Heparin use in management of early onset severe pre-eclampsia

October 28, 2011 | Pregnancy and Birth [1]  
By OBGYN.net Staff [2]

Thrombophilia is claimed in many adverse pregnancy outcomes such as recurrent pregnancy loss, intrauterine growth retardation, abruptio placenta, intrauterine fetal death, and pre-eclampsia with onset before 34 wk.

Introduction
Normal pregnancy characterized by hypercoagulability reflected by increased levels of several clotting factors, a progressive fall in protein S levels, an acquired resistance to activated protein C (APC), and impaired fibrinolysis

Thrombophilia is claimed in many adverse pregnancy outcomes such as recurrent pregnancy loss, intrauterine growth retardation, abruptio placenta, intrauterine fetal death, and pre-eclampsia with onset before 34 wk.

Recent data suggest that thrombophilia associated placental vasculopathy in the form of villous infarcts, multiple infarcts, fibrinoid necrosis of decidual vessels, fetal stem vessel thrombosis, placental hypoplasia and spiral artery thrombosis lead to inadequate fetomaternal circulation and decreased placental perfusion.

Association between thrombophilia and pre-eclampsia is a controversial issue as Several case-control studies found at least 1 thrombophilic defect in 40% to 72% of women with pre-eclampsia compared with 8% to 20% of control women with normal pregnancies . But several other studies found no difference in the prevalence of thrombophilia between women with pre-eclampsia and those with normal pregnancies.

factor V Leiden gene mutation association with pre-eclampsia
Nine case-control studies found a significantly higher prevalence of factor V Leiden in women with pre-eclampsia (8%-26%) compared with women with normal pregnancies (2%-10%) with ORs ranging from 2 to 6 . In contrast, 15 other studies found no association of factor V Leiden with pre-eclampsia.

The prothrombin gene mutation association with pre-eclampsia
The prothrombin gene mutation was found in 7% to 11% of women with pre-eclampsia compared with 1% to 4% of those with normal pregnancies, suggesting a 2- to 7-fold increase in risk.

the MTHFR C677T mutation association with pre-eclampsia
A few studies suggested a homozygous MTHFR C677T mutation confers a 2- to 3-fold increased risk of pre-eclampsia. An elevated plasma homocysteine level in early pregnancy can increase the risk of developing severe pre-eclampsia by almost threefold. On the other hand most have found no association.

Another study found the MTHFR C677T mutation in 41% of women with pre-eclampsia and hyperhomocysteinemia compared with 5.6% of preeclamptic women with normal levels (OR 12). Mean homocysteine levels were higher in homozygous carriers

A large number of studies suggest hyperhomocysteinemia increases the risk of pre-eclampsia. Homocysteine levels greater than 9 to 11 µmol/L conferred a 4- to 5-fold increased risk of pre-eclampsia compared with lower levels.
Women with pre-eclampsia/eclampsia were more likely to have heterozygous factor V Leiden mutation, heterozygous G20210A prothrombin gene mutation, homozygous MTHFR C677T mutation, protein C deficiency, protein S deficiency or activated protein C resistance compared with controls.

**APAS association with pre-eclampsia**

Antiphospholipid antibodies (APAs) are acquired autoantibodies to negatively charged phospholipids. APAS are thought to cause these thrombotic events either by (1) binding and decreasing the function of antithrombin III (38,39) (2) enhancing thromboxane release, which leads to platelet aggregation, or (3) decreasing the activation of protein C, which is needed to inactivate the clotting process.

Extensive infarction, necrosis, and thrombosis have been identified in the placentas from failed pregnancies in women with APS. A spiral arterial vasculopathy in decidual vessels also has been linked to aPL-related fetal loss. This decidual vasculopathy is characterized by acute atherosis, intimal thickening, fibrinoid necrosis, and an absence of the normal physiologic changes in the spiral arteries and also has been associated with pre-eclampsia and fetal growth retardation.

**Multiple thrombophilias increase risk**

Multiple inherited thrombophilias also may interact at the maternal-fetal interface. Consistent with Mendelian inheritance, the fetus will inherit 1 of the maternal alleles at each gene of the clotting-cascade proteins. Chronologically, the fetal arterial supply is established as maternal spiral arteries perfuse the intervillous spaces, with the maternal and fetal blood supply of the placenta present 3 to 4 weeks after conception. Histologically, evidence of placental ischemia can be found on either the maternal or fetal side. It is unknown whether the risk of placental compromise is greater in the presence of maternal or fetal thrombophilia, alone or in combination.

An interesting population based cohort study has shown that Women who had pre-eclampsia had a 1.2-fold higher long-term risk of death (95% confidence interval 1.02 to 1.37) than women who did not have pre-eclampsia. The risk in women with pre-eclampsia and a preterm delivery was 2.71-fold higher (1.99 to 3.68) than in women who did not have pre-eclampsia and whose pregnancies went to term. In particular, the risk of death from cardiovascular causes among women with pre-eclampsia and a preterm delivery was 8.12-fold higher (4.31 to 15.33). However, these women had a 0.36-fold (not significant) decreased risk of cancer.

Also a study published in the Br Med J, 2003 compared 12,849 women admitted to hospital with pre-eclampsia during their pregnancy with 284,188 controls. All women were observed for up to 3 years after discharge from hospital. Findings were: Venous thromboembolism was significantly more common in the pre-eclampsia group than in any of the control groups.

Unfortunately most of the studies of thrombophilias and pregnancy have been retrospective, case-control studies, and therefore may be subject to bias. There will be no single gene to explain the disorder and no single ‘magic therapy’ to treat the disorder. The differences between reports may be related to different populations studied, study design and different definitions of pre-eclampsia. Some studies deal with mild pre-eclampsia and other with severe disease. Several studies include only primigravidas and other both primigravidas and multiparous. Some include also women with recurrent pre-eclampsia.

The fetus may also play a role: When the fetus has inherited thrombophilia from the mother there may be an accelerated of thrombosis in the placenta with ensuing complications compared to a situation with an unaffected fetus. It is also possible that other, as yet undefined genes need to be activated in order to induce thrombophilic states with clinical significance in pre-eclampsia.

**Blood thinners in prophylaxis**

The Pregnancy Loss Study Group which is one of the cochrane calloboration groups, published in (Am J Obst. Gynecol 2000) The gold standard therapy to prevent miscarriages and obstetrical complications is represented by the association of low-dose aspirin and heparin (unfractionated or low molecular weight heparin).

A Systematic review published in (BMJ 2001) stated that The combination of aspirin and heparin or low molecular weight (LMW) heparin is effective in recurrent fetal loss in APS and could be considered for women with inherited thrombophilias and history of severe pre-eclampsia, IUGR,
Heparin use in management of early onset severe pre-eclampsia

Published on OBGYN.Net (http://www.obgyn.net)

Abruptio placentae or fetal loss. (Although no controlled studies on the subject are currently available)

It is fairly documented now to use heparin and low dose aspirin as a prophylactic therapy in subsequent pregnancies. (There is a 15% reduction in the risk of pre-eclampsia associated with the use of antiplatelet agents, there is a 14% reduction in baby deaths with the use of antiplatelet agents (The Cochrane Database of Systematic Reviews 2005 Issue 3)

**Blood thinners in treatment**

Five trials compared antiplatelet agents with placebo or no antiplatelet agent for the treatment of pre-eclampsia. There are insufficient data for any firm conclusions about the possible effects of these agents when used for treatment of pre-eclampsia. (The Cochrane Database of Systematic Reviews 2005 Issue 3)

Pre-eclampsia is common in developing countries constituting about 2.3% of all pregnancies about half of them present with sever pre-eclampsia before 34 weeks gestation. Unfortunately when you face a case of early onset sever pre-eclampsia in a primigravida, termination irrespective of fetal maturity is the short answer of management options in this condition.

**Interventionist versus expectant care for severe pre-eclampsia before term**

As Randomised trials comparing the Interventionist versus expectant care for severe pre-eclampsia before term. (Cochrane Pregnancy and Childbirth Group (April 2002) and the Cochrane Controlled Trials Register (The Cochrane Library, Issue 2, 2002) are consistent with large observational studies and The Growth Restriction Intervention Trial (GRIT) showed that the combination of uterine artery Doppler and cardiotocography provided the best method to determine the timing of delivery. Expectant management in cases of sever pre-eclampsia before term must has a place of management options requiring a place where the mother can be admitted for a prolonged period of time, staff for monitoring, equipment for electronic fetal monitoring (cardiotocography), umbilical artery Doppler and laboratory facilities.

**Case series study:**

**Objectives**

The case series study was designed to determine whether treatment with heparin and low dose aspirin could be used for patients with early onset severe pre-eclampsia to provide clinical efficacy.

**Study design**

- All cases were Nulliparous two of them have history of miscarriage >10wks.
- All were suffering from early onset sever pre-eclampsia (30-34wks.) systolic Bl.P>=160mmg, diastolic Bl.P>=110mmg, and proteinuria > 3gm/L
- Liver and kidney function tests, CBP, abdominal ultrasound and non stress test all were done to all patients on admission.

**Method**

- Eight severe preeclamptic patients (30 to 34 weeks of gestation) all were Nulliparous with gestosis index [GI] greater than or equal to 6 points).
- MgSo4 a total dose of 40 mg over the first 24 hours was given to all patients plus nifedipine 10 mg / 4 h- 8h keeping diastolic Bl.P around 90 mmHg.
- Five of them were given unfractionated heparin and the other three were given LMWH in daily fixed dose (5000u/12h UFH OR 40 mg. enoxaparin/day). Aspirin (75mg daily) was given to all patients.
- At admission platelet count, liver and kidney function tests all were within normal and have been repeated daily or every other day.
- Maternal symptoms were evaluated from the difference of GI before and after treatment, and fetal findings were evaluated from the changes of the biophysical profile score,“IUGR and Oligohydramnios were evident in four cases (max.vertical pocket< 2cm).
- Dexamethasone was given to all patients in a total dose of 24mg. divided on three doses.
Results: (table I)

- Five cases showed good response regarding reduction in blood pressure.
- Proteinuria was improved in three cases falling to (+, ++).
- Liquor amount was increased in all oligohydroamniotic four cases.
- These five cases continued pregnancy and were delivered at 35-37 wk.
- Pregnancy in other three cases was terminated within 5 days on base of either maternal or fetal risk.

<table>
<thead>
<tr>
<th>Case</th>
<th>Onset PE (wk)</th>
<th>termination (wk)</th>
<th>BLP</th>
<th>Proteinuria</th>
<th>MVP (liquor)</th>
<th>Type of heparin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case 1</td>
<td>33</td>
<td>36</td>
<td>▼</td>
<td>▼</td>
<td>&gt;2cm</td>
<td>FH</td>
</tr>
<tr>
<td>Case 2</td>
<td>33</td>
<td>35</td>
<td>◯</td>
<td>◯</td>
<td>&lt;2cm ▲</td>
<td>UFH</td>
</tr>
<tr>
<td>Case 3</td>
<td>31</td>
<td>31+3d</td>
<td>▲</td>
<td>▲</td>
<td>&gt;2cm</td>
<td>FH</td>
</tr>
<tr>
<td>Case 4</td>
<td>34</td>
<td>36</td>
<td>▼</td>
<td>▼</td>
<td>&lt;2cm ▲</td>
<td>UFH</td>
</tr>
<tr>
<td>Case 5</td>
<td>32</td>
<td>32+3d</td>
<td>▲</td>
<td>▲</td>
<td>&gt;2cm</td>
<td>FH</td>
</tr>
<tr>
<td>Case 6</td>
<td>33</td>
<td>33+3d</td>
<td>▲</td>
<td>▲</td>
<td>&lt;2cm ▲</td>
<td>UFH</td>
</tr>
<tr>
<td>Case 7</td>
<td>30</td>
<td>35</td>
<td>▼</td>
<td>▼</td>
<td>&lt;2cm ▲</td>
<td>FH</td>
</tr>
<tr>
<td>Case 8</td>
<td>33</td>
<td>35</td>
<td>◯</td>
<td>◯</td>
<td>&lt;2cm ▲</td>
<td>FH</td>
</tr>
</tbody>
</table>

Author's conclusions

- Heparin (either fractionated or unfractionated) and low dose aspirin can be used as a therapeutic test expecting results within five days in cases of early onset severe pre-eclampsia (after exclusion of HELLP syndrome) under strict maternal and fetal surveillance.
- It is advisable not to start heparin except after lowering B.L.P to less than 160mmHg, systolic and 100mmHg, diastolic.
- There is an urgent need for trials to establish its safety and efficacy.

American Heart Association/American College of Cardiology Clinical Practice Guidelines for Management of Acute Myocardial Infarction. April 2001

Contraindications to thrombolysis

- Severe uncontrolled hypertension (Systolic BP greater than 200, diastolic greater than 120 mmHg).
- Relative Contraindications: Hypertension, systolic BP greater than 180 mmHg and/or diastolic BP greater than 110 mmHg

References:

Dr. Mohammed Abdalla
Domiat.kornish Elnile Street
Domiat general hospital
Egypt.
Send Comments and Inquiries to Dr. Abdalla & OBGYN.net Editor

References:

Heparin use in management of early onset severe pre-eclampsia


26. Cotter AM, Molloy AM, Scott JM, Daly SF. Department of Biochemistry, Trinity College, Dublin, and
Coombe Women's Hospital, Ireland.


Source URL:
http://www.obgyn.net/articles/heparin-use-management-early-onset-severe-pre-eclampsia

Links: