THROMBOPROPHYLAXIS IMPLEMENTATION DURING PREGNANCY IN WOMEN WITH RECURRENT FETAL LOSSES AND THROMBOPHILIA

UTICAJ PRIMENE HEPRINA MALE MOLEKULSKE MASE NA ISHOD TRUDNOĆE KOD ŽENA S TROMBOFILIJOM I PONAVLJANIM SPONTANIM POBAČAJIMA – PRVA ISKUSTVA

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Summary - Recurrent foetal loss is a significant clinical problem, occurring in 1-5% of reproductive females. Inherited or acquired thrombophilia has been diagnosed in 50-65% of women with history of unexplained foetal loss. The low molecular weight heparin was applied in 24 women with inherited thrombophilia and previous recurrent foetal loss and in 6 women with primary antiphospholipid syndrome throughout their following pregnancies. The dose of low molecular weight heparin for the majority of women was 35-75 u/kg. Women with primary antiphospholipid syndrome received both low molecular weight heparin and aspirin 50-100 mg daily. Implementation of thromboprophylaxis resulted in successful pregnancy outcome in 29 out of 38 pregnancies, which represents a significant improvement of pregnancy outcome in comparison to previous 81 pregnancy losses. The number of treated pregnancies in our study is small, but the rate of successful pregnancy outcomes is high (76%), indicating that low molecular weight heparin may be a promising approach to women with thrombophilia and recurrent foetal loss.

Key words: Heparin, Low-Molecular-Weight; Thrombophilia; Abortion, Habitual; Female; Antiphospholipid Syndrome; Pregnancy Outcome

Introduction

Recurrent foetal loss (RFL) is a significant clinical problem, occurring in 1-5% of reproductive females [1]. The association between acquired thrombophilia caused by the presence of antiphospholipid antibodies or myeloproliferative disorders and recurrent foetal loss is well established [2,3]. During the past decade, the link between inherited thrombophilia and RFL was also made [4-9]. Inherited or acquired thrombophilia has been diagnosed in 50-65% of women with history of unexplained foetal loss [5-7]. An association between the presence of thrombophilia and recurrent foetal losses occurring after 12th gestational week has been established in our population [10].

Thrombophilia testing has been part of the diagnostic procedure in women with recurrent foetal losses at the Thrombosis and Haemostasis Unit, Institute of Laboratory Diagnostics, Clinical Centre of Vojvodina, Novi Sad since the year 2002. In women with thrombophilia, in whom genetic abnormalities, anatomic malformations, hormonal, auto-immune and infective disorders were excluded, thromboprophylaxis with low molecular weight heparin (LMWH) is introduced from the beginning of the future pregnancy in order to prevent microthrombosis inside placental vessels and to improve the pregnancy outcome.

Materials and methods

This paper presents the preliminary results of the prospective study of low molecular weight heparin implementation in 24 women with inherited thrombophilia and repeated foetal losses and 6 women with primary antiphospholipid syndrome throughout their following pregnancies.

Thrombophilia testing was performed at the Thrombosis and Haemostasis Unit, Institute of Laboratory Diagnostics, Clinical Centre of Vojvodina, while RFL diagnosis, as well as the exclusion of other possible causes of poor pregnancy outcome, were made at High Risk Pregnancy Unit, Clinic of Gynaecology and Obstetrics, Clinical Centre of Vojvodina and Outpatient Clinic Minerva, Novi Sad.

The authors opted for the prophylactic dosage regimen according to the estimated risk, depending on the type of thrombophilia, outcome of previous pregnancy and previous thrombotic episodes. Heparin was introduced as soon as the pregnancy had been confirmed by an ultrasound examination, between the 5th and 9th gestational weeks and continued throughout the entire pregnancy and 4-6 weeks postpartum.

The starting dose of LMWH in majority of cases was 30-75 U/kg/24h, with only two women receiving a therapeutic (100 U/kg/12h) and sub-therapeutic dose (150 U/kg/24h). All women with primary an-
Statistical analysis

The number of successful pregnancy outcomes during the implementation thromboprophylaxis was compared with previous pregnancy outcomes using $\chi^2$ test, $p$ value < 0.05 was considered to be statistically significant.

Results

Out of 30 women in whom thromboprophylaxis was implemented during pregnancy, 24 had inherited thrombophilia: 12 were with heterozygous FV Leiden mutation, 6 with heterozygous FII G20210A mutation, 6 with natural inhibitor deficiency and 6 women with primary antiphospholipid syndrome. Of 6 women with natural inhibitor deficiency, 3 had antithrombin deficiency and 3 had protein S deficiency. FV Leiden mutation, being the most frequently present inherited thrombophilia in the study group, was found in 50% of cases. The mean age at the beginning of the index pregnancy was 31.6 in the group of patients with inherited thrombophilia and 33.3 in the patients with primary antiphospholipid syndrome. Low molecular weight heparin was used in low prophylactic doses, except in cases with high risk for RFL or in women with previous venous thromboses or natural inhibitor deficiency.

Therapeutic LMWH dose was used in a woman with antithrombin deficiency with two previous unsuccessful pregnancies, first with intrauterine foetal death and second with bilateral iliac vein thrombosis and subsequent venae cavae thrombosis. During the third pregnancy, despite the use of therapeutic dose of LMWH, the spontaneous abortion occurred in the 8th gestational week. Sub-therapeutic dose was used in a woman with FII G20210A mutation and previous ten pregnancy losses, although prophylactic LMWH had been implemented during the tenth pregnancy. During her eleventh pregnancy, sub-therapeutic dose of LMWH was successfully used.

The number of previous unsuccessful pregnancies in the group of women with inherited thrombophilia and antiphospholipid syndrome as well as the number of successful pregnancies upon the use of low molecular weight heparin is shown in Table 1. The number of previous pregnancy losses was 81, 64 in the group with inherited thrombophilia and 17 in the group with antiphospholipid syndrome. Successful pregnancy outcome occurred in 29 out of 38 following pregnancies, the difference being statistically significant.

The significant difference in the pregnancy outcome improvement between the group with FV Leiden and FII G20210A mutations and the group with natural inhibitor deficiency was observed. Administration of LMWH improved the pregnancy outcome in the women with FV and FII mutations, but not in the women with natural inhibitor deficiencies.

Regarding heparin-related complications, four women had minimal bleeding, two of them had vaginal bleeding, one had haemorrhoidal bleeding and one woman with primary antiphospholipid syndrome (PAPS) experienced mild skin bruising in the 4th month of gestation, which was resolved by cessation of aspirin. No cases of clinically relevant bleeding or heparin-induced thrombocytopenia occurred. One case of skin allergic reactions, manifesting as urticarial rash, occurred, and it disappeared after switching to another LMWH.

Discussion

The successful pregnancy outcome depends on adequate placental vascularisation. Impairment of the placental vascularisation is involved in the pathophysiology of various pregnancy complications, such as recurrent foetal losses, intrauterine growth restriction, intrauterine foetal death, placental abruption and pre-

<table>
<thead>
<tr>
<th>Type of thrombophilia</th>
<th>Previous unsuccessful pregnancies</th>
<th>Successful heparin use</th>
<th>Unsuccessful heparin use</th>
<th>$p$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FII</td>
<td>81</td>
<td>29</td>
<td>9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FV</td>
<td>64</td>
<td>24</td>
<td>7</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Table 1. Comparison of pregnancy outcome before and after low molecular heparin implementation

Tabela 1. Poredenje prethodnih neuspešnih trudnoša s ishodom trudnoša tokom primene heparina u celoj grupi

Abbreviations

RFL – recurrent fetal loss
LMWH – low molecular weight heparin/heparin male mole
kulške mase

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tiphospholipid syndrome received both LMWH and aspirin 100 mg daily. During the treatment, laboratory controls of heparinemia, D dimer level, platelet count, activated partial thromboplastin time (aPTT) and prothrombin time (PT) were performed at 2-4 week intervals using Instrumentation Laboratory (IL, Milan, Italy) reagents and ACL 9000 coagulometer manufactured by IL.

The study was approved by the Medical Faculty Ethical Committee and the signed informed consent was obtained from all participants.
Deficit prirodnih inhibitora
Natural inhibitor deficiency

FII G20210A 21 6 2 <0,05
level is low [15]. Without therapy, only 20% of future pregnancies would have favourable outcome [5].

Data on current therapeutic approach to women with inherited thrombophilia were obtained from small series, with low molecular weight heparin as the most frequently used drug. Clinical outcomes of LMWH administration in pregnancy were compared with previous pregnancy outcomes, or with pregnancies treated with other drugs, mostly aspirin.

The results of the use of low molecular heparin during following pregnancies in women with thrombophilia and previous recurrent foetal losses are encouraging. Comparing to the previous pregnancy outcomes or to the treatment with low dose aspirin, the use of LMWH has improved live birth rate [19,20]. A major drawback of previous studies is the lack of untreated or placebo treated control group. The results of several randomised controlled studies that investigated the efficacy of low molecular weight heparin in women with unexplained recurrent foetal loss have recently been published. Two trials reported a statistically significant benefit of low molecular weight heparin use compared to no treatment or placebo [26,27]. The most recently published trials compared efficacy of aspirin alone or with low molecular weight heparin to no treatment or aspirin alone or placebo and failed to demonstrate a difference in the live birth rate [28,29]. However, there is a possibility that LMWH use may be beneficial in thrombophilic women [29]. Until the results of randomised placebo controlled trials of the influence of LMWH on the pregnancy outcome in thrombophilic women with previous RFL become available, the decision whether to use LMWH should be guided by individual risk assessment of the severity of inherited thrombophilia and the estimation of risk for the development of complication [32].

Considering the arguments for and against the use of LMWH in women with repeated foetal losses and thrombophilia, we can conclude that if all other possible causes of foetal losses have been excluded, treatment with preventive antithrombotic regimen seems to be justified. All women, who participated in this study, had been informed about possible treatment complications and about the absence of results from placebo controlled studies. Lack of randomised controlled trials which compare pregnancy outcome in women with thrombophilia and repeated foetal losses treated with LMWH or placebo during following pregnancy is the reason why some experts are restrained or against this therapeutic approach [15,16]. On the other hand, the complexity and unpredictability of reproductive biology and the age of women at the time of thrombophilia testing make women's acceptance to participate in the placebo arm of study rather unlikely.
The number of thrombophilic women receiving LMWH in this study is small, but the percentage of successful pregnancy outcome is high (76.3%), suggesting a possible successful therapeutic approach to this complex clinical entity in carefully selected cases. Similar results were seen in Brenner’s study, where a favourable outcome was recorded in 75% of pregnancies [17]. The difference in the pregnancy outcome in subgroups affected by different thrombophilias may be the result of insufficient heparin dose in the group with severe thrombophilia, such as natural anticoagulant deficiency, which has strong unfavourable influence on pregnancy [33].

Conclusion

The first results of low molecular weight heparin use during pregnancy in women with thrombophilia and repeated foetal losses in our country are encouraging. It is of great importance to emphasize that large controlled randomised clinical trial is needed to compare this therapeutic approach with placebo and to confirm our pilot study results.

References


**Sažetak**

**Uvod**

Ponavljani spontani pobačaji značajan su klinički problem koji postoji kod 1-5% žena u reproduktivnom periodu. Tokom poslednje decenije utvrđeno je postojanje povezanosti nasledne trombofilije i ponavljanih spontanih pobačaja.

**Materijal i metode**

U ovom radu prikazani su rezultati prospektivne studije kojom je dosad obuhvaćeno 30 žena, od toga 24 s naslednom trombofilijom i ponavljanim spontanim pobačajima i 6 s primarnim antifosfolipidnim sindromom, kod kojih je primenjen heparin male molekulske mase tokom narednih trudnoća. Primena heparina je započeta odmah po utvrđivanju trudnoće, između 5. i 9. gestacijske nedelje, i nastavljena tokom čitave trudnoće, kao i tokom 4-6 nedelja pospartalno. Početna doza heparina za većinu ispitanica bila je 30-75 j/kg/24 h. Kod žena s primarnim antifosfolipidnim sindromom uz heparin je primenjivana acetilsalicilna kiselina 50-100 mg dnevno.

**Rezultati**

Broj prethodnih gubitaka ploda u ispitivanoj grupi bio je 81, od toga 64 u grupi s naslednom trombofilijom, a 17 u grupi s primarnim antifosfolipidnim sindromom. Tokom sledećih 38 trudnoća u kojima je primenjen heparin, uspešan ishod je zabeležen u 29, što predstavlja statistički znatno poboljšanje ishoda trudnoće.

**Diskusija i zaključak**

Na osnovu posmatranja različitih trombofilija uočava se statistički znatno poboljšanje ishoda trudnoće primenom heparina za mutacije FV Leiden i FII G20210A, dok kod žena s postojanjem deficita prirodnih inhibitora koagulacije nema statistički bitne razlike u broju uspešnih trudnoća tokom primene heparina. Iako je broj dosad uključenih trudnica mali, prvi rezultati primene niskomolekularnog heparina tokom trudnoće kod žena s dokazanom trombofilijom i ponavljanim spontanim pobačajima jesu ohrabrujući. Izuzetno je važno istaći neophodnost sprovođenja randomiziranih kliničkih studija koje bi poredile ovakav terapijski režim s placebom u skoroj budućnosti i potvrdile naše rezultate.


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