

Treatment of 139 Pregnancies in Antiphospholipid-positive Women Not Fulfilling Criteria for Antiphospholipid Syndrome: A Retrospective Study

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ABSTRACT. Objective. The effect of low-dose aspirin (LDA) on pregnancy outcome in antiphospholipid (aPL)-positive women not fulfilling the criteria for antiphospholipid antibody syndrome (APS) was evaluated retrospectively.

Methods. We evaluated 139 pregnancies of 114 aPL-positive women not fulfilling the Sydney classification criteria for definite APS (104 treated with LDA, 35 untreated). Inclusion criteria consisted of (1) any titer of aPL and no previous pregnancy or no pregnancy losses (defined as aPL carriers); (2) any titer of aPL and 1 or 2 pregnancy losses before the 10th gestational week. No women had previous thrombosis. The rate of pregnancy loss, gestational age at delivery, and birth weight percentile were compared in the treated and untreated patients. Associations between clinical and laboratory characteristics and pregnancy outcomes were investigated.

Results. The rate of pregnancy loss was low in both treated and untreated groups (7.7% vs 2.9%, respectively). There were no statistically significant differences in the rate of pregnancy loss, gestational age at birth, or birth weight percentile in the treated and untreated groups. There were significant associations between gestational age at birth \leq 34th week and positivity for lupus anticoagulant ($p = 0.025$) and anti- β_2 -glycoprotein I IgG antibodies at titers $>$ 99th ($p = 0.016$).

Conclusion. LDA treatment does not appear to improve pregnancy outcome in low-risk women not fulfilling the criteria for APS. Because antibody profile seems to influence pregnancy outcome, further studies of patients stratified according to their antibody profile are warranted. (First Release Feb 15 2013; J Rheumatol 2013;40:425–9; doi:10.3899/jrheum.120576)

Key Indexing Terms:

ANTIPHOSPHOLIPID ANTIBODIES

PREGNANCY

LOW-DOSE ASPIRIN

Obstetrical antiphospholipid syndrome (APS) is defined by the persistent presence of antiphospholipid (aPL) antibodies in patients with pregnancy morbidity characterized by 1 or more unexplained miscarriages at or beyond the 10th week of gestation (type a); eclampsia, severe preeclampsia, or placental insufficiency necessitating delivery before the 34th week of gestation (type b); or 3 or more consecutive unexplained spontaneous abortions before the 10th week of gestation (type c)¹. Laboratory classification criteria are positivity for lupus anticoagulant (LAC) and/or anticardiolipin (aCL) antibodies of IgG and/or IgM isotypes present in medium or high titers [$>$ 40 immunoglobulin G phospholipid (GPL) or immunoglobulin M phospholipid (MPL) units or $>$ 99th percentile] and/or anti- β_2 -glycoprotein I (anti- β_2 -GPI) antibodies of IgG and/or IgM isotypes present

in titers $>$ 99th percentile¹. Because results may be transiently positive, APS should be diagnosed only when 2 tests, performed 12 or more weeks apart, are positive¹.

Following reports on 2 clinical trials^{2,3}, use of prophylactic doses of heparin and low-dose aspirin (LDA) has become standard treatment for obstetrical APS. It is unclear, however, whether aPL-positive women without a definite diagnosis of the syndrome have improved pregnancy outcomes when treated with LDA, because no controlled trials have been conducted to date. These women, some with as many as 2 pregnancy failures and planning to become pregnant or who have already conceived, are turning to their clinicians (obstetricians, rheumatologists, hematologists, and immunologists) for counseling and treatment. Given the lack of evidence of beneficial effects, Derksen, *et al*⁴ concluded in 2004 that there is no indication for pharmacological treatment during pregnancy for healthy aPL-positive women with a history of successful pregnancies or $<$ 3 consecutive early losses. Basing their conclusion on the results of a survey on the practice pattern of expert physicians in the management of controversial aspects of aPL pregnancies, in 2008 Erkan, *et al*⁵ recommended the use of LDA during pregnancy for persistently aPL-positive patients without obstetrical APS. Subsequent expert opinion

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Accepted for publication December 19, 2012.

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has differed: some experts do not suggest treatment⁶, others propose prophylaxis with LDA and/or heparin⁷.

We retrospectively reviewed the medical files related to 139 pregnancies in 114 aPL-positive women without definite obstetrical APS, some treated and others untreated, to verify the efficacy of LDA in improving pregnancy outcome. The primary outcome measure was rate of pregnancy loss. The secondary outcomes were neonatal measures such as gestational age at delivery and birth weight percentile.

MATERIALS AND METHODS

Study population. The study population was selected from subjects referred to us for one or more of the following reasons: previous pregnancy morbidity, autoimmune diseases, aPL carrier status, prolonged partial activated thromboplastin time, and/or biologically false-positive tests for syphilis. Inclusion criteria were (1) any level of aPL positivity and no previous pregnancy or no pregnancy losses (defined as aPL carriers); and (2) any level of aPL positivity and 1 or 2 pregnancy losses before the 10th week of gestation. No women had previous thrombosis. The laboratory criteria were those of the Sapporo consensus⁸ for the 71 pregnancies occurring before February 2006 and those of the Sydney consensus¹ for the 68 pregnancies occurring after that date. Diagnoses of rheumatic diseases were according to the current criteria^{9,10,11,12,13,14,15}.

The medical files relating to 139 pregnancies of 114 women attending our Rheumatology Center between 1993 and 2010 were reviewed. The study protocol was approved by the local Ethics Committee and the medical records of the study were reviewed after informed consent was obtained from all women. The following data were recorded for each pregnancy: presence of autoimmune diseases, previous obstetric history (no pregnancy, number of successful pregnancies and/or spontaneous abortions), maternal age at conception (younger or older than 35 years), pregnancy outcome [gestational age at delivery, (pre)embryonic and fetal loss], birth weight percentile, maternal obstetric complications, if the patient was treated with LDA (100 mg taken orally once daily), gestational age when treatment was begun, and any adverse side effects. LDA was started arbitrarily on the basis of clinician's judgment. Because of the retrospective design of the study, data for causes of first trimester losses, including karyotype and findings concerning complement system, were not available.

aPL assay. aCL and anti- β_2 -GPI of IgG and IgM isotypes were measured using an in-house ELISA following the minimal requirements proposed by the European Forum on Antiphospholipid Antibodies^{16,17}. The results of aCL testing are expressed as GPL or MPL units using international reference material¹⁸. The results of anti- β_2 -GPI assays were calculated as arbitrary units using a standard curve obtained from a pool of positive samples calibrated to Koike's monoclonal antibodies (HCAL for the IgG and EY2C9 for the IgM anti- β_2 -GPI)¹⁹. For both tests the intra- and inter-assay coefficient of variation was < 10%.

In accord with the Sapporo classification criteria⁸, the cutoff values for medium/high titers for aCL antibodies for the pregnancies occurring before February 2006 were 40 GPL and/or MPL. In accord with the Sydney classification criteria¹, for those pregnancies occurring after that date, the cutoff values for medium/high titers for both aCL and anti- β_2 -GPI antibodies were calculated using the 99th percentile obtained by testing 80 age-matched healthy women. Low levels were considered those between the 95th and 99th percentiles. Multiple coagulation tests were performed to assess LAC using platelet-poor plasma samples following internationally accepted guidelines²⁰.

aPL positivity was confirmed after 6 weeks for pregnancies occurring before February 2006 and after 12 weeks for those occurring after that date.

Statistical analysis. Univariate analysis was performed to assess the association between pregnancy outcomes and LDA treatment and other clinical and laboratory variables using corrected chi-square and Fisher tests according to

the number of cases. Mann-Whitney test was performed to assess the difference between the LDA group (women treated with LDA) and the non-LDA group (women who did not receive LDA). A significance level of 0.05 was used. Statistical analyses were carried out using SPSS, version 14.0.

RESULTS

The mean age of women at the time of conception was 34.2 ± 4.2 SD years (range 21.8–44.4). Fifty-one (44.7%) of the 114 women, with a total of 63 pregnancies, were affected by 1 or more autoimmune diseases [24 (47%) autoimmune thyroiditis, 11 (21.6%) undifferentiated connective tissue disease, 4 (7.8%) Sjögren syndrome, 3 (5.9%) rheumatoid arthritis, 3 (5.9%) spondyloarthropathy, 3 (5.9%) discoid lupus erythematosus, 3 (5.9%) systemic lupus erythematosus (SLE), 2 (3.9%) polydermatomyositis, 1 (2%) pernicious anemia, and 1 (2%) myasthenia gravis].

All patients were tested for aPL antibodies before or during each pregnancy. The antibody profile was confirmed 6 or 12 weeks later in 115 (82.7%) out of 139 pregnancies.

Obstetrical profiles and levels of aPL antibodies in the pregnancies are outlined in Table 1. Only 3 patients had IgG aCL and anti- β_2 -GPI antibodies at medium-high titer and positive LAC.

One hundred four (74.8%) pregnancies were treated with LDA and 35 (25.2%) were not. Table 2 shows the frequencies of baseline variables in the treated and untreated groups. Table 3 outlines the distribution of pregnancy treatments in the 2 obstetrical profiles. LDA therapy was begun at a mean gestational age of 8.8 ± 4.4 SD weeks (range 5–28). In only 6 pregnancies was LDA started before conception. Other treatments included thyroxin in 11 pregnancies, steroids in 5, antihypertensive drugs in 3, hydroxychloroquine in 2, and antiepileptic drug in 1.

Side effects of LDA therapy were reported in only 1 case and consisted of epigastralgia not requiring suspension of therapy.

Maternal obstetric complications were reported in 13 pregnancies (9.4%): glucose intolerance/diabetes (3 cases), (pre-)eclampsia (3 cases), mild thrombocytopenia during the third trimester (2 cases), arterial hypertension (2 cases), premature rupture of membranes (2 cases), and respiratory failure (1 case).

The 3 cases of (pre-)eclampsia occurred in the 27th, 34th, and 37th gestational weeks. The antibody profiles of the 3 women were, respectively, high IgG aCL titers (anti- β_2 -GPI not performed), triple aPL positivity, and low IgG aCL titers. No case of thrombosis was recorded during the pregnancies.

One hundred thirty (93.5%) pregnancies concluded successfully with the birth of 134 babies from 126 single and 4 multiple pregnancies, at a mean gestational age of 38.4 ± 2.1 SD weeks (range 27–42). The mean weight of the newborns was 3201.3 ± 509.7 SD grams (range 700–4650 g), the mean birth weight percentile was 45.3 ± 26.4 SD (range 3–100). There were 9 (6.5%) pregnancy failures, 7 of which were (pre)embryonic losses and 2, all during the 12th week of gestation, were fetal losses.

Table 1. Incidence of antiphospholipid (aPL) antibodies in the various obstetrical profiles. Data are number (%).

Obstetrical Profile	N*	aCL IgG		aCL IgM		Anti-β ₂ -GPI IgG**		Anti-β ₂ -GPI IgM**		LAC
		Low	MH	Low	MH	Low	MH	Low	MH	
Absence of obstetrical criteria (aPL carrier)	65 [†] (46.8)	7 (10.8)	19 (29.2)	3 (4.6)	9 (13.8)	8 (12.3)	22 (33.8)	7 (10.8)	15 (23.1)	7 (10.8)
Incomplete obstetrical criteria	74 ^{††} (53.2)	13 (17.6)	15 (20.3)	6 (8.1)	13 (17.6)	8 (10.8)	11 (14.9)	16 (21.6)	13 (17.6)	0 (0.0)
Total	139 (100)	20 (14.4)	34 (24.5)	9 (6.5)	22 (15.8)	16 (11.5)	33 (23.7)	23 (16.5)	28 (20.1)	7 (5.0)

* No. pregnancies. ** Anti-β₂-GPI IgG and IgM were not determined in 11 pregnancies. Low: low titer, ≥ 95th ≤ 99th. MH: medium or high titer, ≥ 99th. [†] 40 women did not have previous pregnancies. ^{††} Of these, 46 women had had 2 abortions. LAC: lupus anticoagulant; aCL: anticardiolipin; GPI: glycoprotein.

Table 2. Frequencies of baseline variables in the groups treated or not treated with low-dose aspirin (LDA). All data are percent unless otherwise indicated.

Characteristic	LDA Group (N* = 104)	Non-LDA Group (N* = 35)
Average maternal age, yrs ± SD	34.8 ± 4.3	32.7 ± 3.4
Previous pregnancy losses	54.8	48.6
Autoimmune disease	45.2	45.7
Medium-high level of aCL IgG	17.3	45.7
Medium-high level of aCL IgM	15.7	23.1
Medium-high level of anti-β ₂ -GPI IgG	23.5	36.4
Medium-high level of anti-β ₂ -GPI IgM	19.6	30.8
Lupus anticoagulant	5.8	2.9

* No. pregnancies. aCL: anticardiolipin; GPI: glycoprotein.

Table 3. Distribution of pregnancy treatment in the 2 obstetrical profiles.

Obstetrical Profile	No. Pregnancies	Prophylaxis with LDA, n* (%)	No LDA, n* (%)
Absence of obstetrical criteria (aPL carrier)	65	47 (72.3)	18 (27.7)
Incomplete obstetrical criteria	74	57 (77.0)	17 (23.0)
Total	139	104 (74.8)	35 (25.2)

*No. pregnancies. LDA: low-dose aspirin; aPL: antiphospholipid.

Of the 104 pregnancies in the LDA group, 96 (92.3%) were successful and 8 (7.7%) were unsuccessful. Of the 35 pregnancies in the non-LDA group, 34 (97.1%) were successful and 1 (2.9%) was unsuccessful. There were no statistically significant differences in the rate of pregnancy loss between the LDA and non-LDA groups (Table 4). Gestational age at birth and neonatal birth weight percentile were not significantly different in the 2 groups (Table 4).

Table 5 shows the pregnancy outcome, including delivery before or after the 34th gestational week, according to treatment in the 2 obstetrical profiles.

Associations were explored between some clinical and laboratory findings and pregnancy outcomes (pregnancy loss rate, gestational age at birth, birth weight percentile). Clinical variables included the presence of autoimmune

Table 4. Pregnancy outcomes in groups receiving low-dose aspirin (LDA) and no LDA.

Outcome	Total Pregnancies, n (%)	LDA Group, n (%)	Non-LDA Group, n (%)	p
Abortions	9 (6.5)	8 (7.7)	1 (2.8)	NS*
Births	130 (93.5)	96 (92.3)	34 (97.2)	NS*
Gestational age at birth, wks ± SD	38.4 ± 2.1	38.4 ± 1.8	38.6 ± 2.8	NS*
Birth weight, percentile ± SD	45.3 ± 26.4	45.3 ± 26.5	45.5 ± 26.5	NS*

* Not statistically significant.

diseases, obstetrical history, and maternal age at conception. Laboratory findings included antibody persistence, profile, and titers. None of these characteristics was significantly associated with fetal loss or with low birth weight percentile. There was a significant association between gestational age at birth ≤ 34th gestational week and the presence of LAC (p = 0.025) and anti-β₂-GPI at titers > 99th (p = 0.016).

It was not possible to investigate the difference in the protective effect of LDA between the pregnancies in the various antibody subgroups including IgM or IgG antibody isotype or triple or single/double aPL positivity: the small numbers of pregnancies within these subgroups were not powerful enough for statistical analysis. For the same reason it was not possible to compare the pregnancies starting LDA before conception with those starting LDA after conception.

DISCUSSION

The rate of pregnancy failure in the aPL-positive women not fulfilling the established obstetrical APS criteria did not differ significantly in the treated (7.7%) and untreated groups (2.8%) we studied. Nor were gestational age at birth or neonatal percentile birth weight significantly different in the 2 groups. A possible explanation of failure of LDA in improving pregnancy outcome could be that if the risk is already low, i.e., not so different from that observed in the general population, it is difficult to lower it further.

In 1997 Cowchock and Reece²¹ collected data from a small number of low-risk pregnant women with persistently

Table 5. Pregnancy outcome according to patients' obstetrical profile and treatment with low-dose aspirin (LDA).

Outcome	Absence of Obstetrical Criteria, n = 65 (%)	Incomplete Obstetrical Criteria, n = 74 (%)
Delivery > 34th wk	58 (89.2)	66 (89.2)
LDA treatment	41 (70.7)	51 (77.3)
No LDA	17 (29.3)	15 (22.7)
Delivery ≤ 34th wk	4 (6.1)	2 (2.7)
LDA treatment	4 (100)	0 (0)
No LDA	0 (0)	2 (100)
Abortions	3 (4.6)	6 (8.1)
LDA treatment	2 (66.7)	6 (100)
No LDA	1 (33.3)	0 (0)

positive test results for IgG or IgM aCL and/or LAC who were identified during a multicenter trial. Pregnant women at low risk were defined as those who had zero to 2 spontaneous abortions, only 1 of which could have occurred after 12 weeks of pregnancy (fetal death). Many of the patients studied had had a prior uncomplicated pregnancy ending in a live birth and many had had no prior spontaneous abortions. Randomly assigned to treatment with LDA or usual care, the 2 groups were not significantly different for pregnancy outcomes. The only randomized study regarding low-risk pregnant aPL-positive patients concluded that pharmacological treatment cannot be justified in these patients, and it confirmed the observations of others that therapy is not always required during uncomplicated pregnancies in aPL-positive healthy women, even those with high titers²².

In the pregnancies we studied LDA prophylaxis was more frequent in the incomplete obstetrical criteria group than in the aPL carrier group, and this reflects the prevalent clinical trend confirmed by a survey from Erkan, *et al*⁵ indicating that clinicians recommend LDA to 92% and 93%, respectively, of aPL-positive patients with 1 or 2 embryonic losses. In our study LDA did not improve pregnancy outcome in aPL-positive women with 1 or 2 miscarriages. Nor was any improvement in live birth rates reported by a recent randomized trial in which women without aPL but with unexplained recurrent miscarriage were treated with LDA²³. The authors of one of the largest treatment trials in pregnant women with a history of recurrent miscarriages reported that pregnancy prognosis is often favorable in these women even without intervention²⁴, and another study suggests that better outcomes can be related to prenatal care, such as ultrasound reassurance and emotional support, especially in the first trimester²⁵. The Guideline of the Royal College of Obstetricians and Gynecologists for treatment of women with unexplained recurrent miscarriages reports an excellent pregnancy prognosis if they are offered supportive care alone in the setting of a dedicated early pregnancy assessment unit²⁶. Thus, prenatal care of our pregnant

women could explain their very good live birth rate, even higher than that in healthy women who become pregnant.

In agreement with some investigators⁴, our results indicate that in aPL-positive women with no previous pregnancies or only successful pregnancies or < 3 consecutive early losses there is no indication for LDA treatment during pregnancy. However, our women started LDA treatment at a mean gestational age of 8.8 weeks and we do not know what would have happened if LDA had been introduced in all cases before pregnancy. Indeed, there are investigators showing the beneficial effect of LDA on the early stages of implantation, i.e., by stimulating interleukin 3 production²⁷.

In our study about 30% of the pregnancies in the aPL carrier group were not treated; of these, 94.4% (17 of 18) concluded successfully. It is noteworthy that medium-high titers of aPL were more frequent in this group and that it was the only group in which LAC positivity was present (Table 1). Lockwood, *et al*²², who also noted positive pregnancy outcomes in untreated healthy women with high titers of aPL, suggested that aPL could be related to adverse pregnancy outcomes in a complex fashion and that therapy is not necessarily required in patients without other risk factors. In our study, on the other hand, births at or before the 34th week of gestation were more frequent in the aPL carrier group than in the incomplete obstetrical criteria group, and occurred in spite of LDA treatment (Table 5). They were, moreover, significantly associated with positivity for LAC ($p = 0.025$) and for anti- β_2 -GPI IgG at titers > 99th ($p = 0.016$). As we pointed out, medium-high aPL titers were more frequent in aPL carriers and this was the only group in which LAC was positive (Table 1).

Antibody profile, rather than past obstetric history or LDA prophylaxis, is the factor that seems to be relevant to pregnancy outcome in aPL-positive women not completely fulfilling the Sydney criteria. Careful consideration should be given to the antibody profile to decide treatment options (supportive care alone or pharmacological treatment) for these pregnancies. LDA should not necessarily be the treatment of choice, even when the outcome appears to be at risk.

Given its minimal maternal and fetal side effects, LDA therapy could be justified because pregnancy and aPL are additional risk factors for vascular thrombosis⁵. However, no case of thrombosis during pregnancy was reported in any of our patients. Moreover, there is no evidence that aspirin is efficacious in preventing thrombosis in pregnant women, and it is not considered sufficient thromboprophylaxis for pregnant women at high risk for venous thromboembolism²⁸. As the risk of thrombosis is greater in the postpartum period, adequate antithrombotic prophylaxis could be limited to that period.

This is the first observational study of LDA treatment of pregnant aPL-positive patients not fulfilling the Sydney criteria for definite obstetrical APS and including mainly

patients confirmed to be aPL-positive who underwent 3 antibody tests (LAC, aCL, and anti- β_2 -GPI). While the number of pregnancies reviewed was quite large, the limitations of our study include its retrospective design, the fact that we are dealing with a heterogeneous group of disorders, and that these disorders are enriched for non-SLE conditions. The small proportion of SLE (only 3 patients) does not permit extension of our results to this disease. Our results are not representative of all aPL-positive women not fulfilling criteria for APS because we considered only the patients referred to our tertiary center. Moreover, the 2 groups studied (treated and untreated) had different numbers of patients. However, as indicated in Table 2, the homogeneous distribution of baseline variables allowed us to perform a correct univariate analysis.

Trials to establish what, if any, treatment improves pregnancy outcome in aPL-positive women not fulfilling the Sydney criteria should ideally be conducted on groups of patients that are homogeneous for laboratory and clinical characteristics. Given the difficulty of carrying out randomized controlled trials, prospective observational studies on patients stratified according to their clinical and laboratory findings could provide a realistic alternative.

ACKNOWLEDGMENT

The authors are grateful to obstetricians Dr. Anna Casaro, Dr. Daniela Fiscon, Dr. Chiara Infantolino, Dr. Silvia Narne, Dr. Patrizia Polonia, and Dr. Alessandra Ruffatti for the clinical work; to Dr. Elisa Salvan for the statistical calculations; and to Linda Inverso Moretti for editing the English version of the manuscript.

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