Treatement of Thrombophilia and Recurrent Pregnancy Loss by Heparin between Facts and Fiction

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Abstract

Recurrent pregnancy loss, (RPL) either early or late is a great problem for any married woman and has both psychological and social impact on all women. Habitual or recurrent miscarriage (RM) defined as loss of 3 or more consecutive clinically recognized pregnancies before 20 weeks gestation this affects 1-2% of women, [1] Thrombophilia is a common cause of RPL and may be seen in 40- 50% of cases [2].

INTRODUCTION

Thrombophilia

Thrombophilia is a term describes a higher tendency for excessive blood clotting and it is normal phenomena during pregnancy, where there is an increase in most clotting factors. Currently many clinicians treat RPL associated with all types of thrombophilia, and even unexplained RPL by low molecular weight heparin (LMWH) combined with low dose aspirin (LDA). Thrombophilia is inherited, acquired or combined.

Inherited or genetic thrombophilia (IT)

Usually there is a family history of excessive clotting or more commonly, diagnosis is based on demonstration of gene mutation as in FV Leiden (FVL) mutation (C677T), hyperhomocysteinemia (A506G) mutation, prothrombin mutation (G20210A), prothrombin II (PTII) mutation and protein S and / or C deficiency. The exact mechanism by which IT causes implantation failure and subsequently RPL is unclear. It is suggested that thrombophilia may lead to syncytiotrophoblast invasion of maternal blood vessels which lead to the formation of microthrombosis at the site of implantation which results in implantation failure and RPL [3].

Acquired thrombophilia

Antiphospholipid syndrome (APS) which can be due to either lupus anticoagulant antibodies or anticardiolipin antibodies as seen in women with systemic lupus erythematosus. In the APS, the body immune system recognizes phospholipids which is part of cell membrane as foreign substance and produces antibodies against it.

Combined thrombophilia

Combined thrombophilia (which is either combination of acquired and inherited thrombophilia or combination of more than one inherited thrombophilic gene defect) has been identified by several researchers as a cause of both early and late RPL.

Treatment of women with antiphospholipid antibodies and lupus antibodies and recurrent pregnancy loss

The evidence in medical literature so far favors treating women who had APS and aPL and suffering from RPL with LMWH and/or LDA [4].

Is inherited thrombophilia associated with recurrent pregnancy loss?

There are prospective case-control studies did not show an association between inherited thrombophilia and adverse pregnancy outcome [5,6]. Other studies, which are prospective case-control studies showed an association between IT and adverse pregnancy outcome [7,8].

Treatment of inherited thrombophilia with recurrent pregnancy loss

There are few studies showed that treatment of women with IT and RPL with anticoagulant is beneficial but those studies have many limitations [9,10].
Heparin treatment for women with unexplained recurrent pregnancy loss

The use of LMWH in the treatment of RPL with no identified thrombophilia was based on 2 retrospective studies that reported higher rates of successful pregnancy outcome. Both studies had methodological limitation [11,12].

The results of those studies showed favorable outcome in women with RPL with and without thrombophilia. Those results were adopted by majority of clinicians worldwide and they started prescribing heparin and aspirin for pregnant women with RPL with and without thrombophilia. But because of limitations of those studies, this stimulated many researchers to conduct controlled randomized double blind multicentre studies to find out whether this current practice of prescribing anticoagulants to women with RPL with and without thrombophilia was justified [13-16].

The results of those 4 studies are summarized in (Table 1).

Based on the results of those studies, it was concluded that in women with RPL not associated with antiphospholipid syndrome, heparin therapy is not superior to either low dose aspirin or placebo and prescribing heparin for such cases may not be recommended.

Table 1:

<table>
<thead>
<tr>
<th>Trial</th>
<th>Patients no.</th>
<th>Miscarriages no. %</th>
<th>Start of medication</th>
<th>Treatment</th>
<th>Live birth</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALIFE 2010</td>
<td>299</td>
<td>2 (40.1) ≥3 (59.9)</td>
<td>≤6 weeks</td>
<td>1. LMWH+ aspirin 2. Aspirin 3. Placebo</td>
<td>69% 62% 67%</td>
<td>0.63</td>
</tr>
<tr>
<td>HABENOX 2011</td>
<td>207</td>
<td>2 (1.0) ≥3 (99.0)</td>
<td>&lt;7 weeks</td>
<td>1. LMWH+ aspirin 2. Aspirin 3. LMWH</td>
<td>65% 61% 71%</td>
<td>0.45</td>
</tr>
<tr>
<td>SPIN 2010</td>
<td>294</td>
<td>2 (57.1) ≥3 (42.9)</td>
<td>&lt;7 weeks</td>
<td>1. LMWH+ aspirin 2. Placebo</td>
<td>78% 80% 85%</td>
<td>0.35</td>
</tr>
<tr>
<td>HepASA 2009</td>
<td>88</td>
<td>2(100)</td>
<td>&lt;6 weeks</td>
<td>1. LMWH+ aspirin 2. Aspirin</td>
<td>77.8 79.2 79.7</td>
<td>0.75</td>
</tr>
</tbody>
</table>

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