Prevalence of anticardiolipin antibody IgG in recurrent first trimester abortions and the role of aspirin in its prevention

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Summary

Background: Approximately 10% of all human pregnancies end in spontaneous abortions. In the majority of such cases the etiology remains unknown, but anticardiolipin antibodies are gaining recognition as potential causes of recurrent miscarriage.

Material/Methods: The prevalence of anticardiolipin antibody IgG (IgG_\text{acl}) in 60 pregnant patients with recurrent first trimester abortions and 60 pregnant controls of comparable age with no history of abortion were examined to find a possible relation between IgG_\text{acl} and spontaneous abortion. The assay for IgG_\text{acl} was done by Enzyme Linked Immunosorbent Assay (ELISA). Positive test results were considered 'strongly elevated' with IgG_\text{acl} levels exceeding 36 GPL units. Aspirin (80 mg per day) was prescribed for patients with recurrent first trimester abortion and strongly elevated levels of IgG_\text{acl}.

Results: Strongly elevated levels of IgG_\text{acl} were detected in a total of 18 patients (30%) with recurrent abortions, and none of the controls (p<0.001). Of all the patients with strongly elevated levels, 16 patients had unexplained abortions and 2 had explicable abortions. The relative risk for strongly elevated IgG_\text{acl} was 3.78. These 16 patients with unexplained abortions were treated with aspirin, 80 mg per day, and a successful pregnancy outcome was observed in 10 patients, while 2 patients were in the third trimester of pregnancy.

Conclusions: IgG_\text{acl} is strongly associated with first trimester recurrent abortions and increases the risk approximately 4-fold. Aspirin is beneficial in patients with recurrent first trimester abortions and strongly elevated levels of IgG_\text{acl}.

key words: anticardiolipin antibody • IgG • aspirin • abortion • fetal loss
BACKGROUND

The IgG antibody is the most abundant immunoglobulin (80% to 85%) circulating in body fluids, and is the most important immunoglobulin in the secondary immune response. It crosses the placenta and provides passive immunity to the fetus. Its serum half-life is approximately 21 days.

In view of the high incidence of spontaneous recurrent abortions of unknown cause, the continuous search for the etiology remains important. Evidence from a broad spectrum of studies has associated anticardiolipin antibodies with recurrent abortions [1]. The autoimmune antibodies associated with recurrent abortions are lupus anticoagulant and anticardiolipin antibodies immunoglobulin G (IgGacl) and immunoglobulin M (IgMcI). The assay for acl is more sensitive and specific for fetal loss in comparison to lupus anticoagulant [2]. First trimester abortion is the most common type of miscarriage in women with an elevated level of these antibodies. Controversies exist regarding the association of IgGacl with recurrent first trimester abortions. The present study in a North Indian population was undertaken to estimate the prevalence of IgGacl in patients with recurrent first trimester abortions, to ascertain if there is a relation between these two facts, and study the outcome after treatment with aspirin, which inhibits thromboxane synthetase, thereby reducing the risk of abortion.

MATERIAL AND METHODS

The study was carried out in a total of 120 pregnant women of North Indian origin, divided into two groups. The experimental group (Group 1) consisted of women with a history of two or more recurrent first trimester spontaneous abortions. These included primary as well as secondary aborters with live births prior to having recurrent abortions. The control group (Group 2) consisted of women with one or more live births and no history of first trimester spontaneous abortion.

The age in Group 1 ranged between 20 and 29 years, with a mean of 25.5±3.0 years; in Group 2, between 19 and 32 years, with a mean of 26.1±3.3 years respectively. The average age in the two groups was comparable (p>0.05, not significant). In Group 1, 83! of the patients were primary aborters, and 17! were secondary aborters. Also, 50! of the women were third gravida, 33.3! fourth gravida, 10! fifth gravida and 6.7! sixth gravida, with a mean gravidity of 3.7±0.9 and a range of 3–6. In Group 2, 60% were second gravida, 13.4! third gravida, 20% fourth gravida, 3.3! fifth gravida and 3% sixth gravida, with a mean gravidity of 2.7±1.1, range of 2–6. The largest number of patients in Group 1 were third gravida, i.e. 50%, whereas in Group 2, 60% were second gravida. We could not compare the gravidity distribution in the two groups because the patients included in Group 1 were at least third gravida, with 2 previous abortions.

A detailed clinical history was taken and a clinical examination performed, with routine investigations, including bleeding time, clotting time and ultrasonography. Blood was collected, serum separated, and the level of IgGacl, estimated by ELISA technique. The test was performed using a well-type kit from Gen Bio ImmunoWELL® cardiolipin antibody IgG Test (quantitative). Levels are reported in GPL units. One GPL unit is defined as the cardiolipin binding activity of 1 µg/ml of an affinity-purified IgGacl preparation from a standard serum [3].

The results in GPL units were interpreted as negative if less than 10, weakly elevated if 10–36, and strongly elevated if greater than 36 (as recommended by the manufacturer of the reagents). Patients with strongly elevated levels of IgGacl were treated with low dose aspirin, i.e. 80 mg. per day. Low dose aspirin selectively inhibits thromboxane synthetase and may restore or maintain a normal prostacyclin-thromboxane relationship, thus reducing the risk of thrombosis and spontaneous abortion [4,5].

RESULTS

The levels of IgGacl were evaluated in all 120 pregnant patients, 60 each from Group 1 and Group 2. IgGacl was observed to be elevated in 42 patients from Group 1 and 10 patients from Group 2, with a relative risk (RR) of 3.05 and 95% confidence interval (CI) of (2.01, 4.63). Strongly elevated levels of IgGacl were found 18 patients from Group 1 and none from Group 2 (RR 3.78, 95% CI 2.54, 5.61), whereas these levels were negative in 18 patients from Group 1 and 50 from Group 2, and weakly elevated in 24 in Group 1 and 10 from Group 2 (RR 2.67, 95% CI 1.70, 4.19; cf. Table 1). Patients with strongly elevated levels of IgGacl were found to be 4 times more at risk for first trimester abortion than those with negative IgGacl levels, whereas with weakly elevated levels the risk was 2.67 times higher.

The total number of patients with recurrent abortion investigated for the presence of IgGacl was 60 (Group 1), of whom 8 had a history of recurrent abortions for which the cause was known, while 52 had no explained cause of the recurrent abortions. In the patients with explained abortions, significantly elevated levels of IgGacl were found in 2 of 8, i.e. 25%, as compared to 16 of 52, i.e. 30.7%, in patients with unexplained cause of recurrent abortions (Figure 1). In 2 patients, toxoplasmosis was observed to be the possible cause for recurrent abortions, so these patients were included as patients with explained cause of recurrent abortions. In 16 patients there was no other infection diagnosed; therefore, they

<table>
<thead>
<tr>
<th>IgG level (GPL Units)</th>
<th>Study group</th>
<th>Control</th>
<th>RR (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total positive (&gt;36)</td>
<td>42 (70)</td>
<td>10 (16.7)</td>
<td>3.05</td>
<td>0.001</td>
</tr>
<tr>
<td>Strongly positive</td>
<td>18 (30)</td>
<td>0</td>
<td>3.78</td>
<td>0.001</td>
</tr>
<tr>
<td>Weakly positive (10–36)</td>
<td>24 (40)</td>
<td>10 (16.7)</td>
<td>2.67</td>
<td>0.001</td>
</tr>
<tr>
<td>Negative (&lt;10)</td>
<td>18 (30)</td>
<td>50 (83.3)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
were included as patients with unexplained cause of recurrent abortions.

Successful pregnancy outcome after treatment with aspirin was observed in 10 patients with strongly elevated IgG_{acl}; 2 were in the third trimester of pregnancy, 4 aborted, and 2 were lost to follow-up. In patients with weakly elevated IgG_{acl}, successful pregnancy outcome without any treatment was observed in 19 patients; 3 aborted and 1 was lost to follow-up.

**DISCUSSION**

Recurrent abortion is a heterogeneous condition which is extremely traumatic emotionally as well as physically. Despite thorough investigation according to various clinical protocols, the underlying etiology remains obscure in the majority of patients, and obstetricians are facing a challenge to determine the cause of these unexplained abortions. Recently, the presence of IgG_{acl} has been associated with approximately 40% of such cases. In our study, strongly elevated levels of IgG_{acl} (more than 36 GPL units) were observed in 18 (30%) patients from Group 1. A wealth of data supports approximately 30% positivity for elevated IgG_{acl} in women with recurrent abortions. Our observation is in close conformity with a report [6] in which the prevalence of IgG_{acl} in 30% of patients with recurrent abortions has been observed, but this study also found positivity in 8% of controls. The levels were not found to be strongly elevated in any of the controls in our study, although the levels were weakly elevated in 10 (16.7%) patients from Group 2. In concurrence with our report, two other studies have reported a 30% to 35% prevalence of IgG_{acl} in recurrent first trimester abortions [7,8].

In several other studies [9–12] the prevalence of IgG_{acl} has been reported in less than 14.0% patients with unexplained recurrent abortions, which is slightly less than half the prevalence of our observation. In another study [13] on 145 patients with recurrent second trimester abortion, IgG_{acl} was observed to be positive in 52.4%, almost double the results of the present study.

We cannot compare the results, however, since this study involved patients in the second trimester, whereas ours was limited to first trimester abortions. In none of these studies [7–13] have the authors reported whether IgG_{acl} levels were weakly positive or strongly positive, in spite of the fact that recurrent abortions are associated with strongly elevated levels of IgG_{acl}, exceeding 40 GPL units. Weakly elevated levels of IgG_{acl} [10–36] were observed even in the control group patients in the present study, which is in conformity with reports [6,10] that IgG_{acl} may be elevated in the low risk obstetric population.

The prevalence of IgG_{acl} in patients with two or more recurrent abortions in our study was 30% (n=18). Significantly elevated IgG_{acl} in cases of unexplained recurrent abortion was 30.7%, and in cases of explained recurrent abortions 25%, which is comparable to a report [7] in which none of the patients with explained recurrent abortions were found to have elevated IgG_{acl}.

This observation was well within the range, i.e. 11%–52.4%, reported by many other researchers. In 26.6% of the patients with two or more recurrent first trimester abortions, we could not find any other factor except for strongly elevated IgG_{acl} to account for their recurrent abortions. With a highly significant p value (less than 0.001) and relative risk of 3.78, an IgG_{acl} level of more than 36 GPL units can be confirmed to increase the risk of first trimester abortion by almost 4 times. This is consistent with a published report [14] that repeated fetal loss occurs in subjects with IgG_{acl} above approximately 40 GPL units. The determination of IgG_{acl} is an integral part of investigation for recurrent abortions in view of the considerable magnitude of the emotional and physical trauma involved, in addition to the loss of man-hours and finances.

In view of the fact that the most frequently recommended type of treatment in such patients is low dose aspirin, which even if taken on a regular basis is known to be safe for the mother as well as the fetus, this was prescribed for Group 1 patients with strongly elevated level of IgG_{acl}, before 12 weeks of gestation, and was continued until delivery. We observed live birth in 12 of 16 patients, i.e. 75% (including two patients with pregnancies continuing as of this writing), which is similar to other reports [15,16] with different treatment regimens, including low dose aspirin. It has been reported [17] that combination therapy with aspirin and heparin may reduce pregnancy loss in women with antiphospholipid antibodies by 54%. Further large, randomized controlled trials with adequate allocation concealment are necessary to exclude significant adverse effects. In a retrospective study [18] of 75 pregnancies in patients with antiphospholipid syndrome (APS), after exclusion of induced abortions and pregnancies occurring before onset of APS, the live birth rate was 58% with different treatment regimens including low dose aspirin. The interpretation of our work may prove useful, though
further research is necessary to resolve the role of aspirin in a larger number of patients with recurrent first trimester abortions and strongly elevated IgG_{ACL}.

CONCLUSIONS

Determination of IgG_{ACL} levels is required in patients with recurrent abortions of unknown etiology, since it is strongly associated with recurrent first trimester abortions and increases the risk by 4 times. Aspirin is beneficial in such patients, since it reduces the risk of thrombosis of the placenta. In view of the prevailing controversies regarding the role of aspirin, continuing research on a larger scale in this area could eventually provide important information on benefits from the use of aspirin in patients with recurrent first trimester abortions and elevated levels of IgG_{ACL}.

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