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# Outcome of pregnancy in patients possessing anticardiolipin antibodies

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# أثر الأجسام المضادة للكارديوليبين على المرأة الحامل

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**الملخص:الهدف :**تحليل أثر وجود الأجسام المضادة للكارديوليبين على الحمل عند دراسة عينة من النساء الحوامل اللواتي يحملن الأجسام المضادة المذكورة بشرط وجود تاريخ مرضي لفقدان الحمل . تحليل فاعلية المعالجة بالأسبرين أو البريدنيزولون في مثل تلك الحالات.**الطريقة** :جمعت المعلومات اللازمة من 21 مريضة عربية وأربع حالات أخرى من أصل أسيوي . تركز اختيار تلك الحالات على وجود الأجسام المضادة للكارديوليبين بالمعدل الطبيعي مع وجود تاريخ مرضي بالاجهاض لمرة واحدة أو أكثر . ثم بعد ذلك قمنا بتحليل المعلومات إحصائيا **النتائج** :-تبين أنه عند وجود ألأجسام المضادة من نوع ج فقط، كان معدل الإجهاض وفقدان الجنين متسا ويا للثلثين الأول والثاني من الحمل، ويزيد زيادة مهمة عن الثلث الأخير ، أما في حالة وجود أجسام مضادة من نوع ج و م معا فإن نسبة الإجهاض في الثلث الأول زادت زيادة مهمة عن الثلثين الثاني والثالث في الحمل . وتبين أنه بإستعمال الجرعة القليلة من الأسبرين لعلاج هذه الحالات بجانب البريدثيزولون أصبحت نسبة نجاح الحمل 75% عما كانت عليه 54% عند استعمال الأسبرين فقط . وعند عدم إعطاء أي علاج كانت النسبة 17% فقط . **الخلاصة :** مما لاشك فيه أن وجود الأجسام المضادة للكارديوليبين من نوع ج عند المرأة الحامل يزيد من إحتمال فقدان الحمل وكذلك تبين إحصائيا أن العلاج بالأسبرين بالجرعة القليلة بغض النظر عن إستخدام الستيرويد معه يزيد من نسبة نجاح الحمل في حالة وجود الأجسام المضادة عند المرأة الحامل .

**ABSTRACT:** ***Objective –*** To analyse the outcome of pregnancy in a sample of patients with a history of fetal loss, and possessing anticardiolipin antibodies (ACAs), and to assess the effectiveness of therapy with aspirin and prednisolone. ***Method –*** Data on a cohort of 21 Arab and 4 other Asian patients who had one or more episodes of fetal loss associated with raised levels of ACAs were analysed retrospectively. Statistical analysis was performed using $\chi^2$ test for assessment of isotype data and the Fischer test for assessment of the effects of therapeutic intervention. ***Results –***Where immunoglobulin G (IgG) ACAs were found alone, abortion rates occurred at the same rate in the first and second trimesters, which was significantly higher than in the third trimester. In the few cases where IgG and immunoglobulin M (IgM) ACAs coexisted, the rate of pregnancy loss was significantly higher in the first trimester than the second and the third. In the group who had received both aspirin and prednisolone, 75% pregnancies were successful compared to 54% in the group receiving aspirin alone and 17% in those who received no therapy. ***Conclusion –*** The presence of IgG antibodies appears to increase the risk of abortions. Low dose aspirin, either alone or with prednisolone, appears to significantly improve the chances for successful pregnancies in patients with ACAs. Further clinical trials are needed to ascertain optimal therapeutic protocols.

**KEY WORDS**: anticardiolipin, antibody, aspirin, prednisolone, pregnancy

Anticardiolipin antibodies (ACAs) are strongly associated with venous and arterial thrombosis, thrombocytopenia and recurrent fetal loss.[1] These findings were first observed during studies of systemic lupus erythematosus (SLE), a disease whose many symptoms include thrombosis. Of the spectrum of auto antibodies described in SLE, two were found to be directed against most negatively charged phospholipids, including cardiolipin.[2] Anti-phospholipid antibodies are known to prolong *in vitro* phospholipid-dependent coagulation tests, and have been historically referred to as the lupus anticoagulant (LAC).

In addition to their occurrence in patients with SLE, ACAs are found in patients with other autoimmune diseases, as well as in some with no apparent previous underlying disease.[3] The term 'antiphospholipid syndrome' is used to describe patients who present with the clinical manifestations described above, in association with ACAs or the LAC.[4] ACAs may bind independently to the negatively charged phospholipid (in which case, they are called 'authentic' ACAs) or they may require a cofactor, beta 2 glycoprotein-I (β2GPI).[5] The role of β2GPI antibodies in fetal loss is under study.[6]

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In pregnancy, the antibodies may react against the trophoblast resulting in sub-placental clots and interfere with further placentation. Necrotizing descidual vascular lesions are seen in the placenta.[7] Thrombosis may occur in all trimesters of pregnancy resulting in complications such as spontaneous abortions and intrauterine growth retardation (IUGR).

In this retrospective study, the outcome of pregnancy in patients with a history of fetal loss, and possessing ACAs, who were attending the outpatient clinic of the obstetrics department of Sultan Qaboos University Hospital, has been analysed. SLE is common is this country and a minority of the patients presented with this condition also. The patients received therapy either with aspirin or with aspirin combined with prednisolone. Due to non-compliance, six patients received no therapy. Like other corticosteroids, prednisolone suppresses antibody production. Low-dose aspirin acts by inhibiting the production of thromboxane A2, a vasoconstrictive prostaglandin associated with platelet aggregation and thrombocytopenia. The data has been further examined to determine the effect of these therapeutic modalities on fetal survival.

## METHOD

During the period 1995–97, 25 patients with ACAs and pregnancy losses were seen in the outpatient clinic of SQU Hospital. Their ages ranged from 20–40 years; 21 were Omani whilst 4 were Asian expatriate. Patients who sustained pregnancy losses from other causes, such as genetic, endocrine or gynaecological abnormalities, rhesus incompatibility or sperm antibodies were excluded from the study.

Table 1 shows the obstetric history of the patients; they had lost from 1–6 (mean ± SD: 2.3 ± 1.9) pregnancies, the abortions occurring mainly in the first and second trimester. All the patients possessed ACAs, and four patients, in addition, possessed antinuclear antibodies (ANAs). All patients were put on therapy as soon as the pregnancy was diagnosed. None had received treatment in previous pregnancies. The therapy was either aspirin, 80 mg daily, alone or in combination with prednisolone, 10–20 mg daily, according to the presence of antibodies and, in some patients, the coexistence of connective tissue disease. Of the 21 patients with ACAs alone, five were treated with aspirin and prednisolone and 11 with aspirin alone. Due to non-compliance the remaining five patients received no therapy. Of the four patients with both ACAs and ANAs, three received both aspirin and prednisolone (one with the addition of cyclophosphamide) and the fourth received no therapy, again due to non-compliance (Table 2).

ACAs were measured using the Kallestad system where the normal range for IgG ACA was < 23 GPL and for IgM ACA was < 11 MPL.

**TABLE 1**

*Obstetric history of patients*

| Stage of losses | No. of pregnancies | No. of losses | No. of live births |
|---|---|---|---|
| T1 | 7 | 3 | 4 |
| | 1 | 1 | 0 |
| | 2 | 2 | 0 |
| | 3 | 2 | 1 |
| | 3 | 3 | 0 |
| | 4 | 4 | 0 |
| | 3 | 3 | 0 |
| | 2 | 2 | 0 |
| | 6 | 3 | 3 |
| | 3 | 3 | 0 |
| | 10 | 2 | 8 |
| | 3 | 2 | 1 |
| | 3 | 2 | 1 |
| T2 | 8 | 2 | 6 |
| | 5 | 4 | 1 |
| | 3 | 2 | 1 |
| | 4 | 4 | 0 |
| | 6 | 3 | 3 |
| T3 | 2 | 2 | 0 |
| | 7 | 4 | 3 |
| | 3 | 3 | 1 |
| T1 &T2 | 8 | 5 | 3 |
| | 6 | 3 | 3 |
| | 7 | 5 | 2 |
| T2 & T3 | 12 | 6 | 6 |

Statistical analysis was performed using $\chi^2$ test for assessment of isotype data and the Fischer test for assessment of the effects of therapeutic intervention.

## RESULTS

The patients were first analysed to assess the effect of therapeutic modality on the outcome of the pregnancies (Table 2). Among the 7 patients receiving both aspirin and prednisolone (five with ACAs only and two with both ACAs and ANAs), there were six (84%) successful pregnancies. One further ACA and ANA positive patient, who received cyclophosphamide in addition to aspirin and prednisolone, underwent an abortion. Among the 11

patients receiving aspirin alone, all of whom possessed ACAs only, there were five (45%) successful pregnancies. Among the 6 patients receiving no therapy, 5 with ACAs only and one with ACAs and ANAs, there was only one (16%) successful pregnancy. Despite the low numbers this suggests that combined aspirin and prednisolone therapy gives better outcome than aspirin alone, and that treatment with either modality is superior to no treatment. Indeed, the advantage attained with combined aspirin and prednisolone therapy is significantly better ($\chi^2$ =5.82, $p<0.05$) than with no therapy.

The patients were secondly analysed to determine the relation of the ACA isotype to the stage of pregnancy disaster. This data is summarized in Table 3. It shows that overall, throughout pregnancy, the coincidence of IgM and IgG ACAs led to the highest rate of abortions and stillbirths, 78%, compared with 71% and 55% respectively when IgM and IgG ACAs were found separately. These differences were significant ($\chi^2$ = 3.98, $p<0.05$) when the presence of IgG ACAs alone is compared with the coincident presence of IgG and IgM ACAs.

Analysis of the effect of ACA isotype on the trimester of the pregnancy disaster shows that where IgG and IgM ACAs coincided in patients, 78% of the total abortions for that group occurred in the first trimester. Where IgM ACAs and IgG ACAs occurred separately in a patient, 30% and 42% of the abortions respectively were in the first trimester. By contrast, where IgM and IgG ACAs were found separately in patients, 70% and 47% respectively of all abortions occurred in the second trimester, whereas only 11% of all abortions in the patient group with coincident IgG and IgM ACAs occurred in this trimester. Disasters in the third trimester of pregnancy were uncommon and occurred in 6% of pregnancies where IgG ACA occurred alone and in 9% where IgM and IgG ACA were found together.

In summary, the presence of IgG ACAs led to a similar frequency of unsuccessful pregnancies in the first and second trimester, the rates being significantly higher than in the third trimester ($\chi^2$ = 12.26, $p<0.001$ and $\chi^2$ = 5.02, $p<0.001$ respectively). Where IgM ACAs occurred alone, more abortions occurred in the second than in the first trimester. The sample size was very small (3 patients, 14 pregnancies) and the increase was not significant ($\chi^2$ = 3.20, $p>0.05$). However, where both IgG and IgM ACAs coincided, the rate of pregnancy losses was significantly higher in the first trimester than in either the second trimester ($\chi^2$ = 16:20, $p<0.001$) or the third trimester ($\chi^2$ = 16:20, $p<0.001$).

## DISCUSSION

ACAs are associated with recurrent abortion and fetal wastage occurs in more than 90% of untreated patients with antiphospholipid syndrome and in those with autoimmune disease.[8] Microinfarction of the placenta,

**TABLE 2**

*The relationship of autoantibodies and therapeutic modality to the outcome of pregnancy*

| | Outcome of pregnancy | Gestation period / Trimester of abortion | Birthweight |
|---|---|---|---|
| **A. ACA only (n=21)** | | | |
| Aspirin + prednisolone (n=5) | 4 normal deliveries | 38–40 weeks | 3.00 – 3.41 kg |
| | 1 abortion | T1 | |
| Aspirin only (n=11) | 5 normal deliveries | 36–39 weeks | 2.60 – 3.40 kg |
| | 4 abortions | T1 | |
| | 1 stillbirth at 29 weeks | T1 | |
| | 1 delivery at 32 weeks with congenital abnormalities – died | T1 | |
| No therapy | 1 normal delivery | 40 weeks | 3.50 kg |
| | 4 abortions | T1 | |
| **B. ACA and ANA (n=4)** | | | |
| Aspirin + prednisolone (n=2) | 2 normal deliveries | 37 – 39 weeks | 3.20 – 3.45 kg |
| Aspirin + prednisolone + cyclophosphamide (n=1) | 1 abortion | T1 | |
| No therapy (n=1) | 1 abortion | T1 | |

**TABLE 3**

*The relationship of anticardiolipin isotype to the trimester (T) where abortion occurred*

| | IgG ACA | IgM ACA | IgG & IgM ACAs |
|---|---|---|---|
| No of women | 14 | 3 | 8 |
| No of pregnancies | 85 | 14 | 23 |
| No abortions over entire pregnancy (T1T2T3) | 47 | 10 | 18 |
| % abortion | 55 | 71 | 78 |
| **Trimester 1** | | | |
| Number of abortions | 20 | 3 | 14 |
| % T1 abortions/pregnancies | 23 | 21 | 61 |
| % T1 abortions/T123 abortions | 42 | 30 | 78 |
| **Trimester 2** | | | |
| Number of abortions | 22 | 7 | 2 |
| % T2 abortions/pregnancies | 26 | 50 | 9 |
| % T2 abortions/T123 abortions | 42 | 70 | 11 |
| **Trimester 3** | | | |
| Number of abortions | 5 | 0 | 2 |
| % T3 abortions/pregnancies | 6 | | 9 |
| % T3 abortions/T123 abortions | 11 | | 11 |

possibly related to interference in prostaglandin metabolism, maybe responsible for the fetal loss, but the role of antiphospholipid antibodies, including ACAs, is not yet definitely ascertained.[9] The antibody involved appears to be the 'authentic' antiphospholipid antibody since ACA and LAC negative patients do not possess antibodies to (β2GPI )[6] and animal models of APS in pregnancy can be induced by infusion of ACAs.[10]

In this study, we have examined the clinical and serological characteristics of patients specifically selected for the presence of IgM and IgG ACAs and multiple fetal losses. The majority were categorized as having the antiphospholipid syndrome, but four of the subjects were also diagnosed with SLE and possessing ANAs. We have investigated the effect of therapeutic intervention on subsequent pregnancies and whether the ACA isotype was implicated in the trimester of the fetal loss.

Previous trials reported successful pharmacological prevention of recurrent fetal loss using heparin,[7] prednisolone and heparin[11] prednisolone and azathioprine,[12] corticosteroids either alone[13] or with low-dose aspirin[14] and high dose intravenous immunoglobulins.[15]

The clinical significance of the different ACA isopes is still under investigation. IgG-ACAs are generally considered to have broader pathological sequelae.[17] The isotypes occur with variable frequency and in individual patients each isotype may occur exclusively or in combination with another isotype. Previous studies of fetal losses indicate that the majority have the IgG isotype (+/– IgM) with a minority having IgM alone.[17] It has been suggested that where IgM ACA occurs alone, the only complaint is pregnancy loss.[18] We have not been able to confirm this. In this study, we have found that 78% of all abortions occur in the first trimester and in these cases, the IgG and IgM ACA isotype are generally both present. Where the IgG isotype occurs alone, abortions occur at the same frequency in the first and second trimester, whereas, on the very limited data available, where the IgM isotype occurs alone, more abortions occur in the second trimester.

## CONCLUSION

In our study, we used low-dose aspirin, either alone or with prednisolone. The patient numbers were low, but both in patients with the antiphospholipid syndrome and with SLE, the highest frequency of successful of pregnancies occurred with the combined therapy. The use of aspirin alone was encouraging and it may be that aspirin is playing the most important role in the prevention of fetal loss. However, a randomised prospective controlled trial is necessary to determine the optimum therapy for pregnancy conservation and prophylaxis.[16]

Further clinical trials should give more precise information about optimal therapeutic protocols for the prevention of fetal loss and the management of patient at risk needs to be standardized. ACAs are rarely found in healthy populations: one study indicates 22 in 1000.[8] Hence there is little benefit in the routine screening of healthy pregnant women for the presence of ACAs.

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