LOW MOLECULAR WEIGHT HEPARIN VERSUS LOW-DOSE ASPIRIN IN WOMEN WITH ONE FETAL LOSS AND A CONSTITUTIONAL THROMBOPHILIC DISORDER


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Running head: Thromboprophylaxis for first fetal loss
Abstract

The prospective evaluation of the effect of thromboprophylaxis in women with one unexplained pregnancy loss from the 10th week of amenorrhea was performed: 160 patients, with heterozygous factor V Leiden mutation, prothrombin G20210A mutation, or protein S deficiency, were given 5 mg folic acid daily before conception, to be continued during pregnancy, and low-dose aspirin, 100 mg daily or low-molecular weight heparin enoxaparin, 40mg, were taken from the 8th week. Twenty three of the 80 patients treated with low-dose aspirin and 69 of the 80 patients treated with enoxaparin had a normal live birth (OR 15.5, 95% CI 7-34, p<0.0001). Enoxaparin was superior to low-dose aspirin in each subgroup defined according to the underlying constitutional thrombophilic disorder. An associated protein Z deficiency, and/or positive anti-protein Z antibodies, were associated with poorer outcomes. The neonate weight was higher in the women successfully treated with enoxaparin and neonates small for gestational age were more frequent in patients treated with low-dose aspirin. No significant side-effects of the treatments could be evidenced in patients or newborns. As there is no argument to prove that low-dose aspirin may had been deleterious, these results support enoxaparin use during such at-risk pregnancies.
The use of serial ultrasonography studies during early pregnancy have shown that the arterial signals in the yolk circulation disappear and the umbilicoplacental circulation increases between 8 and 10 weeks of gestation, indicating that the placenta replaces the yolk sac as an essential source of blood supply to the embryo at that time (1). Thus, it can be deducted that during the switch and at least from the beginning of the 11th week of gestation, the maintenance of the permeability of the maternal placental intervillous space becomes a crucial necessity for the viability of the fetus. This pathophysiologic perception has been reinforced by a demonstration, in the late nineties, mainly by means of a series of case-control studies performed after the first one published by Sanson et al. (2), that thrombophilic disorders in the mother are associated with an increased risk of fetal loss, before or after (still births) 22 weeks of gestation. This has led to a recent meta-analysis showing that factor V Leiden mutation, activated protein C resistance, prothrombin G20210A mutation (factor II G20210A mutation) and protein S deficiency are likely to be associated with a significant risk of fetal loss (3), giving legitimacy to secondary prevention trials using antithrombotic agents, mainly low molecular weight heparin (LMWH).

Concerning antithrombotic prophylaxis in women with thrombophilia and pregnancy complications, two distinct opinions are currently developed. The first one (4), based on the results of non-controlled published studies in which outcomes were compared to the patients’ previous history of pregnancy loss (5,6,7,8), favors the use of LMWH during the next possible pregnancy. The second one (9), due to the absence of controlled studies, does not support the use of LMWH.

It is however very difficult to propose placebo to women with such a potentially harmful, at least in its psychological dimension, medical antecedent. Most patients, due to moral suffering but also to abundant data currently available, i.e. on the web, concerning the use of LMWH during at-risk pregnancies, do not accept it. In spite of our efforts, the great majority of patients did not adhere to it.

We thus performed, in women with a single antecedent of unexplained fetal loss, a prospective trial comparing two antithrombotic therapies: low-molecular weight heparin, enoxaparin, and low-dose aspirin.
PATIENTS AND METHODS

Patient inclusion criteria

This therapeutic trial took place in our Mediterranean Abnormal Pregnancy Study Program, which has led to the previously published NOHA studies on haemostasis-related risk factors for pregnancy losses (10, 11, 12, 13, 14, 15).

Patients were selected from those who had been referred to our laboratory by practitioners and obstetricians of the Southern French Region Languedoc-Roussillon, due to at least one antecedent of pregnancy loss from the 10th week of amenorrhoea.

Medical history with specific attention to obstetric history (pregnancies, child birth, treatments, infectious disease during pregnancy including H.I.V., erythroblastosis fetalis –Rh. disease–, immune thrombocytopenic purpura (I.T.P.) and fetomaternal alloimmune thrombocytopenia (F.A.T.), gravidic hypertension and its complications, trauma, obstetric complications, diabetes mellitus, morphologic malformation in the dead fetus) was taken into consideration by investigators who were unaware of the laboratory results. Any positive pathology mentioned here was an exclusion criteria.

We looked for presumptive etiological factors: hysterosalpingogram, karyotype in both parents, glucose tolerance test, toxoplasmosis serology, thyroid function, serum prolactin levels, normal luteal phase of at least 12 days and plasma progesterone above 25 ng/ml, absence of anti nuclear factor, or antiphospholipid / antiprotein antibodies (lupus anticoagulant, anticardiolipin, anti-β2-glycoprotein I, anti-annexin V, anti-phosphatidylethanolamine, IgG and IgM, by the methods previously described in our laboratory: 12,15), absence of antithrombin or protein C deficiency (11), fasting plasma total homocysteine lower than 15 µM/L. All these data were obtained between 6 and 12 months after fetal loss. All women finally included in the study were negative for the various tests or assessments mentioned here.

Exclusion criteria were: any presumptive etiological factor, as described above; any antecedent of venous or arterial thrombosis; any pregnancy loss before the beginning of the 10th week of amenorrhoea; any lethal fetal defect; fetal hemorrhage; pregnancy-induced hypertension with its complications; any infectious disease during
pregnancy; known erythroblastosis fetalis, I.T.P. or F.A.T.; trauma during pregnancy; diabetes mellitus; tobacco consumption at least equal to 10 cigarettes a days.

Finally, the ultimate inclusion criteria was one single unexplained pregnancy loss from the 10th week of amenorrhoea, -with no unexplained pregnancy losses before the beginning of the 10th week of amenorrhoea and no explained pregnancy losses-, associated with a factor V Leiden mutation, or a factor II G20210A mutation (all heterozygous), or a protein S deficiency (performed as previously described: 11; functional activity in a procoagulant assay and free protein S antigen all lower than 55% of normal values). Protein Z plasma concentrations and anti-protein Z antibodies, IgG and IgM were systematically assayed (13, 14); protein Z was considered to be deficient in the case of concentrations lower than 1 mg/l (13), anti-protein Z IgG were considered positive if higher or equal to 7.1 A.U. in two consecutive evaluations and anti-protein Z IgM if higher or equal to 5.3 A.U. (14). Thus, patients had one principal thrombophilic disorder among the two Leiden mutations and protein S deficiency, and may also have protein Z deficiency or/and positive anti-protein Z antibodies. We pre-included the 184 consecutive patients fulfilling our criteria.

**Treatment regimens.**

The study was approved by our local Hospital Ethics Committee. All patients were fully informed of the aim of the trial and of the proposed treatment regimens and, before definitive study enrolment, informed consent was obtained from all of them.

These 184 patients were offered thromboprophylaxis during the next pregnancy. Beforehand, they were allocated to take either low-dose aspirin, 100 mg daily (Aspégic nourrissons, Sanofi-Synthélabo, France) or low-molecular weight heparin, enoxaparin (Lovenox, Aventis, France), a subcutaneous injection of 40 mg daily. Allocation was performed blindly and at random by an independent statistician in order to equilibrate the two proposals of treatments among women belonging to the same thrombophilic disorders-related subgroups of patients, as defined in table I. Systematically, injections were carried out percutaneously in the abdomen by the patient herself after initiation. Both treatments were administered at 8.00 p.m. Due to the fact that umbilicoplacental circulation increases from the 8th week (1), thromboprophylaxis systematically began at the beginning of the 8th week of amenorrhoea after a positive pregnancy test.
As folates may be involved in thrombotic risk (16), all patients were taking therapeutic doses of folic acid, 5 mg daily, at least one month before conception. This treatment was continued during all new ongoing pregnancies.

Finally, 174 patients gave their consent to participate and conceived. Twelve of them had an early pregnancy loss, before the 8th week and before the beginning of one of the treatments. The clinical characteristics of the remaining 160 patients are found in Table I and the types of thrombophilic disorders they were carrying in Table II. No significant differences, in terms of age, number of pregnancies, moment of fetal loss, body mass index, or categories of these four clinical criteria (as defined in Table I) could be evidenced.

**Analysis.**

The end-points of the study were the following: live birth rates; pregnancy losses from the beginning of the 8th week; haemorrhagic complications in the mother and in the newborn; weight of the neonates; any complications during pregnancy; any abnormal manifestation in the newborn.

Statistical significance was considered at p<0.05 and was tested with Mann-Whitney and Kruskall-Wallis non-parametric tests for continuous variables and with Chi² and F-test for nominal variables. Logistic regression was performed when appropriate.

**RESULTS**

Table II and III show the effects of the two treatments on pregnancy outcome: the use of low-molecular weight heparin enoxaparin was associated with an impressively higher rate of normal live births, in all the women but also in each of the three subgroups defined by their principal underlying thrombophilic disorder (factor V Leiden, factor II G20210A mutation, or protein S deficiency). These results were not significantly influenced by the number of previous pregnancies, by age or classification of age, by the moment of previous fetal loss, by the body mass index values or their classification of values, by tobacco consumption.
The rates of normal live births were the same according to the type of the 3 principal thrombophilic disorders (p=0.15). Positive protein Z deficiency or anti-protein Z antibodies were equally found in patients treated with aspirin and with the LMWH (respectively 36% and 39% in both treated groups). An associated protein Z deficiency, or positive protein Z antibodies, were more frequently present in the case of treatment failures (respectively: p=0.020 and p=0.019), as was the complex protein Z deficiency - positive anti-protein Z antibodies (p=0.004; 15 of the 20 cases led to pregnancy failure, 9 being treated with aspirin, 6 with enoxaparin). Table IV gives the results of the multiparametric logistic regression model, adjusted by the type of treatment, type of principal thrombophilic disorder, protein Z status and anti-protein Z status: the reference being a patient with a factor V Leiden mutation but no protein Z deficiency nor positive anti-protein Z antibodies, treated with low-dose aspirin during pregnancy, low-molecular weight heparin use was associated with a dramatic increase in the chance of giving birth to a living child, protein Z deficiency or anti-protein antibodies were independently associated with a significant decrease of this chance and factor II G20210A mutation and protein S deficiency indicated a non-significant trend for a lower chance of good pregnancy outcome.

Aspirin was associated with 57 pregnancy losses and enoxaparin with 11. In patients taking aspirin, losses occurred between the 11th and the 18th week of amenorrhoea (median: 15 weeks, lower and upper quartiles: 13 and 16 weeks). In patients taking enoxaparin, losses occurred later on: from the 17th to the 24th week (during weeks 23 and 24 in 2 patients).

Seventy six of the 92 successful pregnancies (83%) ended at term after 37 weeks of gestation. Non-severe pre-eclampsia developed in 7 cases, 4 women treated by enoxaparin and 3 with low-dose aspirin, with no pejorative secondary consequence for the women or their neonate. Of the 92 neonates, 65 were delivered vaginally and 29 (32%) by cesarean section.

The neonate weight was higher in the 69 women successfully treated with enoxaparin (median 3043g, interquartile range 373g, range 2310-3787) than in the 23 women treated with low-dose aspirin (median 2742g, interquartile range 522g, range 2010-3268) (p=0.0005). Neonates weights were not, for each of the treatments, correlated to the intensity of tobacco consumption before pregnancy, nor to the residual
tobacco consumption during pregnancy. Neonates small for gestational age, defined as having a weight lower or equal to the 10th percentile corresponding to the gestational age at birth, were delivered by 7 of the 71 successful mothers treated with enoxaparin (10%) and in 7 of the 23 successful mothers treated by aspirin (30%; Fisher’s exact test: p=0.04). None of these small for gestational age neonates had, finally, any significant sequela.

We have not observed any case of heparin-induced thrombocytopenia, of abnormal skin reactions or of clinical manifestation of spontaneous bone pain among the enoxaparin treated women. No case of digestive intolerance to low-dose aspirin either. There were no hemorrhage, except slight bruising at the injection sites for enoxaparin and for both treatments in case of local domestic trauma.

**DISCUSSION**

The present study shows that in women with one pregnancy loss from the 10th week of amenorrhoea, and carrying a factor V Leiden mutation, or a factor II G20210A mutation, or a protein S deficiency, and taking 5 mg folic acid per day, treating the next pregnancy with the low-molecular weight enoxaparin from the 8th week is associated with a greater number of live births and with more normal weight neonates, than using a low-dose aspirin treatment, and without any consistent clinical complications.

This is the first study in which the outcome of antithrombotic-treated, constitutional thrombophilia-associated pregnancies in women with a clearly defined obstetric history is not compared to the patients’ previous history of pregnancy loss but in which two antithrombotic treatments are prospectively compared. One may argue that, in such cases, a placebo-controlled trial should have been done first (9): we agree to this theoretical argument which was tried out, but failed, due to the fact that very few women having suffered fetal loss adhere to placebo trial. However, we are not in a classical situation in which we only try to prevent a special subtype of thrombosis recurrence: here, we try to prevent death recurrence, by treating women who in their special "future mother context" always, in case of failure, lose a part of their own life. We thus thought that comparing two antithrombotic treatments was a humane ethical option.
This study was not a blind test study. Patients and physicians were aware of the treatment being taken. It would have been necessary for blind tests to have access to two placebo formulations, one for oral aspirin, one for subcutaneous low-molecular weight heparin: producing them, for such potentially long treatments, is of significant cost. This trial was performed without any financial support from pharmaceutical industries: it was difficult to imagine that the two laboratories, the one producing aspirin and the other producing the LMWH, would accept to collaborate in the same trial, potentially leading to only one of them supporting the trial. This should have opened the door to the masked criticism of credibility generally associated to studies sponsored by the industry. So, in absence of sufficient institutional funding, we chose not to perform a double-placebo controlled trial and we think that our results are likely to be independent from industrial influences.

Our patients had the 3 constitutional thrombophilic disorders which have been validated by the available meta-analysis of the published studies (3), and mainly the 2 which are the most frequently diagnosed, namely the factor V and factor II mutations. We did not stratify the obtained results by the level of fasting total homocysteinemia, due to the fact that all patients were taking folic acid, from at least one month before conception, in order to eliminate this potential cofactor of vasculo(placental complications (17). However, patients were stratified accordingly to the presence/absence of protein Z deficiency and/or anti-protein Z antibodies, that we had previously described to be associated with poor pregnancy outcome (13,14): protein Z deficiency has been described to increase the severity of the prothrombotic phenotype of factor V Leiden in mice (18) and in patients (19) and it was thus necessary to take into account these potential cofactors. Finally, our results show that protein Z deficiency and positive anti-protein Z antibodies are independent risk factors for a poor outcome of treated pregnancies, particularly in aspirin-treated patients.

The spontaneous prognosis of pregnancy in non-thrombotic women with factor V or factor II mutations or with protein S deficiency, and a single unexplained fetal loss from the 10th week, is basically still unknown. However, Rai et al. (20) recently reported the prospective outcome of untreated pregnancies in 25 women heterozygous for the factor V Leiden mutation: in 16 women with 3 or more miscarriages at less than 12 weeks gestation, the spontaneous live birth rate was 6/16 but, in 9 women with fetal
loss after 12 weeks gestation, was 1/9. Our patients receiving low-dose aspirin had a
good outcome in roughly one third of the cases. Due to the fact that 86% of our patients
had experienced fetal loss after 12 weeks, it is thus not impossible that low-dose aspirin
may have a positive significant clinical effect, by itself or in association with folic acid.
A recent study showed that exposure to aspirin during pregnancy increases miscarriages
(21): the risk was however limited to the prenatal use of aspirin and treatments, in our
patients, did nor begin before the 6th week after the extrapolated date of conception.

In pregnancies with a good outcome, low birth weight has been consistently
shown to be associated with coronary heart disease which appears to be, from an
epidemiological point of view, a developmental disorder that originates through two
widespread biological phenomena, developmental plasticity in utero and compensatory
growth during infancy (22). Treating mothers having the lowest rate of neonates with a
small weight for gestational age may thus be associated to the lowest incidence of
cardiovascular diseases in future adults: if this relationship was also validated after
therapeutic interventions, this would be another reason to prefer low-molecular weight
heparin to low-dose aspirin in our patients.

In conclusion, enoxaparin given from the 8th week of amenorrhoea in order to
prevent pregnancy loss in non-thrombotic women carrying the factor V Leiden
mutation, or the factor II G20210A mutation, or protein S deficiency, and having a
single antecedent of unexplained fetal loss from the 10th week of amenorrhoea, seems to
be a safe, much more effective treatment than low-dose aspirin.

Acknowledgements
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We thank Margaret Manson for editorial assistance.

References


Table I. Clinical characteristics of the patients included in the study.

B.M.I.: body mass index. AllFVL: all patients carrying the heterozygous factor V Leiden mutation; AllFIIL: all patients carrying the heterozygous factor II G20210A mutation; AllPS: all patients carrying a protein S deficiency.

<table>
<thead>
<tr>
<th>Number of pregnancies</th>
<th>Moment of fetal loss -weeks of amenorrhoea-</th>
<th>Age -years-</th>
<th>B.M.I. -kg.m(^{-2})</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median (range)</td>
<td>Median (range)</td>
<td>Median (range)</td>
</tr>
<tr>
<td>All women</td>
<td>1 (1-2)</td>
<td>15 (10-29)</td>
<td>96</td>
</tr>
<tr>
<td>AllFVL</td>
<td>1 (1-2)</td>
<td>15 (10-29)</td>
<td>48</td>
</tr>
<tr>
<td>AllFIIL</td>
<td>1 (1-2)</td>
<td>15 (10-27)</td>
<td>32</td>
</tr>
<tr>
<td>AllPS</td>
<td>1 (1-2)</td>
<td>16 (11-23)</td>
<td>16</td>
</tr>
</tbody>
</table>
Table II. Stratification of the included patients with one unexplained pregnancy loss from the 10th week of amenorrhoea, according to the principal underlying thrombophilic disorders, and effect of the two treatments on the rate of live births.

<table>
<thead>
<tr>
<th>Main thrombophilic disorder</th>
<th>With negative protein Z deficiency and negative anti-protein Z antibodies</th>
<th>With positive protein Z deficiency and negative anti-protein Z antibodies</th>
<th>With negative protein Z deficiency and positive anti-protein Z antibodies</th>
<th>With positive protein Z deficiency and positive anti-protein Z antibodies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-dose aspirin</td>
<td>06/13</td>
<td>02/08</td>
<td>03/10</td>
<td>01/05</td>
</tr>
<tr>
<td>Factor V Leiden mutation</td>
<td>26</td>
<td>16</td>
<td>20</td>
<td>10</td>
</tr>
<tr>
<td>Enoxaparin</td>
<td>13/13</td>
<td>08/08</td>
<td>10/10</td>
<td>03/05</td>
</tr>
<tr>
<td>Low-dose aspirin</td>
<td>07/15</td>
<td>01/05</td>
<td>02/07</td>
<td>00/03</td>
</tr>
<tr>
<td>Prothrombin G20210A mutation</td>
<td>30</td>
<td>10</td>
<td>14</td>
<td>06</td>
</tr>
<tr>
<td>Enoxaparin</td>
<td>14/15</td>
<td>04/05</td>
<td>05/07</td>
<td>01/03</td>
</tr>
<tr>
<td>Low-dose aspirin</td>
<td>01/02</td>
<td>00/06</td>
<td>00/04</td>
<td>00/02</td>
</tr>
<tr>
<td>Protein S deficiency</td>
<td>04</td>
<td>12</td>
<td>08</td>
<td>04</td>
</tr>
<tr>
<td>Enoxaparin</td>
<td>02/02</td>
<td>06/06</td>
<td>03/04</td>
<td>00/02</td>
</tr>
<tr>
<td>Low-dose aspirin</td>
<td>14/30</td>
<td>03/19</td>
<td>05/21</td>
<td>01/10</td>
</tr>
<tr>
<td>Patients : total</td>
<td>60</td>
<td>38</td>
<td>42</td>
<td>20</td>
</tr>
<tr>
<td>Enoxaparin</td>
<td>29/30</td>
<td>18/19</td>
<td>18/21</td>
<td>04/10</td>
</tr>
</tbody>
</table>
Table III. Effect of the two treatments on pregnancy outcome.

O.R.: crude odds ratio for giving birth to a live normal baby after treatment with low-molecular weight heparin enoxaparin, low-dose aspirin being the treatment of reference. C.I.: confidence interval. AllFVL: all patients carrying the heterozygous factor V Leiden mutation; AllFIIL: all patients carrying the heterozygous factor II G20210A mutation; AllPS: all patients carrying a protein S deficiency.

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Live births</th>
<th>P (Chi²)</th>
<th>O.R.</th>
<th>95% C.I.</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>All women</td>
<td></td>
<td></td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>80</td>
<td>23 (29%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enoxaparin</td>
<td>80</td>
<td>69 (86%)</td>
<td></td>
<td>15.5</td>
<td>7 – 34</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>AllFVL</td>
<td></td>
<td></td>
<td>&lt; 0.0001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>36</td>
<td>12 (33%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enoxaparin</td>
<td>36</td>
<td>34 (94%)</td>
<td></td>
<td>34</td>
<td>7 – 166</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>AllFIIL</td>
<td></td>
<td></td>
<td>0.0007</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>30</td>
<td>10 (33%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enoxaparin</td>
<td>30</td>
<td>24 (80%)</td>
<td></td>
<td>8</td>
<td>2.5 – 26</td>
<td>0.0005</td>
</tr>
<tr>
<td>AllPS</td>
<td></td>
<td></td>
<td>0.0006</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>14</td>
<td>01 (07%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enoxaparin</td>
<td>14</td>
<td>11 (79%)</td>
<td></td>
<td>48</td>
<td>4 – 526</td>
<td>0.0016</td>
</tr>
</tbody>
</table>
Table IV. Multiparametric logistic regression model on a normal live birth after treated pregnancy.


<table>
<thead>
<tr>
<th></th>
<th>Adjusted O.R.</th>
<th>95% C.I.</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enoxaparin use</td>
<td>32</td>
<td>11 - 89</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Factor II G20210A mutation</td>
<td>0.44</td>
<td>0.17 - 1.15</td>
<td>0.095</td>
</tr>
<tr>
<td>Protein S deficiency</td>
<td>0.29</td>
<td>0.08 – 1.02</td>
<td>0.053</td>
</tr>
<tr>
<td>Positive protein Z deficiency</td>
<td>0.22</td>
<td>0.08 – 0.58</td>
<td>0.002</td>
</tr>
<tr>
<td>Positive anti-protein Z antibodies</td>
<td>0.20</td>
<td>0.08 – 0.51</td>
<td>0.0009</td>
</tr>
</tbody>
</table>
Low molecular weight heparin versus low-dose aspirin in women with one fetal loss and a constitutional thrombophilic disorder

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