. Thus the data of 256 women were analyzed (138 and 118 women in the enoxaparin and placebo groups, respectively). No woman was lost to follow-up, but some did not complete the treatment as planned in the protocol (Figure 1). Only 1 woman declined injections early after inclusion (3 weeks of injections). Five other patients preferred to stop injections after the first trimester of pregnancy, because they were reassured regarding the risk of pregnancy loss and consequently less motivated for the self-injections. The investigators decided to discontinue the injections in 3 women (always after the first trimester of pregnancy) because of suspected side effects: cervix bruising (n = 1, placebo arm), skin reaction (n = 1, enoxaparin arm), thrombocytopenia (n = 1, enoxaparin arm). Heparin-induced thrombocytopenia was ruled out in the latter 2 cases.

Baseline characteristics were similar between the study groups and are summarized in Table 1. Mean age was 32 years (range 18–44), and 72% of women had ≥3 previous miscarriages. The mean gestational age at randomization (ie, time at which the injections were started) was 39 days of amenorrhea.

### Study monitoring

According to the study protocol, a data and safety monitoring board,14 whose members were unaware of the study group assignments, had to perform 2 planned blinded interim analyses, after 200 (~one-third of the planned inclusions) and 400 women (~two-thirds of the planned inclusions) were randomized. The first planned data and safety monitoring board meeting was held on September 4, 2012. The analysis included the data from 207 women in whom the primary outcome had occurred or in whom a miscarriage had occurred by June 1, 2012. On the basis of this analysis, the board advised discontinuation of the study because of futility. The recruitment stopped on October 31, 2012. The study was discontinued on September 2, 2013 after the last woman completed the last visit planned in the protocol.
Table 2. Live-birth rate (primary outcome)

<table>
<thead>
<tr>
<th>Enoxaparin</th>
<th>Placebo</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intention-to-treat analysis, n</td>
<td>138</td>
<td>118</td>
</tr>
<tr>
<td>Live birth, n (%)</td>
<td>92 (66.6)</td>
<td>86 (72.9)</td>
</tr>
<tr>
<td>Relative risk (95% CI)</td>
<td>0.91 (0.78 to 1.07)</td>
<td></td>
</tr>
<tr>
<td>Absolute difference in live-birth rate (95% CI)</td>
<td>−6 (−17.1 to 5.1)</td>
<td></td>
</tr>
<tr>
<td>Per-protocol analysis, n</td>
<td>116</td>
<td>101</td>
</tr>
<tr>
<td>Live birth, n (%)</td>
<td>85 (73.3)</td>
<td>74 (73.3)</td>
</tr>
<tr>
<td>Relative risk (95% CI)</td>
<td>1 (0.85-1.17)</td>
<td></td>
</tr>
<tr>
<td>Absolute difference in live-birth rate (95% CI)</td>
<td>0 (−12 to 12)</td>
<td></td>
</tr>
</tbody>
</table>

The women included in the per-protocol analysis were treated at least 7 days until loss or beyond 12 weeks’ gestation, and the injections were started before 6 weeks’ gestation or at least 1 week before the most advanced term reached before during previous pregnancies.

We did not observe any significant difference in secondary outcomes between the 2 groups (Table 3). During the study, 30.4% of women enrolled in the enoxaparin group vs 23.7% in the placebo group had a subsequent miscarriage (relative risk, 1.28; 95% CI, 0.85-1.93). Most of the losses (84.3%) occurred before 10 weeks’ gestation.

Maternal adverse events are displayed in Table 3. Seven women (4 in the enoxaparin arm, 3 in the placebo arm) developed thrombocytopenia, but none were diagnosed with heparin-induced thrombocytopenia. Two women in the enoxaparin group required blood transfusions after delivery, whereas injections were discontinued for >10 days. One woman in the enoxaparin group displayed indurations at the injection sites, leading to an interruption of the study intervention at 12 weeks’ gestation. Within the 2 following weeks, she had an unexplained intrauterine fetal death. She had no heparin-induced thrombocytopenia (negative enzyme-linked immunosorbent assay test), and no cause was found to explain the intrauterine death after placenta and fetus examination. Among the premature infants, one in each group died in intensive care unit.

There were no significant interactions between the study group assignment and the number of previous miscarriages, the presence or absence of a previous live birth, the presence or absence of a previous loss after 10 weeks’ gestation, age, or the strata of randomization (Figure 2).

Discussion

In this first reported randomized, double-blind, placebo-controlled trial, enoxaparin given at the daily dose of 40 mg did not improve the chance of a live birth in nonthrombophilic women with a history of unexplained recurrent miscarriage. Enoxaparin use at a daily dose of 40 mg was safe during early pregnancy. Our trial was designed to detect a minimal clinically important difference of 10% in live-birth rates. The upper limit of the 95% confidence interval around the difference in rates of live birth between groups excludes a 10% benefit with enoxaparin (absolute difference of −6% [95% CI, −17.1 to 5.1]).

Since the initiation of our study in 2006, the results of several randomized trials were reported in unexplained recurrent miscarriage.15-22 Only one trial was placebo-controlled (the ALIFE study), a randomized trial among all-comer women (−85% had a negative thrombophilia workup), which resulted in a turning point: the lack of any benefit of aspirin was clearly demonstrated. In addition, the use of open-label LMWH combined with aspirin in a third intervention arm did not show any improvement in live-birth rates vs oral placebo.18 The SPIN study showed no efficacy of open-label LMWH plus aspirin vs intense pregnancy surveillance alone (all-comer women).19 Yet a detrimental effect of aspirin could not be ruled out and might explain the lack of efficacy of the combination with LMWH.10,18 As regards the use of LMWH alone, 2 randomized open-label but underpowered trials did not show a significant benefit of enoxaparin vs aspirin,15,20 although in the HABENOX trial,20 the live-birth rate was higher with LMWH (71% vs 61% for enoxaparin and aspirin, respectively, P = .45, all-comer women). Finally, in a randomized single-blinded trial with some methodologic limitations, live-birth rates were significantly higher among women assigned to receive enoxaparin than among those assigned to receive a not-well-characterized oral placebo (81% vs 48%); all had a negative hereditary thrombophilia workup.16 Thus, conclusive data were still lacking concerning the effect of LMWH alone in improving the outcome of pregnancy in women with unexplained recurrent miscarriage. This is supported by the last meta-analysis23 in which the authors state that only the data of 6 patients22 could be

Table 3. Secondary outcomes

<table>
<thead>
<tr>
<th>Enoxaparin</th>
<th>Placebo</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse events</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>138</td>
<td>118</td>
</tr>
<tr>
<td>Congenital abnormality*, n (%)</td>
<td>7 (5)</td>
<td>3 (2.5)</td>
</tr>
<tr>
<td>Major bleeding, n (%)</td>
<td>2 (1.4)</td>
<td>2 (1.7)</td>
</tr>
<tr>
<td>Blood transfusion†, n</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Fall in hemoglobin level ≥20 g/L, n</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Minor bleeding, n (%)</td>
<td>33 (23.9)</td>
<td>17 (14.4)</td>
</tr>
<tr>
<td>Bruising, n (%)</td>
<td>11 (7.9)</td>
<td>4 (3.4)</td>
</tr>
<tr>
<td>Nausea, n (%)</td>
<td>10 (7.2)</td>
<td>5 (4.2)</td>
</tr>
<tr>
<td>Bleeding gums, n (%)</td>
<td>3 (2.2)</td>
<td>2 (1.7)</td>
</tr>
<tr>
<td>Minor vaginal bleeding, n (%)</td>
<td>9 (6.5)</td>
<td>6 (5.0)</td>
</tr>
<tr>
<td>Severe skin reaction at the injection site, n (%)</td>
<td>1 (0.7)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Thrombocytopenia*, n (%)</td>
<td>4 (2.9)</td>
<td>3 (2.5)</td>
</tr>
<tr>
<td>Pregnancy outcomes before 20 weeks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>138</td>
<td>118</td>
</tr>
<tr>
<td>Miscarriage, n (%)</td>
<td>42 (30.4)</td>
<td>28 (23.7)</td>
</tr>
<tr>
<td>Gestational age at miscarriage, wk (mean [SD])</td>
<td>8.2 (1.97)</td>
<td>8.5 (2.8)</td>
</tr>
<tr>
<td>Medically indicated termination of pregnancy§, n (%)</td>
<td>2 (1.4)</td>
<td>1 (0.8)</td>
</tr>
<tr>
<td>Ectopic pregnancy, n (%)</td>
<td>2 (1.4)</td>
<td>1 (0.8)</td>
</tr>
<tr>
<td>Outcomes of ongoing pregnancies after 20 weeks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>92</td>
<td>88</td>
</tr>
<tr>
<td>Intrauterine fetal death, n (%)</td>
<td>0 (0)</td>
<td>1 (1.1)</td>
</tr>
<tr>
<td>Medically indicated termination of pregnancy§, n (%)</td>
<td>0 (0)</td>
<td>1 (1.1)</td>
</tr>
<tr>
<td>Preeclampsia, n (%)</td>
<td>6 (6.5)</td>
<td>2 (2.3)</td>
</tr>
<tr>
<td>Placental abruption, n (%)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Small for gestational age (&lt;10th percentile), n (%)</td>
<td>1 (1)</td>
<td>3 (3.4)</td>
</tr>
<tr>
<td>Premature delivery, n (%)</td>
<td>7 (7.6)</td>
<td>7 (7.9)</td>
</tr>
<tr>
<td>≥24 to &lt;28 weeks, n</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>≥28 to &lt;32 weeks, n</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>≥32 to &lt;37 weeks, n</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Multiple gestation, n (%)</td>
<td>1 (1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Outcomes of pregnancies with live birth</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>92</td>
<td>86</td>
</tr>
<tr>
<td>Birth weight, g (mean [SD])</td>
<td>3283 (554)</td>
<td>3142 (537)</td>
</tr>
<tr>
<td>Gestation at delivery, weeks (mean [SD])</td>
<td>39.3 (2.2)</td>
<td>38.9 (3.2)</td>
</tr>
</tbody>
</table>

*Placebo group: 1 arthrogryposis, 1 polymalformative syndrome, and 1 hydrocephrosis. Enoxaparin group: 1 trisomy 21, 1 polymalformative syndrome, 1 neonatal epilepsy, 1 interventricular communication, 1 hairless line, 1 congenital nevus, 1 ear lobe anomaly.
†The injections were stopped for 10 or more days when hemorrhage occurred.
§Maternal thrombocytopenia was defined as a platelet count <0.6× baseline platelet count or as a platelet count <100,000/mm³. No heparin-induced thrombocytopenia was observed.
§§Medically indicated termination of pregnancy as a result of a congenital abnormality cited in the first footnote.
¶One missing data.
analyzed about the effect of heparin alone vs no treatment, when excluding studies with a high risk of bias.16,17

The use of LMWH was supported by some studies in which a basal prothrombotic state outside of pregnancy was measured in women with previous recurrent miscarriage and without known thrombophilia.24-26 In addition, heparin and LMWH have other biological properties that could be critical for implantation and placentation.27-35 It is possible that to be beneficial, heparins may require administration at the time of the initial implantation. Our study was not designed to test such a hypothesis. The injections were most often initiated at 5 to 6 weeks' gestation, although the instruction was to begin the treatment at the earliest during pregnancy. In the per-protocol analysis, taking into account the appropriate exposure to the assigned study drug (early and long enough), the rates of live birth in each intervention group were similar (73.3%). Likewise, the subgroup analysis did not suggest any clinical benefit from enoxaparin for any subset of patients with a higher risk for recurrence.

Other limitations of our study warrant consideration. We initially planned to recruit 305 patients in each group. Nevertheless, physicians often convinced of LMWH efficacy were sometimes reluctant to include their patients in the trial, because of the inclusion of placebo injections. As a result, the recruitment process was slower than expected. On the basis of the review of the first planned blinded interim analysis, the steering committee decided to prematurely close the study. More than 5 additional years of recruitment would have been necessary to reach statistical significance, and after unblinding treatment allocation, this would have been useful to demonstrate superiority of placebo. Another limitation is that this trial did not assess enoxaparin in women with known inherited thrombophilias (factor V Leiden or prothrombin G20210A mutations, proteins S, C, and antithrombin III deficiencies). No previous reported study was designed to robustly examine the subgroup of women with thrombophilia. In a recently reported open-label trial (TIPPS), 35 of 69 thrombophilic women with previous recurrent miscarriage were randomized to receive antepartum LMWH without any impact on the live birth rate.36 Finally, we used a broad definition of recurrent miscarriage, more consistent with the current medical practice (ie, ≥2 miscarriages). However, ~70% of our patients had ≥3 losses compared with 100%, 60%, and 43% of the women enrolled in HABENOX,20 ALIFE,18 and SPIN,19 respectively. Moreover, in our study, the live-birth rates were 66.6% and 72.9% in the enoxaparin and placebo groups, respectively (P = .34). These live-birth rates were consistent with those of the longitudinal study of Brigham et al,12 and of the HABENOX20 and ALIFE18 trials, suggesting similar disease severity. The mean gestational age at miscarriage observed in our study was similar to the one reported in ALIFE.18

In conclusion, in this first reported randomized, double-blind, placebo-controlled trial, enoxaparin given at a daily dose of 40 mg did not improve the chance of a live birth in nonthrombophilic women with a history of unexplained recurrent miscarriage. Prophylactic doses of LMWH do not improve the chance of a live birth in nonthrombophilic women with unexplained recurrent miscarriage and should consequently no longer be routinely prescribed in this clinical setting.

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Authorship

received support from Sanofi-Aventis. The remaining authors declare no competing financial interests.

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References

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