Clinical Study

Review of Management and Outcomes in Women with Thrombophilia Risk during Pregnancy at a Single Institution

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Received 10 October 2013; Accepted 26 November 2013; Published 17 February 2014

Academic Editors: M. Kühnert, P. Pacora, and S. Palomba

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Pregnancy is a hypercoagulable state associated with an increased risk of venous thromboembolic disease (VTE). We retrospectively studied 38 Caucasian pregnant women with thrombophilia risk and compared their obstetric outcomes with a matched cohort without known thrombophilia risk during the period between January 2007 and December 2010. There were (2) cases with factor V Leiden, (6) prothrombin gene mutation, (1) antithrombin III deficiency, (2) protein C deficiency, (3) protein S deficiency, (10) MTHFR mutation, (7) anti-cardiolipin antibodies, and (1) lupus anticoagulant. Patients without thrombophilia who presented with recurrent unprovoked VTE were considered as high risk (6 cases). Most patients received anticoagulation (34/38) with aspirin only (6), enoxaparin (27), and warfarin (1). Twenty-six out of thirty-eight pregnant women (68.4%) with an increased risk of thrombophilia experienced one or more obstetric complications defined as hypertension, preeclampsia, placenta abruptio, VTE, and oligohydramnios, compared with 15 out of 40 (37.5%) pregnant women in the control group (OR 3.6; 95% CI 1.42, 9.21, \( P < 0.001 \)). The incidence of obstetric complications was significantly higher in the thrombophilia group compared to the controls. However, these complications were the lowest among patients who received full-dose anticoagulation. Our study suggests that strict application of anticoagulation therapy for thrombophilia of pregnancy is associated with an improved pregnancy outcome. The study was registered in the Australian and New Zealand Clinical Trials Registry under ACTRN12612001094864.

1. Introduction

Pregnancy is associated with major physiological changes that affect coagulation and the fibrinolytic system [1–3]. An imbalance in this system leads to a hypercoagulable state and pregnant women are therefore at an increased risk of venous thromboembolic disease (VTE), especially if they are affected by an associated acquired or inherited thrombophilia [2–4]. There are two factors that may exaggerate this risk: the high-risk nature of the thrombophilia and a history of a previous unprovoked VTE [5, 6]. High-risk hereditary thrombophilia includes antithrombin deficiency, prothrombin gene mutation (PGM), and factor V Leiden (FVL), while the presence of lupus anticoagulant or anti-cardiolipin antibodies are considered as acquired risk factors [7, 8]. Furthermore, homozygosity or presence of a combination of thrombophilia factors will aggravate the VTE risk by certain fold [7–9].

Apart from the occurrence of VTE, maternal thrombophilia has also been variably associated with an increased risk of early miscarriages, intrauterine growth restriction (IUGR), and pregnancy loss [10, 11]. Although it may seem intuitive to treat pregnant women with high-risk thrombophilia with anticoagulants prophylactically, there is a paucity of randomised trials in this area, and the balance of intervention versus conservative management should be carefully evaluated from both fetal and...


Table 1: Table 1: (a) Demographic details of the study population. (b) Association of maternal VTE and different risk factors.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Pregnant women with positive thrombophilic screening test (n = 38)</th>
<th>Pregnant women without positive thrombophilic screening test (n = 40)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (SD)</td>
<td>30.58 (5.07)</td>
<td>27.38 (7.31)</td>
<td></td>
</tr>
<tr>
<td>BMI (SD)</td>
<td>27.91 (5.08)</td>
<td>27.44 (7.30)</td>
<td>0.34</td>
</tr>
<tr>
<td>Primiparity</td>
<td>4</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Infant birth weight (g)</td>
<td>3298</td>
<td>3249.23</td>
<td>0.79</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>OR</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal weight</td>
<td>23.2 (0.94 to 2,926)</td>
<td>0.067</td>
</tr>
<tr>
<td>History of thromboembolic events</td>
<td>9.52 (1.02 to ∞)</td>
<td>0.024</td>
</tr>
<tr>
<td>Inherited thrombophilia</td>
<td>1.00 (0.00 to 39.0)</td>
<td>1.00</td>
</tr>
</tbody>
</table>

maternal points of view. Evidence-based guidelines have been published in an attempt to provide a more uniform clinical approach; however, there appears to be a lack of consistency among different guidelines [12, 13].

The decision to recommend anticoagulant prophylaxis to women with thrombophilia is based on the risk assessment or balance of bleeding versus VTE risk, as well as the potential effect that VTE and anticoagulants can have on pregnancy [14]. However, the use of anticoagulants in pregnancy is challenging because of the potential maternal and fetal complications [15, 16]. Despite this and the lack of controlled trials, there has been increased use of anticoagulants to prevent VTE and adverse pregnancy outcomes [17].

In this retrospective study, the management strategies of seventy-eight Caucasian women who received antenatal care at a single institution during the period between January 2007 and December 2010 were reviewed and analysed. Thirty-eight women with a thrombophilia risk and forty consecutive pregnant women who served as a control group received antenatal care at a single institution to determine the best management strategies based on the outcomes of the pregnancies.

2. Methods

2.1. Participants. The study was approved by the Human Research Ethics Committee. The study was registered in the Australian and New Zealand Clinical Trials Registry at http://www.anzctr.org.au/ under ACTRN12612001094864.

Thirty-eight pregnant women with a median age of 30 years and positive history for VTE or confirmed thrombophilia were recruited from the Queen Victoria Maternity Unit (QVMU) at our institution. All had been attending the antenatal clinic since the confirmation of a positive pregnancy test. At the same time, forty pregnant subjects with a median age of 27 years attending the QVMU antenatal clinic during the study period served as controls (Table 1). As per our standard practice, the patients with established history of thrombophilia were referred to a special clinic run by the Haematology Department at the LGH. All patients with thrombophilia risk who attended this high-risk clinic at our institution were included in this observational study. As a part of routine assessment of high-risk patients, a thrombophilia screen was performed for all cases.

The patients’ medical records were reviewed by a trainee of the Royal Australian and New Zealand College of Obstetricians and Gynaecologists and supervised by senior obstetricians. All patients were co-managed by a haematologist who assessed the patients and determined the need for anticoagulation and the appropriate anticoagulant regimen as per the Royal College of Obstetricians and Gynaecologists (RCOG) 2004 guidelines “Thromboprophylaxis during Pregnancy, Labour and after Vaginal Delivery” and their subsequent edition in 2009 “Green-Top Guideline 37a” [12]. An assessment form was designed and used to collect medical, obstetric, and family history for each patient as well as risk factors for thrombosis and previous VTE. Outcomes of previous and current pregnancies were also recorded.

2.2. Determination of Thrombophilia Risk. All blood tests were performed during the first antenatal assessment and included assays of antithrombin III, protein C activity, free and total antigen protein S, activated protein C resistance, anti-cardiolipin antibodies (IgG and IgM), lupus anticoagulant, and fasting plasma homocysteine. Genetic studies were performed to look for factor V Leiden mutation if the patients had an elevated activated protein C resistance (APCR), prothrombin gene mutation, and homozygous status for the gene encoding methylenetetrahydrofolate reductase enzyme (MTHFR). Other risks of thrombophilia including immobilisation, the presence of recent major surgery, trauma, malignancy, and family history of VTE were obtained from the patients. The prevalence of the various risk factors in the group of pregnant women with suspected or confirmed thrombophilia is shown in Table 2. Data of age and parity matched, as possible, control pregnant women were collected from 40 consecutive pregnancies at the same institution without known thrombophilia risks and history suggestive for VTE and served as a control group. No anticoagulation treatment was initiated in the control group.
<table>
<thead>
<tr>
<th>Thrombophilia Risk</th>
<th>Number of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inherited or Acquired</td>
<td></td>
</tr>
<tr>
<td>Factor V Leiden mutation</td>
<td>3</td>
</tr>
<tr>
<td>MTHFR mutation</td>
<td>9</td>
</tr>
<tr>
<td>Prothrombin gene mutation</td>
<td>1</td>
</tr>
<tr>
<td>Hyperhomocysteinemia</td>
<td>1</td>
</tr>
<tr>
<td>Protein C deficiency</td>
<td>2</td>
</tr>
<tr>
<td>Protein S deficiency</td>
<td>1</td>
</tr>
<tr>
<td>Antithrombin deficiency</td>
<td>1</td>
</tr>
<tr>
<td>Antiphospholipid syndrome</td>
<td>1</td>
</tr>
<tr>
<td>Lupus anticoagulant</td>
<td>1</td>
</tr>
<tr>
<td>Personal history of venous thrombotic event (VTE)</td>
<td>16</td>
</tr>
<tr>
<td>Positive family history of VTE</td>
<td>6</td>
</tr>
</tbody>
</table>

Criteria of diagnosis of DVT were based on ultrasound Doppler in these cases. A follow-up ultrasound was instated to check for residual thrombosis in positive cases.

The British RCOG Guideline for risk stratification was applied (Green-Top Guideline 37a 2009) [12]. Low-risk patients received treatment with oral aspirin 100 mg daily only throughout pregnancy (6 cases) versus no treatment (4 cases). Intermediate risk patients received prophylactic treatment with enoxaparin 40 mg subcutaneously daily throughout pregnancy (11 cases) in combination with aspirin 100 mg orally daily in case of the presence of antiphospholipid syndrome, lupus anticoagulant, or SLE (6 cases). High-risk patients (11 cases) received treatment doses of low molecular weight heparin (LMWH) with enoxaparin as 1 mg/Kg body weight subcutaneously twice daily or 1.5 mg/Kg body weight subcutaneously daily. One patient was on oral vitamin K antagonist (warfarin) therapy prior to her unplanned pregnancy and then switched to LMWH once the pregnancy was confirmed at 8 weeks. Folic acid 5 mg taken orally daily was added in case of homozygous status of MTHFR. Anticoagulation was continued for at least 4 weeks postpartum in the intermediate and high-risk groups.

2.3. Statistical Analysis. A multivariate analysis of pregnancy outcome in correlation with risk factors of pregnancy was performed by using Stata 10.0 software. Numerical data was summarised with means and standard deviations, categorical data with numbers and percentages. Adjustment for putative confounders such as age, parity, and other risk factors was performed with unconditional logistic regression. Relative risks associated with laboratory thrombophilia abnormalities were expressed as odds ratios, with 95% confidence intervals. The association between the categorical variables was assessed by Fisher's exact test for small groups. For non-categorical variables, Student's t test was used. Furthermore, P value < 0.05 was considered as statistically significant.

3. Results

Twenty-six out of thirty-eight pregnant women (68.4%) with increased thrombophilia risk experienced one or more obstetric complications defined as diabetes, hypertension, pre-eclampsia, placenta abruptio, VTE, or oligohydramnios, compared with 15 out of 40 (37.5%) pregnant women in the control group (OR 3.6; 95% CI 1.42, 9.21, \( P < 0.001 \)). The prevalence of obstetric complications in both thrombophilia cases and the controls is given in Figure 1. VTE appears to be the most common obstetric complication experienced by the group of pregnant women with an increased thrombophilia risk (12/38) and occurred during the first trimester as proximal DVT. Of the thirty-eight pregnant women in the thrombophilia risk group, only four did not commence anticoagulant treatment because of relatively low risk such as presence of heterozygous status of MTHFR gene mutation with family history of VTE without additional risk factors. Some guidelines consider that MTHFR is not a thrombophilia risk factor; however we included only the homozygous cases.

Six out of ten women, who received anticoagulation therapy before pregnancy because of recurrent or recent VTE and continued during pregnancy, experienced obstetric complications compared to 12 out of 18 women who were offered anticoagulants after confirmation of pregnancy in the antenatal period. The incidence of obstetric complications such as pre-eclampsia, placenta abruptio, oligohydramnios, and VTE was significantly higher in the women of the increased thrombophilia risk group compared to the control group (\( P < 0.001 \)) (Figure 1).

Types of anticoagulant used during pregnancy are demonstrated in Table 3 and obstetric complications observed are given in Table 4. The pregnant women with thrombophilia risk classified as high risk (11/38), moderate...
Management of women with an increased risk of thrombophilia during pregnancy warrants a complete evaluation of patients clinically suspected of having VTE [25]. There is a lack of trials that assess the safety and accuracy of objective testing in pregnancy and no evidence to suggest that routine screening in pregnancy is cost-effective in low-risk populations [26]. VTE remains a substantial problem despite the dramatic decline in pregnancy-related mortality in industrialized countries over the past century. Nevertheless, VTE is the main direct cause of maternal mortality and a major contributor to morbidity in pregnancy [27].

5. Conclusion

Thromboembolic disease is one of the major and increasing causes of morbidity and mortality in the developed world. Management of women with an increased risk of thrombophilia with active anticoagulation is associated with less complications and improved obstetric outcomes. Therefore, it is important to follow the available guidelines and recommendations such as those of the Royal College of Obstetricians and Gynaecologists [12], whenever possible, to achieve the best possible outcome in pregnancy. Further studies to confirm our findings are warranted.
Abbreviations

APCR: Activated protein C resistance
DVT: Deep venous thrombosis
FVL: Factor V Leiden
HELLP: Haemolysis, elevated liver enzymes, and low platelet count syndrome
IUFD: Intrauterine fetal death
IUGR: Intrauterine growth restriction
LMWH: Low molecular weight heparin
MTHFR: Methylene tetrahydrofolate reductase
PGM: Prothrombin gene mutation
VTE: Venous thromboembolic disease.

Disclosure

There are no financial associations that may be relevant or seen as relevant to the submitted paper.

Conflict of Interests

The authors declare that they have no competing interests.

Acknowledgments

The authors wish to thank sincerely Dr. Andrew Maclaine-Cross and Dr. Ray Wilson, Consultant Physicians at the Launceston General Hospital, Tasmania, Australia, for their generous support in conducting this study.

References
