Gestational Outcome in Thrombophilic Women with Recurrent Pregnancy Loss Treated by Enoxaparin

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Key words

Pregnancy, thrombophilia, factor V Leiden, low molecular weight heparin

Summary

Inherited and acquired thrombophilia are associated with recurrent pregnancy loss (RPL). We have evaluated the efficacy and safety of the low molecular weight heparin enoxaparin in 50 women, (mean age 26 ± 3 years) with RPL (≥3 losses in 1st, ≥2 losses in 2nd and ≥1 loss in 3rd trimester) who were found to harbor thrombophilia. Twenty-seven had a solitary thrombophilic defect, and twenty-three women had combined thrombophilic defects: 17 – two defects and 6 – three defects. Following diagnosis of thrombophilia, sixty-one subsequent pregnancies were treated with the low molecular weight heparin enoxaparin throughout gestation until 4 weeks after delivery. Dosage was 40 mg/day in women with solitary defect and 80 mg/day in combined defects. Aspirin, 75 mg daily was given in addition to enoxaparin to women with antiphospholipid syndrome. Forty-six out of 61 (75%) gestations treated by enoxaparin resulted in live birth compared to only 38/193 (20%) of the untreated pregnancies in these 50 women prior to diagnosis of thrombophilia (p <0.00001). In 23 women without a single living child following 82 untreated gestations, antithrombotic therapy resulted in 26/31 (84%) successful deliveries (p <0.0001). In 20 women with a prior living child, antithrombotic therapy improved successful delivery from 33/86 (38%) to 20/21 (95%) (p <0.0001). Enoxaparin dose of 40 mg/day resulted in live birth in 24/35 (69%) of gestations, compared to 19/23 (83%) gestations in women treated with 80 mg/day (p = 0.37). Only one thrombotic episode and one mild-bleeding episode were noticed during enoxaparin therapy. Enoxaparin is safe and effective in prevention of pregnancy loss in women with inherited and acquired thrombophilia.

Introduction

Recurrent pregnancy loss (RPL) is a major health problem affecting 1-2% of women at the reproductive age. While chromosomal aberrations, endocrinologic dysfunction and uterine abnormalities are etiologic factors, until recently in most cases, a cause for RPL could not be identified (1, 2). RPL is a well established finding in women with anti-phospholipid syndrome (APS), an acquired autoimmune thrombophilic state (3). Recently, inherited thrombophilia has been suggested to be associated with RPL (4) with evidence for an increased prevalence of RPL in women with dysfibrinogenemia (5), antithrombin III, protein C and protein S deficiencies (6). More recently, an increased prevalence of APC-resistance (7), factor V Leiden mutation (8-10) and hyper-homocysteinemia (11) was reported in women with RPL. However, not all reports have documented association between thrombophilia and RPL (12).

Altogether, inherited or acquired thrombophilia can be found in 50-65% of women with RPL of unknown cause (10) as well as in women with other vascular placental pathologies such as preeclampsia, intrauterine growth restriction and placental abruption (13).

Gestational outcome in women with inherited thrombophilia who present with RPL is poor with less than 25% of pregnancies resulting in live birth (10). Reduced placental flow and placental infarctions have been reported in women with thrombophilia and RPL (14, 15). Assuming that RPL in women with inherited thrombophilia may result from prothrombotic mechanisms in the materno-fetal circulation, and based upon the successful gestational outcome following antithrombotic therapy in women with antiphospholipid syndrome (APS) (16, 17), we hypothesized that antithrombotic therapy may also improve gestational outcome in women with inherited thrombophilia who had previous RPL. In the present report we describe the outcome of 61 gestations in 50 consecutive women with RPL who following diagnosis of inherited or acquired thrombophilia were treated throughout subsequent gestations with the low molecular weight heparin, enoxaparin. The data suggest that enoxaparin result in a significant improved gestational outcome in women with thrombophilia.

Methods

Patients

One hundred forty-five women with RPL without known cause were referred for evaluation to the Thrombosis and Hemostasis Unit, at Rambam Medical Center during a 39-month period from 1/1/1995 to 31/3/1998. Criteria for RPL were three or more first trimester (7-12 weeks of gestation) pregnancy losses, two or more second trimester (12-24 weeks of gestation) losses or at least one intrauterine fetal death (IUFD) (above 24th weeks of gestation).

Only cases with post-embryonic loss after an ultrasonic disappearance of fetal pulse from the intrauterine fetal pole were included in the study. Documented first trimester preclinical and blighted ovum abortions were excluded. Pregnancy losses that were the result of documented fetal malformation or the result of an infectious complication were also excluded.

All women were in good general health without previous history of diabetes mellitus or thyroid dysfunction. They all had a thorough investigation, which was negative for potential causes of fetal demise including fasting glucose, basal FSH, LH and estradiol levels on day 3 of a natural cycle, TSH and prolactin levels. In addition, transvaginal scanning was performed to verify ovarian morphology. In addition, women with 3 or more first trimester or 2 or more second

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trimester pregnancy losses underwent a hysterosalpingography and/or hysteroscopy to confirm uterine cavity normalcy and both partners were also investigated for chromosomal aberrations. Women were not pregnant at the time of investigation with a period of at least 3 month between sampling and last pregnancy and none of them were taking oral contraceptives.

After obtaining informed consent, blood samples were collected by venipuncture into 3.8% citrate and EDTA tubes. Genomic DNA was extracted from blood leukocytes by standard techniques. Plasma aliquots were frozen in −70°C until further analysis.

Coagulation Assays

Protein C activity was determined by a chromogenic assay, using the protein C StaChrom kit (normal range 70-130 U/dl). Antithrombin III activity was determined by chromogenic assay using Antithrombin III Asserachrom kit (normal range 74-130 U/dl). Total and free Protein S antigen levels were determined by electroimmunoassay using Asseraplate protein S kit (normal range 70-130 U/dl and 65-130 U/dl respectively). (All kits Stago Diagnostics Asnières, France.)

Lupus anticoagulant assays were performed using the DRVVT kit (18) (Screen and Confirm, Gradipore, North Ryde, Australia) according to the recommendations of the SSC (19). Positive samples were further confirmed by the thromboplastin titration index (TTI) assay.

Plasma homocysteine levels were determined by HPLC (normal range 5-14 μmol/L). The anticoagulant response of plasma samples to protein C was determined by the addition of activated protein C (APC) to aPTT assay, using a Coatest APC resistance kit (Chromogenix AB, Moetnald, Sweden). Response to APC was expressed by the APC sensitivity ratio. Mean value in 50 controls women without pregnancy loss was 2.67 ± 0.3. APC-resistance was defined as APC SR < 2.07.

Thrombophilic Polymorphisms Analysis

Factor V G1691A. A 208 bp genomic DNA fragment of factor V around nucleotide 1691 was amplified by PCR and digested with Mnl-I as previously described (20).

Factor II G20210A. A 253 bp DNA fragment of the 3’-untranslated region of the prothrombin gene that includes the nucleotide 20210 was amplified with the primer 5’-CAACCGCTGGTATCAAATGG-3’ and a mutagenic primer of the prothrombin gene that includes the nucleotide 20210 was amplified with primer 5’-CAACCGCTGGTATCAAATGG-3’ and a mutagenic primer as described by Poort et al. (21). The amplified fragment was digested with Hind III.

TL-MTHFR C677T. The MTHFR 677C→T substitution was performed by amplification of a 198 bp DNA fragment and followed by Hinf I digestion, as described by De Franchis et al. (22).

Digested fragments were electrophoresed on 10% polyacrylamide gels and visualized by ethidium bromide staining.

Antithrombotic Regimens

Of the 145 women with RPL, 96 were diagnosed as having thrombophilia (23). Fifty of the 96 thrombophilic women who had one or more gestations after diagnosis of thrombophilia were included in this prospective open dose finding study.

No antithrombotic therapy was given during gestations prior to diagnosis of thrombophilia. Following diagnosis of thrombophilia all subsequent pregnancies were treated with enoxaparin (Rhone Poulenc Rorer, France) from pregnancy verification throughout gestation and 4 weeks into the post-partum period. Women with antecedent thrombosis received enoxaparin for 6 weeks after delivery. Enoxaparin dose was 40 mg once daily in women with solitary thrombophilia and 80-120 mg daily (40 mg or 60 mg every 12 h) in women with combined thrombophilia. This higher dose was used based upon the significantly higher risk for pregnancy loss and still birth in women with combined thrombophilia (6). Aspirin at a dose of 75 mg daily was given in addition to enoxaparin to women with antiphospholipid syndrome from verification of pregnancy until 35th gestational week. All women received folic acid 1 mg daily.

Monthly follow-up visits included evaluation by obstetrician (ZB, ZW, JY) and by a hematologist (BB, RH). Patients were asked about bleeding episodes, thrombotic signs, and symptoms of bone pain. Blood pressure, weight gain, proteinuria and platelet counts were evaluated monthly. Ultrasound examination was performed at 6-8 weeks intervals with careful monitoring of fetal growth. Placental perfusion was evaluated by Doppler waveflow velocimetry studies at 18-20 weeks and every 6-8 thereafter. Plasma Anti-xa levels were recorded in 10 randomly selected gestations treated by enoxaparin.

Statistical analysis. Data was evaluated by SPSS/PC + software, using Fisher’s Exact Test for categorical variables, and by paired non-parametric test (Wilcoxon matched-pairs signs ranks test).

Results

The study population included fifty women with thrombophilia. Their mean age was 26 ± 3 years. Regarding ethnic background, 26 were of Arab origin and 24 were of Jewish origin. Their thrombophilic profile is presented in Table 1. Twenty-seven women had a solitary thrombophilic defect, while 23 women had combined thrombophilic defects. The most common solitary defect was factor V Leiden (11 patients) followed by protein S deficiency, antiphospholipid syndrome and APC-resistance without factor V Leiden mutation, presented in 4 patients each. Factor II G20210A and MTHFR C677T mutations were each the solitary defect in 2 women. A variety of combined thrombophilic defects were found in 23 women (Table 1). Seventeen women had 2 defects, and 6 women had 3 abnormalities. Factor V Leiden was the most common thrombophilic defect presenting in 20/50 women (40%) as solitary finding in 11 women and in 9 women as a part of a combined defect. APC-resistance without factor V Leiden was present in 9 women (18%), 4 as a solitary defect and in 5 in combination with other defects. APS was present in 11 women (22%), 4 as a solitary defect and in 7 in combination with other defects. Protein S deficiency was found in 10 women (20%), 4 as a solitary defect and in 6 in combination with other defects.

Out of a total of 254 gestations, 84 gestations (33%) ended by live birth and 170 (67%) resulted in pregnancy loss. Of the 170 pregnancy losses 63% occurred in the first trimester, 28% in the second trimester and 9% in the third trimester manifesting as intra-uterine fetal death. Prior to diagnosis of thrombophilia live birth occurred in 38 out of 193 (20%) gestations (Table 2). These gestations were not treated by antithrombotic therapy. After diagnosis of thrombophilia, 61 subsequent gestations, 50 in women with inherited thrombophilia and 11 in women with APS were treated by antithrombotic therapy. Live birth occurred in 46 out of 61 treated gestations (p < 0.00001), compared to untreated gestations by Fisher’s Exact Test (Table 2).

Mean neonate weight in women in the treatment group was 3020 g. Of the 46 neonates, 33 were delivered vaginally and 13 (28%) by cesarean section. Thirty-six gestations (77%) ended at term after 37 weeks of gestation. One twin gestation ended at 30 weeks with neonates’ weight of 1100 and 700 g. The latter neonate died of sepsis. Another gestation ended at 32 weeks with neonate weighting 1300 g. These neonates were ventilated for several days. Seven other neonates were delivered at weeks 33 to 36 with birth weights ranging from 1800 g to 2400 g. None of the neonates had any significant sequela.

Thirty-five gestations were treated by enoxaparin at a dose of 40 mg/day and resulted in live birth in 24 pregnancies (69%). Twenty-three gestations in women with combined thrombophilia or abnormal placental perfusion, by Doppler waveflow velocimetry studies were treated by enoxaparin at a dose of 80 mg/day (40 mg b.i.d) and resulted in live birth in 19 pregnancies (83%). Three gestations in women
with multiple thrombophilic defects who, in prior gestations, did not respond to doses of 40-80 mg were treated by a dose of 120 mg/day (60 mg b.i.d.). All three gestations resulted in live birth. There was no difference in gestational outcome in women treated with or without aspirin.

The 50 women were subdivided according to gestational outcome into 3 groups.

- **Group A** – 23 women who had no living child prior to therapy but had at least one living child after antithrombotic therapy. Successful gestational outcome in this group following antithrombotic therapy was 26/31 (84%) compared to 0/82 (0%) without therapy (p < 0.0001) (Table 3).

- **Group B** – 20 women who had at least one living child before therapy and had at least another living child after therapy. Successful gestational outcome in this group after therapy was 20/21 (95%) compared to 33/86 (38%) without therapy (p < 0.0001) by Wilcoxon matched-pairs signs rank test.

- **Group C** – 7 women who after treatment in 9 gestations had no living child. These women included 3 women who had no living child prior to therapy and 4 women who had 5 living children out of 16 gestations before therapy. There was no statistical difference regarding gestational outcome in these 7 women before and after antithrombotic therapy (Table 3).

Anti-Xa levels were not tested in the majority of enoxaparin treated gestations. However, in 10 treated pregnancies where anti-Xa levels were measured, a level of 0.2 U ± 0.05 three hours post injection was documented in women treated with 40 mg/day, and a level of 0.4 U ± 0.05 was found in women treated with a dose of 80 mg/day.

Thrombotic manifestations observed prior to diagnosis of thrombophilia included deep leg vein thrombosis post pregnancy loss in 4 women, one with factor V Leiden, one with factor II G20210A mutation and 2 with combined thrombophilic defects. Two thrombotic manifestations were observed in association or proximity with the 61 treated gestations. A 26-year-old woman, homozygous for factor V Leiden mutation who had previous RPL and was treated with enoxaparin 40 mg/day presented with hepatic vein thrombosis 10 weeks after a second trimester pregnancy loss, 6 weeks after cessation of enoxaparin therapy. Thus, thrombosis occurred in 1/61 (1.6%) gestations treated with enoxaparin.

### Table 1: Thrombophilic characteristics in 50 women with recurrent pregnancy loss

<table>
<thead>
<tr>
<th>Solitary defect</th>
<th>No</th>
<th>Combined defects</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factor V Leiden Het</td>
<td>10</td>
<td>Factor V Leiden Het + PS def</td>
<td>4</td>
</tr>
<tr>
<td>Factor V Leiden Hom</td>
<td>1</td>
<td>Factor V Leiden Hom + PS def</td>
<td>1</td>
</tr>
<tr>
<td>APC-R</td>
<td>4</td>
<td>HHC + PS def</td>
<td>3</td>
</tr>
<tr>
<td>MTHFR C677T</td>
<td>2</td>
<td>APS + PS def</td>
<td>2</td>
</tr>
<tr>
<td>Factor II G20210A</td>
<td>2</td>
<td>APS + PS def + APC-R</td>
<td>3</td>
</tr>
<tr>
<td>PS def</td>
<td>1</td>
<td>Factor V Leiden Het + APS + HHC</td>
<td>1</td>
</tr>
<tr>
<td>APS</td>
<td>4</td>
<td>Factor V Leiden Het + MTHFR C677T</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>APS + MTHFR C677T + APC-R</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Factor II G20210A + MTHFR C677T</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Factor II G20210A + APC-R</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Factor II G20210A + Factor V Leiden Het + MTHFR C677T</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>AT-III def + MTHFR C677T</td>
<td>1</td>
</tr>
</tbody>
</table>

**APC-R** – Activated protein C resistance  
**APS** – Antiphospholipid syndrome  
**HHC** – Hyperhomocysteinemia  
**MTHFR** – Metlenetetrahydrofolate reductase  
**PS def** – Protein S deficiency  
**AT-III def** – Antithrombin III deficiency  
**Het** – Heterozygous  
**Hom** – Homozygous

### Table 2: Gestational outcome in 50 thrombophilic women with recurrent pregnancy loss – role of enoxaparin

<table>
<thead>
<tr>
<th>Anti-thrombotic treatment</th>
<th>Gestations</th>
<th>Live birth</th>
<th>Percent</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>193</td>
<td>38</td>
<td>20</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Enoxaparin</td>
<td>61</td>
<td>46</td>
<td>75</td>
<td>0.37</td>
</tr>
<tr>
<td>40mg</td>
<td>35</td>
<td>24</td>
<td>69</td>
<td>0.37</td>
</tr>
<tr>
<td>80mg</td>
<td>23</td>
<td>19</td>
<td>83</td>
<td>0.001</td>
</tr>
<tr>
<td>120mg</td>
<td>3</td>
<td>3</td>
<td>100</td>
<td>0.001</td>
</tr>
</tbody>
</table>

### Table 3: Gestational outcome in women with or without successful pretreatment delivery

<table>
<thead>
<tr>
<th>Antithrombotic therapy</th>
<th>Group</th>
<th>No</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>23</td>
<td>0/82 (0%)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>B</td>
<td>20</td>
<td>33/86 (38%)</td>
<td>20/21 (95%)</td>
</tr>
<tr>
<td>C</td>
<td>7</td>
<td>5/25 (20%)</td>
<td>0/9 (0%)</td>
</tr>
</tbody>
</table>

**Group A** – Women without a living child before antithrombotic therapy.  
**Group B** – Women with a living child before and after antithrombotic therapy.  
**Group C** – Women without a living child after antithrombotic therapy.
A single bleeding episode manifested as subchorionic hematoma was noted in a woman with 5 consecutive first trimester losses found to have APS and low protein S, and treated with enoxaparin at 40 mg b.i.d. and aspirin 75 mg/day at 11 weeks of gestation. Enoxaparin and aspirin were withheld and the hematoma gradually resolved over several weeks. She delivered a healthy neonate at term. We have not observed any case of heparin-induced thrombocytopenia among the 61 enoxaparin treated gestations. Likewise, there were no clinical manifestations of bone pain in any of the 50 women during or following the 61 treated gestations.

Discussion

The present report demonstrates that in women with RPL who were found to have inherited or acquired thrombophilia, antithrombotic therapy with the LMWH enoxaparin with or without aspirin in subsequent gestations, resulted in a significant improvement in fetal outcome, compared to previous untreated gestations. The findings of the present study if confirmed by larger randomized trials may have wide clinical implications as up to two thirds of women with RPL or other vascular complication of pregnancy are found to have inherited or acquired thrombophilia (10, 13).

The outcome in previous untreated pregnancies in these women was poor with only 20% out of 193 gestations ending by live birth. In sharp contrast, antithrombotic therapy with enoxaparin with or without aspirin throughout gestation resulted in live birth in 75% out of 61 treated gestations. This significant improvement in gestational outcome is in accordance with the results reported in women with antiphospholipid syndrome and RPL who had been treated with antithrombotic therapy. Without antithrombotic therapy, live birth occurs in less than 20% of gestations in APS women with RPL (24). Two randomized studies have documented improved gestational outcome (71% and 80%) in APS women with RPL who were treated with heparin plus aspirin compared to aspirin alone (42% and 44%) (16, 17). Thus, the results obtained following antithrombotic therapy in the present case series of women with thrombophilia are very similar to those reported in women with APS and RPL. Interestingly, 23/50 (46%) of thrombophilic women with RPL had combined defects. This high percentage may reflect the additive risk of multiple mild thrombophilic defects previously reported to have an impact on the expression of thrombosis in patients with thrombophilia (20, 25, 26), and suggest that these women were at high risk for RPL.

As 92% of the women with thrombophilia had pregnancy loss but no antecedent thrombosis, enoxaparin was continued for 4 weeks after delivery except for women with a thrombotic history where enoxaparin was continued for 6 weeks post-partum. The 2 patients who had thrombotic episodes while on preventive dose of enoxaparin, received 1 mg/kg dose of enoxaparin followed by long-term warfarin. Thrombotic manifestations appeared prior to diagnosis of thrombophilia in only 8% of the women with RPL in our series, suggesting that most women with thrombophilia and RPL do not have systemic vascular manifestations. Of interest, all 6 thrombotic events, 4 prior to diagnosis of thrombophilia and 2 after diagnosis of thrombophilia occurred either during gestation or the post-partum period suggesting that anticoagulant therapy may have beneficial effect on prevention of thrombotic tendency during this period (27). In fact, during enoxaparin therapy, thrombosis occurred in only 1 out of 61 gestations in a woman with combined thrombophilia. The other post partum thrombotic event, hepatic vein occlusion occurred 10 weeks after delivery in a woman homozygous for factor V Leiden, suggesting that the optimal duration of post partum anticoagulation for women with high risk thrombophilia is not yet established.

Although our study is neither prospective nor randomized, the extremely significant improvement in gestational outcome is unlikely to be coincidental. This is based on the large number of gestations (193) in these 50 women prior to diagnosis of thrombophilia of which only 20% resulted in live birth. In sharp contrast, enoxaparin therapy with or without aspirin resulted in live birth in 46/61 (75%) of subsequent gestations (p <0.00001).

Moreover, analysis of the 23 women without a living child prior to antithrombotic therapy demonstrated successful delivery in 84% of gestations treated by enoxaparin (Table 3). The value of antithrombotic treatment was further demonstrated in the group of 20 women who had a successful delivery in 95% of gestations treated by enoxaparin compared to only 38% of untreated gestations. The outcome in the 7 women who had no successful delivery following 9 gestations treated by enoxaparin was not statistically different from the outcome in 25 untreated gestations. This may suggest that more gestations per women may be needed for successful delivery in this group.

The dose of enoxaparin was 40 mg/day in patients with solitary thrombophilia and 80 mg/day in patients with combined thrombophilia. The results in women with combined thrombophilia were at least as good as those with solitary thrombophilia (83% Vs 69%, p = 0.37) suggesting that a higher dose of enoxaparin is potentially useful in women with increased thrombotic risk. This is further illustrated in 3 women with combined thrombophilia who had pregnancy loss with a dose of 40 mg × 2/day, but a dose of 60 mg × 2/day on subsequent gestation resulted in successful outcome.

Twenty-five percent of treated gestations did not end by live birth, 13/46 (28%) of neonates were delivered by cesarean section and 10/46 (23%) of neonates were delivered prematurely. Encouragingly, only 3 neonates weighted less than 1500 g and none of the 45 surviving neonates had sequelae. However, these data suggest that the optimal dose of anticoagulant therapy in this setting has yet to be determined.

Bleeding is a potential complication of anticoagulant therapy. Data in pregnant women suggest that LMWH are safe and are associated with a low incidence of bleeding manifestations in the mother (27). Like heparin, LMWH do not cross the placenta and therefore are not associated with bleeding in the fetus (27). Indeed, we have observed only one case of bleeding among the 61 treated gestations with subchorionic hematoma which resolved following cessation of antithrombotic therapy, suggesting that enoxaparin in doses of 40 mg and 80 mg per day is safe. The present report strengthen and broaden recent preliminary reports suggesting that LMWH with or without aspirin is safe and effective in primary early recurrent aborters with an impaired fibrinolytic capacity (28) and in prevention of gestational vascular placental pathologies in thrombophilic women with a history of preeclampsia, intrauterine growth retardation, placental abruption and intrauterine fetal death (29-31).

Heparin-induced thrombocytopenia has been observed less commonly in patients treated with LMWH compared to unfractionated heparin (27). In our series of 61 gestations treated with enoxaparin, we have not observed a single case of heparin-induced thrombocytopenia.

Osteoporosis is a rare serious side effect reported in pregnant women treated with unfractionated heparin. Data accumulated so far in women treated with LMWH throughout gestation suggest a low prevalence of symptomatic osteoporosis (27). We have not documented bone pain in any of the 61 treated gestations.

In conclusion, enoxaparin is safe and effective in prevention of pregnancy loss in women with thrombophilia. Prospective randomized
trials in a large number of women with thrombophilia are warranted to verify our observations and to evaluate the optimal therapeutic regimen for thrombophilic women with RPL.

References


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