

# Recurrent miscarriage associated with antiphospholipid antibodies: Prophylactic treatment with low-dose aspirin and fish oil derivatives

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## Summary

**Problem:** The aim of this study was to evaluate the effects of two different prophylactic protocols, low-dose aspirin and fish oil derivatives, in the treatment of patients with recurrent pregnancy loss associated with antiphospholipid antibodies (APA) syndrome.

**Methods:** A prospective study included 30 patients who were alternately assigned to treatment. Each patient had had at least two consecutive spontaneous abortions, positive antiphospholipid antibodies on two occasions, and a complete evaluation.

**Results:** Among patients treated with low-dose aspirin, 12 out of the 15 (80%) pregnancies ended in live births. In the fish oil derivate group 11 out of the 15 (73.3%) ended in live births ( $p > 0.05$ ). There were no significant differences between the low-dose aspirin and the fish oil derivatives groups with respect to gestational age at delivery ( $39.9 \pm 0.4$  vs  $39 \pm 1.5$  weeks), fetal birth weight ( $3290 \pm 200$  g vs  $3560 \pm 100$  g), number of cesarean sections (25% vs 18%), or complications.

**Conclusion:** There were no significant differences in terms of pregnancy outcome between women with recurrent pregnancy loss associated with APA syndrome treated with low-dose aspirin or fish oil derivatives.

**Key words:** Recurrent miscarriage; Antiphospholipid antibodies. Low-dose aspirin; Fish oil.

## Introduction

Recurrent spontaneous abortion is a health care concern occurring in 2-5% of couples attempting to reproduce [1]. The diagnostic criteria of recurrent spontaneous abortion is that at least two consecutive pregnancies should end in spontaneous abortion [2].

A growing amount of evidence is accumulating that, in the majority of cases, recurrent spontaneous abortion has an immunologic background [3]. Autoantibodies reported to be associated with recurrent spontaneous abortion (RSA) include antiphospholipid antibodies antinuclear and antithyroid antibodies [1, 2, 4, 5]. Much work has been done to elucidate the activity of antiphospholipid antibodies (APA). Antiphospholipid antibodies are a family of autoantibodies that exhibit a broad range of target specificities and affinities. Women with APA have an unusually high proportion of pregnancy losses within the fetal period (10 or more weeks of gestation). Pregnancies in women who are positive for APA can also be complicated by premature delivery due to pregnancy-associated hypertensive disease and utero-placental insufficiency. Adverse pregnancy outcomes in women with APA syndrome may result from poor placental perfusion due to localized thrombosis, perhaps through interference with trophoblastic annexin V which is mediated by antiphospholipid antibodies [6]. Prompted by dismal outcomes in untreated pregnancies in women with APA syndrome, clinicians have used various treatments in an attempt to enhance fetal survival. Treatments include aspirin, heparin, glucocorticoids and intravenous immunoglobulin [1].

It has been suggested that fish oil supplementation in the diet might lessen the occurrence of obstetric complications. Fish oil induces a decreased thrombocyte aggregation and is a powerful inhibitor of platelet adhesiveness [7].

The aim of this study was to assess the effect of two prophylactic protocols (low dose aspirin and fish oil) to prevent thrombotic events in patients with RSA associated with antiphospholipid syndrome.

## Materials and Method

### Patient

Thirty-one patients were enrolled in this study and followed during their pregnancies.

Criteria for inclusion required the presence of two or more previous unexplained first trimester miscarriages and the exclusion of non-APA factors, according to the diagnostic flow chart on RSA. The diagnosis of APA syndrome required the presence at least one of two clinical criteria and at least one of two laboratory criteria (Table 1) [6]. All women had moderate levels of APA; only one patient had thrombotic events in her medical history and was excluded. As shown in Table 2, there were no significant differences in patient age at entry, total number of prior miscarriages, gestational age of loss and anticardiolipin antibodies (ACA) levels.

Fifteen patients were treated with a mixture of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) (4 g daily), while 15 patients were treated with low-dose aspirin (ASA, 100 mg daily). Treatment was started before conception and was stopped at the time of miscarriage or at 32 weeks of gestation.

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Table 1. — *International consensus statement on preliminary criteria for the classification of antiphospholipid syndrome.*

CLINICAL CRITERIA
<b>Vascular thrombosis</b>
One or more clinical episodes of arterial, venous, or small-vessel thrombosis, occurring within any tissue or organ.
<b>Complication of pregnancy</b>
One or more unexplained deaths of morphologically normal fetuses at or after the 10th week of gestation; or one or more premature births of morphologically normal neonates at or before the 34th week of gestation; or three or more unexplained consecutive spontaneous abortions before the 10th week of gestation.
LABORATORY CRITERIA
<b>Anticardiolipin antibodies*</b>
Anticardiolipin IgG or IgM antibodies present at moderate or high levels in the blood on two or more occasions at least six weeks apart.
<b>Lupus anticoagulant antibodies**</b>
Lupus anticoagulant antibodies detected in the blood on two or more occasions at least six weeks apart.

\*The following antiphospholipid antibodies are currently not included in the laboratory criteria: Anticardiolipin IgA antibodies, anti-b-glycoprotein I antibodies, and antiphospholipid antibodies directed against phospholipids other than cardiolipin.

\*\*The threshold used to distinguish moderate or high levels of anticardiolipin antibodies from low levels has not been standardized. Many laboratories use 15 or 20 IU as the threshold separating low from moderate levels of anticardiolipin antibodies. Others define the threshold as 2.0 or 2.5 times the median level of cardiolipin antibodies or as the 99th percentile of cardiolipin levels within a normal population. Until an international consensus is reached, any of these three definitions seems reasonable.

Table 2. — *Comparison of study patients in each treatment group.*

	Low dose aspirin (n = 15)	Fish oil (n = 15)
Age at entry	33.2 ± 4.2	33.5 ± 5.8
Total previous abortions	3.3 ± 2	2.6 ± 0.6
Mean abortion week	8.2 ± 1.9	7.2 ± 2
APA IU	35.1 ± 2.3	31.6 ± 2.1

### Method

Lupus anticoagulant antibodies were identified by prolongation of coagulation in at least one phospholipid-dependent *in vitro* coagulation assay with the use of platelet-poor plasma. These assays evaluate various portions of the coagulation cascade as follows: the extrinsic coagulation pathway (dilute prothrombin time), the intrinsic coagulation pathway (dilute activated partial-thromboplastin time and kaolin clotting time) and the final common coagulation pathway (dilute Russell's viper-venom time). The use of two or more assays sensitive to lupus anticoagulant antibodies is recommended before the presence of lupus anticoagulant antibodies is excluded. The two assays should evaluate distinct portions of the coagulation cascade. ACA were detected by enzyme-linked immunosorbent assay performed on cardiolipin-coated plates in presence of bovine serum  $\beta_2$ -glycoprotein I (anticardiolipin antibodies from patients with antiphospholipid syndrome are  $\beta_2$ -glycoprotein I-dependent; antibodies from patients with infectious disease are  $\beta_2$ -glycoprotein I-independent). Values were expressed in ACA units for IgG or IgM, and sera were considered positive when levels were > 15 units.

### Statistical analysis

The results were analyzed by the  $\chi^2$ -square test. Differences in p values < 0.05 were considered statistically significant.

### Results

The results of the two different treatment protocols in terms of pregnancy outcome are shown on Table 3.

Table 3. — *Outcome data in each treatment group.*

	Low dose aspirin (n = 15)	Fish oil (n = 15)
No. of live births	12 (80%)	11 (73.3%)
Gestational age at birth	39.1 ± 1	39 ± 1.5
Birth weight	3.350 ± 212	3.290 ± 200
No. of miscarriages	3 (20%)	4 (26.7%)
Gestational age at loss	7.8 ± 0.8	7.3 ± 0.5
Preterm birth	2 (16%)	1 (9%)
IUGR	1 (12%)	1 (9%)
Gestational diabetes	1 (12%)	2 (18%)
No. of vaginal deliveries	9 (75%)	9 (82%)
No. of cesarean sections	3 (25%)	2 (18%)

Twelve out of 15 pregnancies (80%) treated with ASA resulted in live births. No statistically significant higher rate of live birth was observed in the fish oil group: 11 out of 15 (73.3%,  $p > 0.05$ ). No significant differences were found in terms of mean week at delivery, fetal birth weight among patients treated with low-dose aspirin and fish oil:  $39.9 \pm 0.4$  (range 37-42) and  $39 \pm 1.5$  (range 37-41.6) for mean week at delivery,  $3290 \pm 200$  g (range 2.300-4.100) and  $3.560 \pm 100$  g (range 3.200-3.500) for fetal birth weight, respectively.

Three women treated with ASA and four treated with fish oil had a recurrent loss after enrollment in the study. The estimated gestational age at the loss time on the basis of the last menstrual period did not differ in the two groups ( $7.8 \pm 0.8$  weeks vs  $7.3 \pm 0.5$  weeks).

The differences in the incidence of complications such as preterm births, gestational diabetes and intrauterine growth retardation (IUGR) or percentage of vaginal deliveries versus cesarean sections in the two treatment groups were not statistically significant ( $p > 0.05$ ).

### Discussion

The mechanism of adverse pregnancy outcome in women with APA may result from poor placental perfusion due to localized thrombosis. Paeceman *et al.* have reported that the IgG fraction obtained from patients with lupus anticoagulant, when incubated with placental explants from normal human pregnancies, leads to a significant increase in thromboxane synthesis when compared to the immunoglobulin fraction obtained from normal controls. Annexin V is a protein which binds to exteriorised anionic phospholipids to render their surface non-thrombogenic by preventing the binding of activated factor X and prothrombin. Rand *et al.* reported that women with APA have a significantly lower distribution of annexin V covering the intervillous surface of their

placentae compared with both normal controls and APA-negative women with a history of miscarriages [8].

Several regimens have been proposed for the treatment of APA syndrome, including aspirin alone, prednisone and aspirin, and heparin and aspirin, and intravenous immunoglobulin [1, 4]. Low-dose aspirin alone has been advocated in the treatment of recurrent spontaneous abortion associated with APA. A rationale for the use of low-dose aspirin therapy during pregnancy for women with APA syndrome is to selectively decrease the concentration of placental thromboxane. Platelets produce thromboxane resulting in vasoconstrictor and platelet aggregation. Thromboxane production leads to thrombosis. Low-dose aspirin has been shown to be a thromboxane inhibitor [1]. There are only few data available on the therapeutic use of fish oil derivatives in pregnancy. Fatty acids have several hematovascular effects, and in particular they are able to reduce platelet adhesiveness and aggregation. EPA and DHA are fatty acids derived from marine plancton. The antithrombotic action of EPA/DHA has been demonstrated. A reduction in thromboxane A<sub>2</sub> (TXA<sub>2</sub>) production and a preserved prostaglandin 2 (PGI<sub>2</sub>) supplemented by prostaglandin 3 (PGI<sub>3</sub>) production, leading to an antithrombotic action, have been observed with a fish oil diet [7]. We suppose that the same anti-platelet activity may explain the therapeutic effectiveness of fish oil derivatives reported in our study. The treatment is completely devoid of side-effects. Some patients complained of an unpleasant fishy taste for several hours after intake of fish oil. There were no significant differences between the low-dose aspirin and the EPA/DHA groups with respect to live birth rate, fetal birth weight, gestational age at delivery, number of cesarean sections or complications. Thus, the mixture of EPA and DHA could be an effective alternative to low-

dose aspirin in the treatment of RSA associated to APA syndrome, especially in patients with an allergy to aspirin. Notwithstanding the positive results, further studies would be helpful in knowing the effectiveness of fish oil derivatives in preventing thrombotic events in patients with RSA and APA syndrome.

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