Comparison of two therapeutic protocols in patients with antiphospholipid antibodies and recurrent miscarriages

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Aim. To compare the effects of two therapeutic protocols for the patients with recurrent miscarriages associated with the presence of antiphospholipid (anticardiolipin) antibodies.

Methods. A prospective observational study included 20 patients with antiphospholipid antibodies in the first group who received low-molecular heparin and aspirin. The second group of 20 patients, in addition to this therapy, received immunotherapy (intravenous immunoglobulin). Aspirin was administered at the time of a positive pregnancy test, and low-molecular heparin not before the fetal heart activity registration by ultrasound. Intravenous immunoglobulin was given prior to the conception or at the beginning of the pregnancy. We compared these groups according to the pregnancy outcomes and the occurrence of complications during pregnancy, using standard statistical tests.

Results. The rate of positive gestational outcome in the patients treated with aspirin and low-molecular heparin was 85% (17/20), and in the second group it was 90% (18/20). There was no significant difference in pregnancy outcomes between these groups (p > 0.05), except for the occurrence of preeclampsia and thrombocytopenia, which were recorded only in the aspirin and low-molecular heparin group, but with no statistical significance (p > 0.05) compared to the second group, which received immunoglobulin additionally.

Conclusion. There was no significant difference (p > 0.05) in pregnancy outcomes between the two studied therapeutic protocols, but the therapy with aspirin and low-molecular heparin was cheaper and easier to apply than the therapy with immunoglobulins. The results of our study confirmed that the final pathogenic mechanisms in recurrent fetal miscarriages were inflammation and thrombosis of the uteroplacental blood vessels.

Key words: antibodies, antiphospholipid; abortion, spontaneous; heparin, low-molecular-weight; aspirin; immunoglobulins; pregnancy outcome.

Introduction

Antiphospholipid syndrome (APAS) is characterized by the presence of circulating autoantibodies against negatively ionized phospholipids, which is clinically manifested by thrombosis, thrombocytopenia, and recurrent miscarriages (1). The incidence of recurrent spontaneous abortions in patients with antiphospholipid antibodies (APA) may range up to 90%, of which 75% occurs in the first trimester (2).

It is possible that the repeated abortions are caused by the thrombotic events in the placental blood vessels, which results in extensive infarctions causing placental insufficiency (2).
bined treatment with aspirin and heparin is a reasonable and well accepted therapeutic approach in pregnant women with APAS (4, 5). In fact, this combination may promote a successful embryonic implantation in the early stages of pregnancy, and protect against thrombosis of uteroplacental blood vessels after a successful placentation (3–5).

Immunotherapy with intravenous gamma-globulin (IVIG) has recently gained considerable attention in the literature (6–8). IVIG probably reacts with the receptors on the macrophage surface, blocking the Fc receptors and increasing the number of suppressor T cells (6, 7).

In addition, the therapy combined with immunosuppressives (high dose corticosteroids) and antiplatelet drugs (low-dose heparin or aspirin) was associated with a variety of complications during pregnancy (7, 8).

The aim of the study was to compare the effects of two therapeutic protocols for the patients with recurrent miscarriages associated with the presence of antiphospholipid antibodies.

Methods

Our study was conducted in the Institute of Gynecology and Obstetrics of the Clinical Center of Serbia, from 1998 to 2002. It was a prospective clinical trial including 40 patients with recurrent fetal loss associated with the presence of antiphospholipid antibodies, and treated with aspirin and heparin (n = 20) in the first group, and aspirin, and heparin and IVIG (n = 20) in the second group. Their main characteristics are given in Table 1. The mean gestational age of the patients in the first group (aspirin and heparin) was 29.3 ± 2.5 weeks, while in the second, triple therapy group, it was 30.2 ± 2.0 weeks. We compared the gestational age results between these two groups. Patients included in this study had two or more consecutive spontaneous abortions, caused by the immune disorders. The average number of spontaneous abortions in the aspirin and heparin group was 4.1 ± 1.6, while in the second, triple therapy group, it was 4.6 ± 1.2. Antiphospholipid antibodies were detected by an enzyme-linked immunosorbent assay (ELISA). The IgG anticardiolipin level of ≥ 5U/L, and the IgM anticardiolipin level of ≥ 3U/L were considered positive. In our study, aspirin was given in a dose of 100 mg daily, after the pregnancy test was positive. Low-molecular weight heparin was started when fetal heart activity was registered by ultrasound, and it was given in a dose of 0.3 units subcutaneously at 12-hour intervals. The treatment was interrupted in case of miscarriage, or at 34 weeks of gestation. IVIG was given prior to the conception, or at the beginning of pregnancy in a dose of 10 g once a month until 34 weeks of gestation.

Pregnancies were controlled by Doppler ultrasound, and by biochemical measuring of the levels of antibodies. According to the level of autoantibodies, patients were devided into two groups, a group with a moderate, and a group with a high antibody level, respectively.

Results

Eighteen patients in the aspirin and heparin group had a moderate level of APA, while seventeen of the patients in the triple therapy group had similar antibody level.

The differences in characteristics between the groups were assessed by the Fisher's exact test for categorical variable, and the Student's t-test for continuous variable; a p-value of 0.05 or less was considered statistically significant.

There was no significant difference (p > 0.05) in the mean gestational age nor in the average number of sponta-

Table 1.

<table>
<thead>
<tr>
<th>Characteristics of patients included in the study</th>
<th>Heparin + Aspirin</th>
<th>Heparin + Aspirin + IVIG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational success</td>
<td>17/20 (85%)</td>
<td>18/20 (90%)</td>
</tr>
<tr>
<td>Preterm birth (before 37 g.w.)</td>
<td>4/20 (20%)</td>
<td>2/20 (10%)</td>
</tr>
<tr>
<td>Average gestational age</td>
<td>36.05 ± 1.68</td>
<td>37.15 ± 1.05</td>
</tr>
<tr>
<td>Median birthweight of infants</td>
<td>2 253 ± 1 145</td>
<td>2 718 ± 589</td>
</tr>
<tr>
<td>Preeclampsia</td>
<td>3/20 (15%)</td>
<td>0/20</td>
</tr>
<tr>
<td>Intrauterine growth restriction</td>
<td>3/20 (15%)</td>
<td>2/20 (10%)</td>
</tr>
<tr>
<td>Thrombocytopenia (tr &lt;50 000)</td>
<td>3/20 (15%)</td>
<td>0/20</td>
</tr>
<tr>
<td>Premature labour with rupture of membranes</td>
<td>2/20 (10%)</td>
<td>2/20 (10%)</td>
</tr>
<tr>
<td>Apgar score at 5 min &lt; 7</td>
<td>7/20 (35%)</td>
<td>5/20 (25%)</td>
</tr>
<tr>
<td>Cesarean delivery</td>
<td>9/20 (45%)</td>
<td>11/20 (55%)</td>
</tr>
</tbody>
</table>
Gestational success reached 85% (17/20) in the aspirin- and heparin-group, and the rate of success in the second group treated with heparin, aspirin and IVIG was 90% (18/20). There was no statistical significance ($\chi^2 = 0.02855$, $p > 0.05$) in pregnancy outcome between the two studied therapeutic protocols. Three pregnancies (15%) terminated with a miscarriage in the aspirin and heparin group, mainly in the first trimester of pregnancy, and the two women (10%) from the second group had spontaneous abortion within this study. One woman (5%) from the aspirin and heparin group had a stillbirth.

Two patients (10%) per each group had premature labor with rupture of membranes. Pregnancy induced hypertension and thrombocytopenia ($tr < 50,000/L$) complicated 15% (3/20) of the pregnancies, and antepartal hemorrhage 5% (1/20) in the aspirin and heparin group. The average gestational age at the delivery was 36.05 ± 1.68 weeks in the aspirin and heparin group, while in the second group it was 37.15 ± 1.05 weeks. There was no significant difference in the gestational age at the delivery between the studied groups ($t = 0.25, p > 0.05$). Twenty percent (4/20) in the first group and 10% of the babies (2/20) in the second group were born before 37 weeks of gestation. The median birthweight of the infants in the aspirin and heparin group was 2,253 ± 1,145 g, respectively, while the median birth weight was 2,718 ± 589 g in the triple therapy group. However, 15% (3/20) of the infants were small for their gestational age (intrauterine growth restriction) in the first group, and 10% (2/20) in the second, triple therapy group. There was no significant difference in the average birthweight between the groups ($t = 1.6, p > 0.05$). In each case of neonatal birth weight above the 10th centile growth curve, the uterine artery Doppler tracing demonstrated the abnormal blood velocity waveforms, indicating placental insufficiency. Apgar score at 5 min < 7 was recorded in 35% (7/20) of the patients in the heparin and aspirin group, while in the women with triple therapy in 25% (5/20). In the aspirin and heparin group, cesarean delivery was performed because of the signs of fetal distress in six cases, and in three cases the indication for cesarean delivery was maternal hypertension. In the second group, cesarean delivery was performed in the eleven cases.

**Discussion**

Pregnancy outcome in women with spontaneous abortion associated with antiphospholipid antibodies, was enhanced by the various treatments causing variable side-effects (7, 8). Final pathogenic mechanisms in APAS leading to the abortion were inflammation and thrombosis, and it could be prevented by the antithrombotic and antiinflammatory activities of heparin and aspirin (8). Two recent publications have demonstrated that the combination of heparin and aspirin was more effective than aspirin alone in pregnancies with the previous fetal loss associated with APA (8, 9). In one of them, the gestational results in the group of 25 women treated with aspirin and heparin were compared with the results of the group of 25 women who were given only aspirin (9). Gestational success was 80% in the first group, and only 44% in the aspirin only group (9).

These results suggested that heparin played the major role in the prevention of the recurrent fetal loss, yet the complete mechanism of action of this drug was still unknown (10). Except for its main effect, heparin has the capacity to adsorb ASA (10). Phosphatidylserine and phosphatidylethanolamine are the phospholipids that participate as the adhesion molecules in the fusion of syncytiotrophoblast, therefore, antiphospholipid antibodies could cause abortion, so heparin could inhibit that effect (11). Accordingly, heparin has been used in trying to improve the implantation of in vitro fertilization programs (12). Sher et al. (13, 14) reported significant difference in the number of viable pregnancies among the infertile patients with APAS treated with heparin and aspirin, compared with the control group.

Our experience with the combined treatment with aspirin and heparin also confirmed a high live-birth rate among the women with recurrent fetal loss and APAS (14). At the University of Utah (15), approximately one-third of APAS pregnancies resulted in live births and the deliveries prior to 34 weeks' gestation, which was also recorded in our study, in which only 20% of all the pregnancies was delivered preterm. Our findings that most miscarriages (12.5% pregnancies) occurred in the first trimester confirmed the previous prospective observational study (15).

Despite the increased rates of live birth, the pregnant women treated with heparin and aspirin had some obstetric complications (preeclampsia, intrauterine growth restriction, preterm birth) (16). These complications have prompted a search for the better therapy. The treatment with IVIG was confirmed as promising in a small number of cases refractory to heparin and prednisone (17). Obstetric complications, such as preeclampsia and thrombocytopenia, occurred rarely in patients treated with IVIG, and the reason for that could be their immunological origin (18). A high dose of intravenous immunoglobulin therapy appeared to inhibit anticoagulant antibodies in pregnant and non-pregnant women by suppressing the autoantibody production (19). Since the efficacy of IVIG has not been proven yet in the appropriately designed studies, and the drug is extremely expensive, it has still not been recommended as the common therapy (19).

In our study, two pregnancies (10%) were lost in the triple therapy group, and three (15%) in the aspirin and heparin group, providing evidence that abnormal placentation could not be avoided in spite of the optimal treatment (aspirin, heparin, immunoglobulin). In fact, these patients had the highly positive level of autoantibodies, and their live-birth rate was lower, than in the patients with moderate APA level. However, the therapy was useful in treating the cases with the moderate level of autoantibodies (eighteen patients from the heparin and aspirin group, and...
seventeen patients from the triple therapy group), so that the distinction between the two groups was justified. According to recent publications, some authors suggested the initiation of the therapy with aspirin and heparin prior to the conception in women with recurrent pregnancy loss, so that the problem in early gestations could be avoided (20–22).

Also, there were suggestions that in some cases (idiopathic thrombocytopenia and preeclampsia) the use of immunotherapy was favorable (19). Successful pregnancy outcomes in the women with APAS in our study, treated with heparin and aspirin, confirmed the findings that the mechanisms in pathogenesis of recurrent fetal loss included thrombosis and inflammation of the uteroplacental blood vessels (23).

Conclusion

In the women with recurrent miscarriages associated with the presence of antiphospholipid antibodies, the therapy with aspirin and heparin was effective, cheaper (which is important for the developing countries), and easier to provide than the therapy which included intravenous immunoglobulins. A close antenatal surveillance and the planned delivery of these pregnancies were necessary for achieving the positive perinatal results. On the other hand, the results of this study suggested that the inflammation and thrombosis of the uteroplacental blood vessels were included in the pathogenesis of recurrent pregnancy loss in women with APAS.

REFERENCES


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**Апстракт**


**ПОРЕДЕЊЕ ДВА ТЕРАПИЈСКА ПРОТОКОЛА КОД БОЛЕСНИКА СА АНТИФОСФОЛИПИДНИМА АНТИТЕЛАМА И ТРИБАЈИМА**

**Циљ.** Циљ ове студије био је поредење ефикасности два терапијских протокола у лечењу болесника са хабитуалним побрачињем и присутвом ан蒂фосфолипидних антикодиолипинских антитела. **Метод.** Проксептивном опсервацијском студијом обухваћено је 40 болесника са присутним антифосфолипидним антителима од којих је њих 20 у првој grupi добијало aspirin и нискомолекулски хепарин, а других 20 испитанак је пored ove терапије добијало и имуноглобулин. Aspirin je dat kada je ustanovljena trudnoća, dok se niskomolekulski heparin davao nakon ultrazvučno registrovane srčane активности ploda. Imunoglobulinii su dati ili pre začeka ili na početku trudnoće. Ефикасност променjene терапије procenjivana je на осnovу ишода trudnoće, као и компликациjа u tokу trudnoće. За процену ефикасности кorišćeni su standardni статистички тестови.

**Резултати.** Позитivan перинаталni ishod u prvoj grupi (aspirin i heparin) уstanovljen je kog 85% болесника, dok je u drugoj grupi bio 90%, što nije bilo статистички значајно (p > 0,05). Preeklampsija и trombocitopenija су se kao компликациjе javile samo u grupi trudnica које су добијале aspirin и niskomolekulski heparin, без статистички значаjне разлике (p > 0,05) у односu на grupu коja je pored ove терапије добијала и имуноглобулин. **Закључак.** S обзиром на то да je усpeшан перинаталni ishod био podjeđnako zastupljen у обе испитане grupe, код болесника са присутним антифосфолипидним антителима и хабитуалним побрациjем može se preporučiti примена аспирина и нискомолекулског heparina, tim pre što je ова терапиjа једноставниja за примenu и jeftinija od терапиjе koja uključuje и primenu imunoglobulina. Osim toga, нашi резultati потврдjuju da je mehanizam оvих poremećaja baziran na inflamaciji и trombozi крвних судова placente.

**Кључне речи:** antitela, antifosfolipidna; abortus; heparin, niskomolekulski; aspirin; imunoglobulinii; trudnoćа, išod.

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