TABLE 2 Correlation of clinical index of RF-positive RA with p-Btk expression on $CD19^+$ B cells ($n = 29$)

| | Simple regression correlation coefficient | *P*-value | Multiple regression correlation coefficient | *P*-value |
|---|---|---|---|---|
| Age, years | 0.230 | 0.231 | 0.123 | 0.470 |
| Sex | 0.098 | 0.613 | 0.231 | 0.168 |
| Prednisolone treatment, mg/day | 0.217 | 0.783 | 0.201 | 0.227 |
| MTX treatment, mg/week | −0.087 | 0.653 | 0.027 | 0.874 |
| Simple Disease Activity Index | 0.065 | 0.739 | 0.194 | 0.251 |
| CRP, mg/dl | 0.038 | 0.843 | 0.058 | 0.726 |
| ESR, mm/h | 0.171 | 0.375 | −0.008 | 0.962 |
| MMP-3, ng/ml | −0.151 | 0.433 | −0.154 | 0.350 |
| IgG, mg/dl | −0.051 | 0.792 | −0.141 | 0.401 |
| RF, IU/ml | 0.539 | 0.003 | 0.539 | 0.003 |

Correlation between p-Btk expression (mean fluorescence intensity units) in $CD19^+$ B cells and various clinicopathological variables of RF-positive RA patients.

it is well-known that IL-21 is spontaneously produced by T follicular helper cells and provides direct support to B cell development and plasma cell differentiation, thereby ensuring long-term humoral immunity [9, 10]. In this study we failed to find a correlation between p-Btk level and disease activity. This might be due to the fact that IL-21 plays important roles in long-lived plasma cell differentiation and autoantibody production, indicating that this cytokine may not be necessary in synovitis progression. Therefore inhibition of Btk might be more useful in regulating the immune abnormalities in early stage rather than in established RA. Previous studies have demonstrated that the irreversible Btk inhibitor PCI-32765 blocked BCR signalling in human peripheral B cells and completely suppressed disease activity in a CIA model as well as autoantibody secretion in a lupus model [7, 23]. Already, two irreversible Btk inhibitors, Compound 4 and CGI1746, have shown significant efficacy, which included improvement of arthritis scores in collagen antibody-induced arthritis and CIA models [23]. These studies have provided a new understanding of the function of Btk in B cell- or myeloid cell-driven disease processes, as well as a convincing rationale for targeting Btk in the treatment of RA.

Our study of human primary B cells highlights the important role of Btk in B cell development following BCR, CD40/BAFF and IL-21 stimulation. We also provide a novel insight into Btk-mediated signals that selectively regulate IL-21-induced STAT1 phosphorylation and/or translocation in the nucleus, thereby allowing efficient propagation of IL-21 signalling, which is critical for B cell differentiation and CSR in human B cells. Finally, in support of these findings, we identified a significantly high level of phosphorylation of Btk in the peripheral B cells of patients with RA compared with healthy subjects. Among RF-positive RA patients, p-Btk levels in B cells correlated significantly with RF titre, underscoring the relevance of Btk phosphorylation in the potential pathological processes of RA. Targeting of Btk proteins may thus prove therapeutically beneficial for various autoimmune diseases.

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## Supplementary data

Supplementary data are available at *Rheumatology* Online

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# LETTER TO THE EDITOR

## An independent validation of the Global Anti-Phospholipid Syndrome Score in a Japanese cohort of patients with autoimmune diseases

Sir,

We previously proposed a quantitative score defined as 'antiphospholipid score (aPL-S)', in which, by testing multiple antiphospholipid antibodies (aPL), thrombotic risk may be evaluated in antiphospholipid syndrome (APS) patients.[1] This score is validated in our cohort, as well as cohorts in other institution, as a useful quantitative index for diagnosing APS and predicting thrombosis in autoimmune diseases.[2]

Recently, Sciascia et al.[3] broadened this idea by taking into account the aPL profile with conventional cardiovascular risks, and developed and validated the 'Global Anti-Phospholipid Syndrome Score' (GAPSS) as a marker of APS manifestations.

In order to validate the GAPSS independently, we applied it to a cohort of 282 consecutive patients who attended the Hokkaido University Hospital rheumatology clinic from January 2002 to December 2003. There were 41 APS (17 primary APS) patients, 88 systemic lupus erythematosus (SLE) without APS, 50 rheumatoid arthritis, 16 Sjogren's syndrome, 21 systemic sclerosis, 10 polymyositis/dermatomyositis and 56 other autoimmune diseases. Overall, thrombosis and/or pregnancy loss (APS manifestations) were observed in 43 patients (38 arterial thrombosis, 24 venous thrombosis and 11 pregnancy loss).

Higher values of GAPSS were observed in patients who had experienced one or more of the APS manifestations compared with the patients without APS manifestations (Figure 1). When clinical subgroups were analyzed, patients with a history of arterial and/or venous thrombosis showed higher GAPSS compared with patients without APS manifestations. Patients with a history of pregnancy morbidity failed to show a significant difference in GAPSS compared with patients without APS manifestations (Figure 1). The smaller number of patients with history of pregnancy loss in our cohort was likely to be a primary factor in the insignificance of GAPSS in evaluating risks of pregnancy loss.

The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (PLR), negative likelihood ratio (NLR), and area under the curve (AUC) of the receiver operating characteristic (ROC) curve at various levels of GAPSS cut-off are shown in Table 1. In our cohort, maximum AUC of ROC curve was at the cut-off level of GAPSS 6, lower than the cut-off level of GAPSS 10 in the original cohort in the UK.[3]

The reason for differences in adequate cut-off levels of ROC curve in GAPSS between two cohorts may be attributed to their different characteristic backgrounds. Our cohort consists of patients with various autoimmune diseases, while the original UK cohort comprised patients with APS and/or SLE. In our cohort, non-APS patients who scored GAPSS $> 10$ were all SLE patients (6/282). The high GAPSS in SLE patients was mainly due to the high incidence of 'aPL carriers'. The adequate cut-off value of GAPSS may differ among patients with and without SLE.

We demonstrated that aPL profile with conventional cardiovascular risks can be successfully quantified by GAPSS in an independent cohort of patients with autoimmune diseases. GAPSS correlated with a history of APS manifestations, particularly with thrombosis, suggesting that it is a suitable quantitative marker for APS. However, one should consider the appropriate cut-off to be adapted to different kinds of cohorts by reviewing their basic characteristics.

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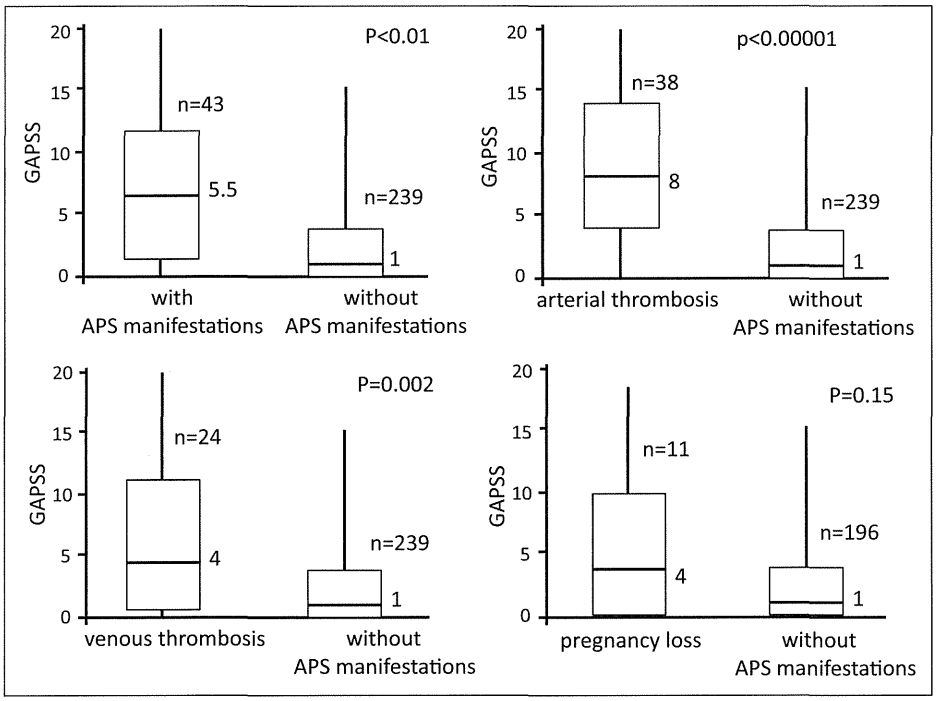


**Figure 1** Global Anti-phospholipid Syndrome Score (GAPSS) in patients with autoimmune diseases. The GAPSS was calculated according to Sciscia et al. Data are shown as box plots, where each box represents the 25th to 75th percentiles: lines inside the box represent the median. The whiskers represent the 95% CI. Higher values of GAPSS were seen in patients who experienced APS manifestations when compared with those without APS manifestations ($p > 0.01$ by Mann–Whitney U test). When analysed separately, patients who experienced thrombosis showed higher GAPSS when compared with those without APS manifestations.

**Table 1** Diagnostic accuracy including sensitivity, specificity, PPV, NPV, PLR and NLR for different cut-off values of GAPSS

| *Cut off* | *AUC* | *Sensitivity* | *Specificity* | *PPPV* | *NPV* | *PLR* | *NLR* | p *value* |
|---|---|---|---|---|---|---|---|---|
| 4 | 0.781 | 0.878 | 0.683 | 0.319 | 0.971 | 2.771 | 0.179 | 0.001> |
| 6 | 0.857 | 0.805 | 0.912 | 0.600 | 0.965 | 8.890 | 0.215 | 0.001> |
| 8 | 0.840 | 0.732 | 0.947 | 0.698 | 0.954 | 13.67 | 0.028 | 0.001> |
| 10 | 0.752 | 0.537 | 0.967 | 0.733 | 0.925 | 16.30 | 0.479 | 0.001> |
| 12 | 0.732 | 0.488 | 0.975 | 0.769 | 0.919 | 19.76 | 0.525 | 0.001> |
| 15 | 0.693 | 0.390 | 0.996 | 0.941 | 0.906 | 94.83 | 0.612 | 0.001> |

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PAPER

# Primary prophylaxis to prevent obstetric complications in asymptomatic women with antiphospholipid antibodies: a systematic review

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**Objective:** Obstetric complications are common in patients with antiphospholipid syndrome. However, the impact of antiphosholipid antibodies (aPL) in the pregnancy outcomes of asymptomatic aPL carriers is uncertain. The aim of this systematic review is to assess whether primary prophylaxis is beneficial to prevent obstetric complications during pregnancy in asymptomatic women positive for aPL who have no history of recurrent pregnancy loss or intrauterine fetal death. **Methods:** Studies evaluating the effect of prophylactic treatment versus no treatment in asymptomatic pregnant aPL carriers were identified in an electronic database search. Design, population and outcome homogeneity of studies was assessed and meta-analysis was performed. The pooled Mantel–Haenszel relative risk of specific pregnancy outcomes was obtained using random effects models. Heterogeneity was measured with the $I^2$ statistic. All analyses were conducted using Review Manager 5.3. **Results:** Data from five studies involving 154 pregnancies were included and three studies were meta-analysed. The risk ratio and 95% confidence interval (CI) of live birth rates, preterm birth, low birth weight and overall pregnancy complications in treated and untreated pregnancies were 1.14 (0.18–7.31); 1.71 (0.32–8.98); 0.98 (0.07–13.54) and 2.15 (0.63–7.33),respectively. Results from the meta-analysis revealed that prophylactic treatment with aspirin is not superior to placebo to prevent pregnancy complications in asymptomatic aPL carriers. **Conclusion:** This systematic review did not find evidence of the superiority of prophylactic treatment with aspirin compared to placebo or usual care to prevent unfavourable obstetric outcomes in otherwise healthy women with aPL during the first pregnancy. *Lupus* (2015) **24,** 1135–1142.

**Key words:** Pregnancy morbidity; obstetric outcome; aspirin; lupus anticoagulant; anticardiolipin antibodies

## Introduction

Antiphospholipid antibodies (aPL) are autoantibodies directed against phospholipid binding proteins including lupus anticoagulant, detected by clotting assays and anticardiolipin or anti-β2glycoprotein I antibodies, measured by enzyme linked immunosorbent assays. The occurrence of recurrent thrombotic events and/or pregnancy morbidity in conjunction with persistent presence of aPL, at least 12 weeks apart, defined the antiphospholipid syndrome (APS).[1]

Antiphospholipid antibodies can be found in otherwise healthy subjects with an estimated prevalence ranging from 1% to 5%.[2] In patients with systemic lupus erythematosus (SLE), aPL can be detected in up to 40% of patients, but only one third develop clinical manifestations of APS.[3] In addition, aPL have been observed during infections, after vaccination and as a reaction to several drugs; in these cases, the antibodies are usually transient, at low titre, and without clear association with clinical manifestations of APS.[4,5]

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Poor obstetric outcome is one of the manifestations of APS. According to the international criteria, obstetric APS includes three or more early miscarriages, one or more intrauterine fetal deaths and preterm births caused by pre-eclampsia or placental insufficiency.[1] Furthermore, intrauterine growth restriction and HELLP syndrome (haemolytic anaemia, elevated liver enzymes and low platelet count) have been observed in aPL-positive women.[6–8] A meta-analysis demonstrated the superiority of the heparin and aspirin combination with aspirin alone in achieving more live births in patients with aPL and recurrent pregnancy loss.[9]

Positive aPL can be recognized through the screening of otherwise asymptomatic pregnancies.[10] The impact of the type of aPL and the evolution of aPL titres during the pregnancy is, however, poorly understood.

The presence of aPL in high-risk pregnancies may be associated with elevated probability of further pregnancy loss in untreated patients.[11] On the other hand, it has yet to be established whether asymptomatic aPL carriers are at higher risk of pregnancy complications during the first pregnancy.

Clinicians encountering asymptomatic pregnant women with aPL have to consider whether prophylactic therapy should be used to prevent obstetric complications. The answer to this question is a matter of controversy, which largely stems from expert opinions. If no clear benefit exists from prophylactic therapy for these women, the screening of aPL should be avoided.

The aim of this systematic review is to assess whether prophylaxis with aspirin and/or heparin would be beneficial to prevent obstetric complications during the first pregnancy in women with aPL without a history of clinical manifestations of APS.

## Methods

We performed a systematic review and meta-analysis of studies in which any prophylactic therapy was tested in terms of pregnancy outcomes in pregnant women with positive aPL and no previous diagnosis of APS. The literature search was performed in the major databases: Medline from 1950 via PubMed, Embase and the Cochrane Central Register of Controlled Trials (search completed 28 February 2014). The search strategy combined free text search, exploded medical subject headings (MESH/EMTREE) terms and all synonyms of the following MESH terms to identify relevant published articles: 'antiphospholipid syndrome', 'antiphospholipid antibodies,' 'anticardiolipin' antibodies', 'lupus anticoagulant', 'lupus coagulation inhibitor', 'pregnancy', 'pregnant', 'prophylaxis', 'prevention', 'heparin', 'aspirin', 'low dose aspirin', 'antithrombocytic agent', 'platelet aggregation inhibitor', 'anticoagulant' and 'fibrinolytic agent' (see Appendix 1, online supplementary material, for full details of the search strategy). In addition, we searched conference abstracts from January 2012 to July 2014 on the official webpages of the American College of Rheumatology (ACR), the European League against Rheumatism (EULAR), the International Society of Thrombosis and Haemostasis (ISTH), the American College of Obstetricians and Gynaecologists (ACOG), the European Congress of Obstetrics and Gynaecology (EBCOG) and the Royal College of Obstetricians and Gynaecologists World Congress (RCOG).

Studies were selected for the review if they met the following criteria: (1) at least one group of subjects were pregnant women with aPL without APS; (2) pregnancy outcomes were reported (live birth, preterm birth, pre-eclampsia, fetal death, low birth weight, and miscarriage); (3) prophylactic treatment was evaluated; (4) the study was a clinical trial or a cohort study of low risk of bias. Studies with abstracts in languages other than English, Spanish or Japanese were excluded.

Two investigators (OA and DF) independently screened titles and abstracts identified in the database search against the selection criteria. All discrepancies were resolved by consensus. When consensus could not be reached, OA made the final judgement for study eligibility. The full text of the selected studies was then retrieved and data were extracted in ad hoc data extraction forms.

Risk of bias for two observational studies was examined using a pre-specified scale based on the Newcastle–Ottawa scale[12] containing the following items: (1) selection of patients: low if patients were very representative of patients with aPL without previous pregnancy; high if patients were selected (such as those who did not have a poor outcome, as can be found in a case report); (2) case definition: low if aPL definition is clear; (3) randomization: low only if patients were randomly assigned to prophylactic alternatives; (4) adjustment: low if analyses were adjusted for important prognostic and confounding factors, or if groups were randomly assigned at the start of trial; and (5) detection: low if follow-up was sufficiently long and complete to assure that all outcomes were registered and blinded to the group assignment in

trials. Risk of bias assessment for three randomized controlled trials (RCTs) was performed using the Cochrane risk of bias tool as described in the Cochrane Handbook[13] and assessed the following domains: (a) random sequence generation; (b) allocation concealment; (c) blinding of participants and personnel; (d) blinding of outcome assessment; (e) incomplete outcome data; (f) selective outcome reporting, and (g) other bias.

Studies were compiled into an evidence table. Meta-analysis was performed after assessment of the homogeneity of designs, populations and outcomes. The grouped effect size selected was the pooled Mantel–Haenszel relative risk of specific pregnancy outcomes obtained from random effects models. Heterogeneity was measured with the $I^2$ statistic. Subgroup analysis was conducted by study design (RCTs versus retrospective cohort study) to assess interaction between study designs. All analyses were conducted using Review Manager version 5.3.

## Results

The search strategy identified 3328 studies (Figure 1). After initial screening, 58 articles were selected by consensus for detailed assessment. Manuscripts were further assessed for eligibility and 53 were excluded, as they did not meet the inclusion criteria (see Appendix 2, online supplementary material, for a list of studies with reasons for exclusion). Finally, five articles were included for qualitative synthesis.[14–18] Table 1 gives a brief overview of these studies. Risk of bias in all studies was moderate to good (Figure 2). Risk of bias assessment for three RCTs was performed using the Cochrane risk of bias tool and showed low to unclear risk of bias (Appendix 3).

A total of 154 pregnancies were evaluated. Prophylactic treatment was administered in 92 pregnancies; in 98% of cases, women were treated with a low dose of aspirin. Only two treated pregnancies did not include aspirin; a woman received prednisone and another woman received prednisone plus heparin.[15] In 62 pregnancies, women did not receive any prophylactic treatment. Some pregnant women included in this review did not have a history of previous pregnancy,[15,18] some women had a history of full-term deliveries,[15] and for other women a clearly detailed obstetric history was lacking.[14,16–18]

In four out of the five selected studies, differences in obstetric outcomes between treated and

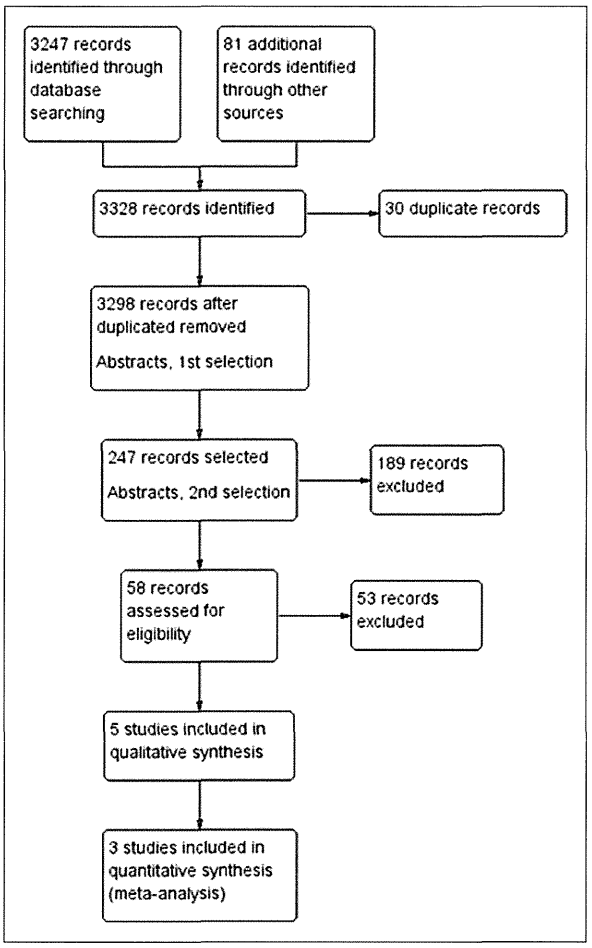


**Figure 1** Flow chart of literature search. Other sources include results of the abstracts and guideline search of the official conference webpages, described in the Methods section.

untreated pregnancies were not statistically significant (Table 2).[14,16–18] In the study by Julkunen et al.,[15] which evaluated 16 pregnancies in aPL carriers with SLE, obstetric complications were observed in 100% of the untreated pregnancies in comparison with 25% in the treated group (Table 3).

Three studies including aPL-positive asymptomatic women without SLE were meta-analysed.[16–18] Although two of the studies were randomized trials and one was observational, we considered that there was enough similarity and the outcomes were hard enough not to be influenced by the design. Pregnancy outcomes were evaluated in a total of 132 pregnancies, and the results are shown in Figure 3. The risk ratio (RR) of live birth rates in treated and untreated pregnancies was 1.14 (95% confidence interval (CI) 0.18 to 7.31, 132 women, $I^2$=0%) (Figure 3(a)). The outcome of overall pregnancy complications was not

**Table 1** Evidence table of included studies

| *Author, year* | *Study design* | *Population* | *Women (pregnancies)* | *aPL tests* | *Intervention/ comparison* | *Pregnancy complications assessed* |
|---|---|---|---|---|---|---|
| Kaaja et al., 1993[14] | RCT | SLE aPL (+)[a] | 6 (6) | IgG aCL LA | ASA (50 mg/day) (F 2, P 2) vs. placebo (F 4, P 4) | Spontaneous abortion Pre-eclampsia Birth weight |
| Julkunenet al., 1994[15] | Retrospective | SLE aPL (+) | 8 (16) | LA | Medical treatment (F 4, P 4)[b] vs. non-treatment (F 4, P 12) | Fetal death Prematurity IUGR |
| Cowchock and Reece, 1997[16] | RCT | Low-risk pregnant women with aPL (+)[c] | 19 (19) | IgG/M aCL LA | ASA (81 mg/day) (F 11, P 11) vs. usual care (F 8, P 8)[d] | Fetal death, Fetal distress at term Birth weight |
| Kahwa et al., 2006[17] | RCT | Primiparae aCL (+)[e] | 48 (48) | IgG/M/A aCL >1 occasion IgG/M/A anti-β2GPI only in aCL (+) | ASA (60 mg/day) (F 28, P 28) vs. placebo (F 20, P 20) | Spontaneous abortion Stillbirth, Pre-term delivery Low birth weight Pre-eclampsia, Eclampsia |
| Del Ross et al., 2013[18] | Retrospective | Asymptomatic aPL carriers[f] | 40 + X (65)[g] | IgG/M aCL, IgG/M anti-β2GPI LA confirmed 6 or 12 weeks apart | ASA (P –47) vs. non-treatment (P 18) | Spontaneous abortion Delivery ≤ 34 weeks |

aPL: antiphospholipid antibodies; RCT: randomized controlled trial; F: number of women; P: number of pregnancies, (+): positive; aCL: anticardiolipin antibodies; LA: lupus anticoagulant, anti-β2GPI: anti-β2glycoprotein I antibodies; ASA: acetylsalicylic acid; IUGR: intrauterine growth retardation; SLE: systemic lupus erythematosus.

[a]Three women with antiphospholipid antibodies and systemic lupus erythematosus had a history of one miscarriage during the first trimester of gestation.

[b]Medical treatment: prednisone and aspirin, prednisone and heparin, prednisone and aspirin or prednisone alone.

[c]Women were identified in the course of a multicentre trial.[20] Pregnant woman at low risk were defined as those who had zero to two spontaneous abortions.

[d]One patient in the aspirin group and two patients in the usual care group had a history of two or fewer spontaneous abortions.

[e]Of the pregnant women who participated in the Jamaica Low Dose Aspirin Trial and consented to phlebotomy,[21] 901 women were evaluated and a history of previous pregnancies was identified in 45 women (91% had only one pregnancy), in which 24 had spontaneous abortions and 21 had elective abortions.

[f]Defined as any titre of aPL and no previous pregnancy or no pregnancy loss. Some women might have non-specified autoimmune disease.

[g]Sixty-five pregnancies occurred in aPL carriers: 40 occurred in woman who did not have any previous pregnancy and 25 occurred in a non-defined number of women.

statistically significant (RR 2.15; 95% CI 0.63 to 7.33, 132 women, $I^2$=0%) (Figure 3(b)). No statistical significance was observed to reduce preterm birth (RR 1.71; 95% CI 0.32 to 8.98, 132 women, $I^2$=0%) (Figure 3(c)) or low birth weight (RR 0.98; 95% CI 0.07 to 13.54, 132 women, $I^2$=33%) (Figure 3(d), Table 3), and no statistically significant interaction was noted between subgroups (study design).

## Discussion

Based on the available literature, there is no evidence to show the benefit of prophylactic treatment with aspirin to prevent pregnancy complications in aPL carriers in the absence of other risk factors; however, this evidence is not yet fully confirmed.

According to the literature search, five published articles addressed, in part, our research question. The selected articles examined asymptomatic patients with aPL: two studies were performed in women with SLE,[14,15] and three in asymptomatic women with different backgrounds.[16–18] The pregnancy outcomes assessed in these studies did not favour the use of aspirin as prophylactic treatment.

Pregnant women might have aPL and these antibodies could be persistently positive before pregnancy or appear for the first time during pregnancy. Physicians encountering asymptomatic primigravida with aPL but no history of thrombosis have to consider the beneficial effect of

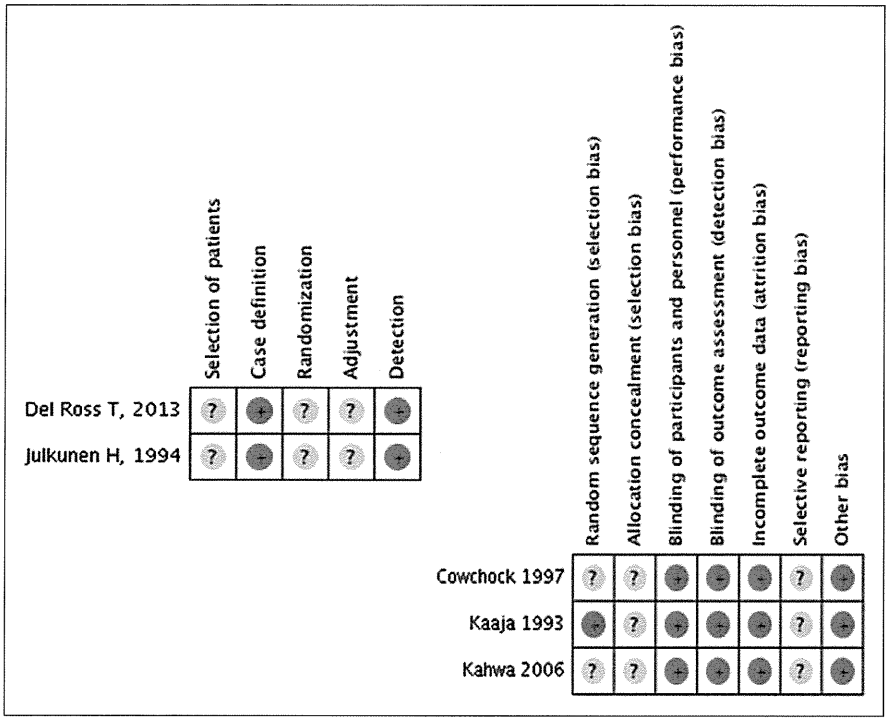


**Figure 2** Risk of bias summary. Investigators' judgements of risk of bias items for each included study.

**Table 2** Pregnancy complications in included studies

| *Author, year* | *Results/conclusion* |
|---|---|
| Kaaja et al., 1993[14] | No pregnancy complications reported in women treated with ASA or placebo.<br>No differences in birth weights observed between infants born to mothers treated with ASA and those receiving placebo. |
| Julkunen et al., 1994[15] | In the treatment group, one (25%) pregnancy ended in prematurity and three pregnancies were full term without IUGR. Fisher test, $P=0.00714$.<br>100% of untreated pregnancies had pregnancy complications (nine abortions, two preterm births (one resulted in neonatal death) and one IUGR). |
| Cowchock and Reece, 1997[16] | No statistically significant differences were found in the obstetric outcome between both groups ($P<0.05$).<br>Prevalence of any complication in the ASA group was 18% (one fetal death and one fetal distress at term) compared with 13% in the control group (one low birth weight delivery) (OR 1.55, 95% CI 0.1–20.85). |
| Kahwa et al., 2006[17] | No differences in pregnancy outcome was observed between ASA and placebo treated primiparae.<br>Prevalence of any pregnancy complication in the ASA group was 14% (one stillbirth, two low birth weight deliveries and one preterm birth) compared with 5% in the control group (one preterm birth) (OR 3.1, 95% CI 0.3–30.73). |
| Del Ross et al., 2013[18] | No differences in pregnancy outcome was observed between ASA and placebo groups.<br>Prevalence of evaluated pregnancy complications in the ASA group was 13% (two abortions and four deliveries ≤34 weeks) compared with 6% in the untreated group (one abortion) (OR 2.5, 95% CI 0.3–22.3). |

ASA: acetylsalicylic acid; IUGR: intrauterine growth retardation; OR: odds ratio, CI: confidence interval.

**Table 3** Outcome of pregnancies in published studies comparing aspirin and placebo in asymptomatic pregnant women with antiphospholipid antibodies

| *Outcome* | *Studies* | *Pregnancies* | *Effect estimate Risk ratio (95% CI)* | *Heterogeneity $I^2$ (%)* |
|---|---|---|---|---|
| Complicated pregnancy | 3 | 132 | 2.15 (0.63–7.33) | 0 |
| Spontaneous abortion and/or fetal death | 3 | 132 | 1.14 (0.18–7.31) | 0 |
| Preterm birth | 3 | 132 | 1.71 (0.32–8.98) | 0 |
| Low birth weight | 3 | 67 | 0.98 (0.07–13.54) | 33 |

CI: confidence interval.

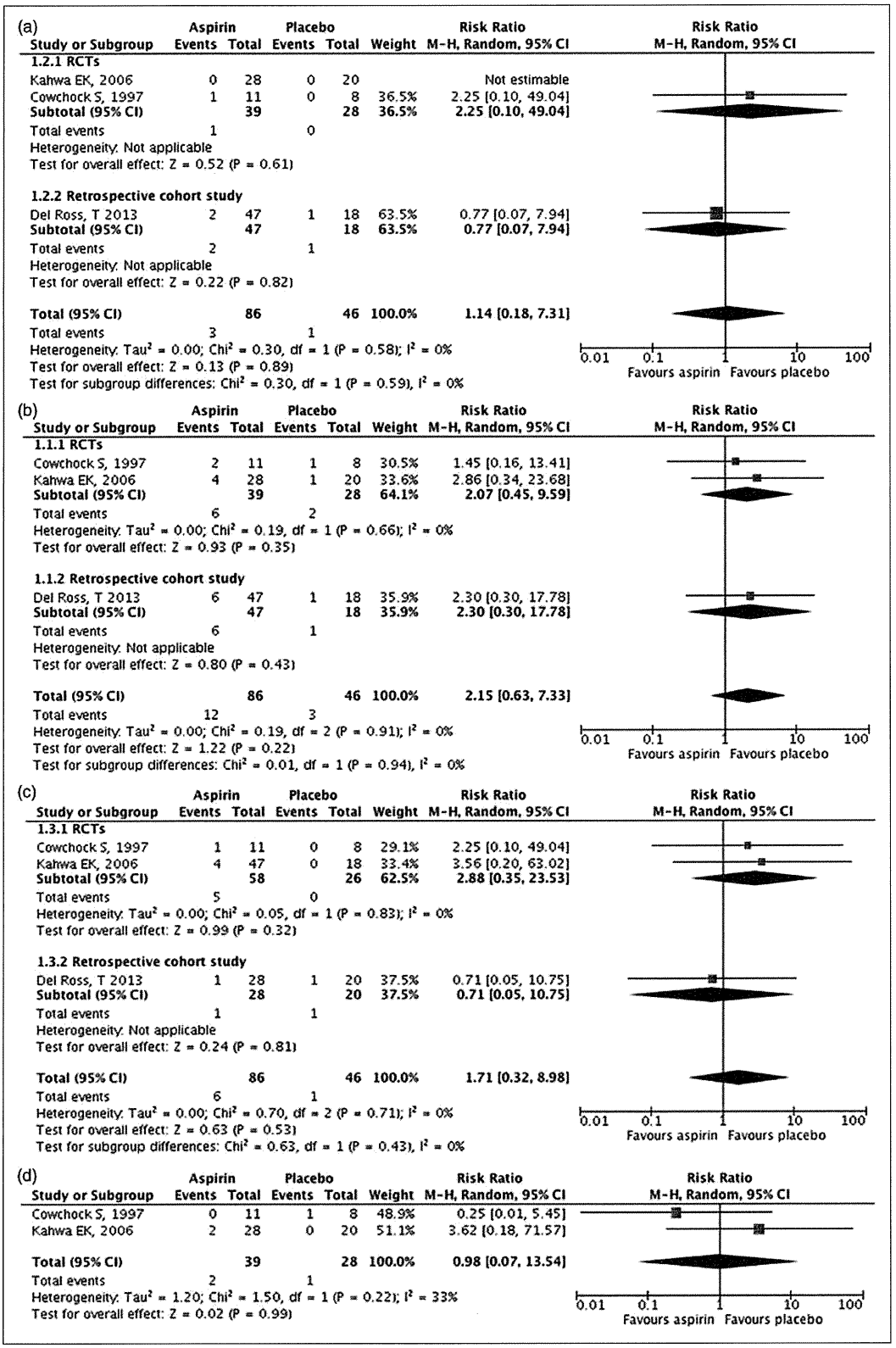


**Figure 3** (a) Forest plot of spontaneous abortion and/or fetal death. Comparison of aspirin versus placebo in asymptomatic women with antiphospholipid antibodies in 132 pregnancies. (b) Forest plot of pregnancy complications. Comparison of aspirin versus placebo in asymptomatic women with antiphospholipid antibodies in 132 pregnancies. (c) Forest plot of preterm delivery. Comparison of aspirin versus placebo in asymptomatic women with antiphospholipid antibodies in 132 pregnancies. (d) Forest plot of low birth weight delivery. Comparison of aspirin versus placebo in asymptomatic women with antiphospholipid antibodies in 67 pregnancies.

prophylactic treatment to prevent obstetric complications.

In this review, our clinical question was initially centred on asymptomatic pregnant women with aPL and no history of previous pregnancy. However, most clinicians do not routinely investigate the presence of aPL in otherwise asymptomatic pregnant women, and rarely before the first pregnancy. We consider this group of asymptomatic aPL carriers especially vulnerable because the risk of unfavourable obstetric outcome is not known. Unfortunately, in asymptomatic women with no underlying autoimmune disease, aPL testing is usually conducted after the first pregnancy failure, but rarely as of the first pregnancy. Therefore, studies with asymptomatic primigravida who are aPL carriers are limited. We extended our selection criteria to include asymptomatic aPL-positive pregnant women with a history of successful pregnancies. A major problem when trying to identify from the literature an optimal prophylactic therapy for women with aPL during pregnancy was the difficulty of stratifying women by the presence or absence of obstetric history in most studies. In some instances, past obstetric history is referred to as 'no abortion' history,[16] and women for whom the only clinical manifestations are one or two early miscarriages (primiparae) are regarded as having the same condition as primigravida women.

Another difficulty of this review is that participants' characteristics varied between studies. Two studies included only women with SLE,[14,15] and three studies enrolled a heterogeneous population of aPL-positive pregnant women,[16,17] containing patients with non-specific autoimmune disease.[18] Nevertheless, this mixed population may reflect the variety of patients that clinicians manage in daily clinical practice, thus we accepted these studies as relevant enough for the analysis. In patients with underlying autoimmune disease, especially patients with SLE, aPL are routinely tested before pregnancy. Among asymptomatic aPL-positive SLE patients, primary prophylaxis with aspirin and hydroxychloroquine appeared to reduce the frequency of thrombotic events.[19]

Four out of the five studies included in this review could not find significant benefits for primary prophylaxis with aspirin.[14,16–18] On the other hand, the study reported by Julkunen et al.[15] showed that medical treatment during pregnancy seems to have a beneficial role in the obstetric outcome of aPL-positive patients with SLE. In the latter study, all treated women received prednisone, either alone or in combination with aspirin or heparin, while in the other four studies treatment consisted of aspirin alone. Discrepancies in the results might therefore be related to the different prophylactic treatment regimens administered.

In conclusion, this systematic review could find no evidence to show that the use of aspirin is superior to placebo or usual care to prevent unfavourable obstetric outcomes in otherwise healthy women with aPL during the first pregnancy. Pregnant women with aPL should be informed of the potential risk during pregnancy and advised on the different treatments available, with the final decision on treatment made by the patient in conjunction with the physician and obstetrician.

Large RCTs or prospective observational studies are needed to explore the real benefit of prophylactic treatments for pregnancy complications in asymptomatic aPL carriers. As clinicians often manage asymptomatic aPL carriers with SLE, and the condition could pose an additional risk for obstetric complications, there is a particular need for future studies to distinguish women suffering from SLE.

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## Conflict of interest statement

Atsuko Murashima has taken part in speakers' bureaus for Mitsubishi Tanabe Pharma Co., Takeda Pharmaceutical Co. Ltd. and Astellas Pharma Inc. Tatsuya Atsumi has received grant/research support from Chugai Pharmaceutical Co. Ltd., Eisai Co. Ltd., Bristol-Myers Squibb Co., Astellas Pharma Inc., Daiichi Sankyo Co. Ltd. and Mitsubishi Tanabe Pharma Co., and has taken part in speakers' bureaus for Astellas Pharma Inc. and Mitsubishi Tanabe Pharma Co. The other authors have no conflicts of interest to declare.

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INTERNAL MEDICINE

□ CASE REPORT □

# Two Cases of Adult-onset Still's Disease with Orbital Inflammatory Lesions Originating from the Lacrimal Gland

Ei Bannai, Hiroyuki Yamashita, Yuko Takahashi, Haruka Tsuchiya and Akio Mimori

## Abstract

Orbital inflammation has been rarely associated with adult-onset Still's disease (AOSD). We herein describe two AOSD patients who developed lacrimal gland enlargement with inflammation spreading to the contiguous tissues in the orbit. Case 1 was a 26-year-old woman who developed bilateral eyelid swelling while taking prednisolone (22.5 mg/day) for AOSD. The swelling of the eyelid worsened after other symptoms emerged, such as a fever, a rash, and arthritis. The laboratory findings, including leukocytosis, liver dysfunction, and ferritin elevation, also suggested an AOSD flare-up. Case 2 was a 62-year-old woman who presented with left eyelid swelling. She was diagnosed with AOSD at 45 years of age but sustained remission. During admission, she subsequently developed a fever, a rash, arthritis, lymphadenopathy, and ocular hyperemia. AOSD was suspected from the clinical course. We speculate that dacryoadenitis and orbital inflammation are manifestations of AOSD.

**Key words:** adult-onset Still's disease, dacryoadenitis, orbital inflammation

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## Introduction

Adult-onset Still's disease (AOSD) is a systemic inflammatory condition that typically presents with a recurring spiking fever with a concomitant salmon pink rash and arthralgia. Orbital inflammation is a rare complication associated with this disease (1-5). In this article, we report two AOSD patients who developed lacrimal gland enlargement with inflammation that spread to the contiguous tissues in the orbit.

## Case Reports

### *Case 1*

Patient 1 was a 26-year-old woman who presented with right eyelid swelling. Two years previously, she had presented with complaints of a fever, arthritis, a typical rash, and sore throat; at that time, the possibilities of infectious disease, a malignant tumor, or other rheumatic diseases were ruled out. She was diagnosed with AOSD according to the diagnostic criteria of Yamaguchi et al. and was administered 22.5 mg/day of prednisolone on admission. Biological agents were used even after a previous treatment with a tapering dose of prednisolone because recurrence had occurred. However, the third dose of infliximab induced an allergic reaction, and etanercept was ineffective and thus discontinued after several doses. Prednisolone was gradually reduced. On this admission, erythema with tenderness was present over the exterior palpebral superior region. There was no induration in the regional lymph node, extraocular motility disturbance, or chemosis. The pupil mydriasis and light reflex were normal, thus indicating the lesion to be periorbital. The left side developed identical symptoms after 11 days of unsuccessful treatment with 300 mg/day of cefcapene pivoxil. Contrast-enhanced magnetic resonance imaging (MRI) of the orbit revealed a circumscribed, enhancing mass in the bilateral eyelid consistent with the lacrimal gland extending to the anterior temporal side through the orbital soft tissues (Fig. 1A). The white blood cell count (12,100/μL), erythrocyte sedimentation rate (ESR) (21 mm/h), C-reactive protein (CRP) level (4.21 mg/dL), and ferritin level (180 ng/mL) were elevated. The eosinophil counts and

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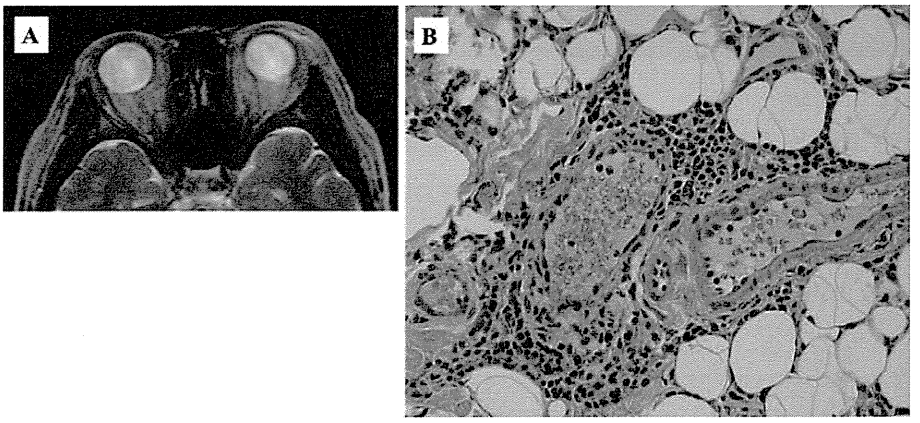


**Figure 1. The findings indicated orbital inflammation in patient 1. A: An orbital enhanced MRI (T2-weighted image) showing a strong, solidly enlarged pseudotumor invasively spreading from both sides of the lacrimal gland and continuing to the upper exorbital area. B: A biopsy of the left upper eyelid showed lacrimal gland infiltration of the mild lymphoid cells around the small vessels and fibroconnective tissue, consistent with mild chronic inflammation (Hematoxylin and Eosin staining, 400×).**

liver enzyme levels were within the normal ranges. Negative results were noted on the assays for antinuclear antibodies (ANA), anti-dsDNA, anti-Ro, anti-La, cytoplasmic and myeloperoxidase anti-neutrophil cytoplasmic antibodies (ANCA), and rheumatoid factor (RF). The soluble IL-2 receptor (sIL-2R), angiotensin-converting enzyme (ACE), and β-D glucan levels were within the normal ranges. A biopsy of the left upper eyelid showed the lacrimal gland infiltrated with mild lymphoid cells around the small vessels and fibroconnective tissue consistent with mild chronic inflammation (Fig. 1B). Two weeks later, the eyelid swelling worsened and the patient developed additional symptoms, including a fever, an evanescent rash, and arthritis, suggesting a diagnosis of an AOSD exacerbation with dacryoadenitis. Prednisolone (60 mg/day, body weight 53.3 kg) was commenced and dramatically improved her systemic and ocular symptoms; however, when prednisolone was tapered to 11 mg/day, partial recurrence of the bilateral eyelid swelling and tenderness was observed. The prednisolone dose was increased to 60 mg/day to induce remission and tocilizumab (TCZ) was administered for its immediate expected effect and to replace the prednisolone treatment. The prednisolone therapy was tapered in a stepwise manner, and she is currently being maintained on intravenous injections of TCZ every nine weeks.

### *Case 2*

Patient 2 was a 62-year-old woman admitted after a three-week history of left eyelid swelling and tenderness without systemic symptoms. At 45 years of age, she presented with a fever, arthritis, and a typical rash, and the possibilities of infectious disease, a malignant tumor, and other rheumatic diseases were ruled out. Accordingly, she was diagnosed with AOSD based on the diagnostic criteria of Yamaguchi et al. and administered 60 mg/day of prednisolone as steroid therapy, which lead to remission. Her condition was stable without medication for the previous 5 years. She had additionally received 1-methyl-2-mercaptoimidazole treatment for Basedow's disease, which was diagnosed at 49 years of age. A physical examination showed left periorbital erythema and edema, but no proptosis and normal ocular movements. In the laboratory evaluation, no specific abnormalities were found, including those for the levels of RF, ANA, cytoplasmic and myeloperoxidase ANCA, CRP, and liver enzymes, and the results of the white blood cell count, ESR, and thyroid function were normal. Fundoscopy showed healthy optic discs. Contrast-enhanced MRI (Fig. 2A) revealed left lacrimal gland and periorbital soft tissue swelling with strong contrast enhancement extending into the temporal occipitofrontalis muscles, rectus superior muscles, and the enthesis of the levator palpebrae superioris muscles. The contrast was also slightly enhanced in the sclera. Fluorodeoxyglucose-positron emission tomography (Fig. 2B) showed the highest uptake in the left lacrimal gland, suggesting that the inflammation spread from the main lesion to the contiguous tissues. Two weeks of ceftriaxone treatment failed to improve her symptom, and a subsequent naproxen administration was also unsuccessful in treating her symptom. One month after this admission, the patient developed a fever of >39°C, a salmon-pink rash, bilateral gonitis, and left cervical lymphadenopathy. Complete ptosis suggested that the inflammation extended to the levator palpebrae superioris muscles (Fig. 2C). Ocular hyperemia developed, and episcleritis was diagnosed on an ophthalmological examination. The laboratory data revealed leukocytosis (peak: 7,520/μL), elevated hepatic enzyme levels (aspartate aminotransferase level: 64 U/L, alanine transaminase: 28 U/L), increased CRP (7.41 mg/dL) and ferritin (1,731 mg/dL) levels, and mild thrombocytopenia (platelet count: 98,000/μL). A biopsy of the left eyelid showed a lymphoplasmacytic infiltration and fibrosis (Fig. 2D). Immunostaining of the cervical lymph node specimen did not

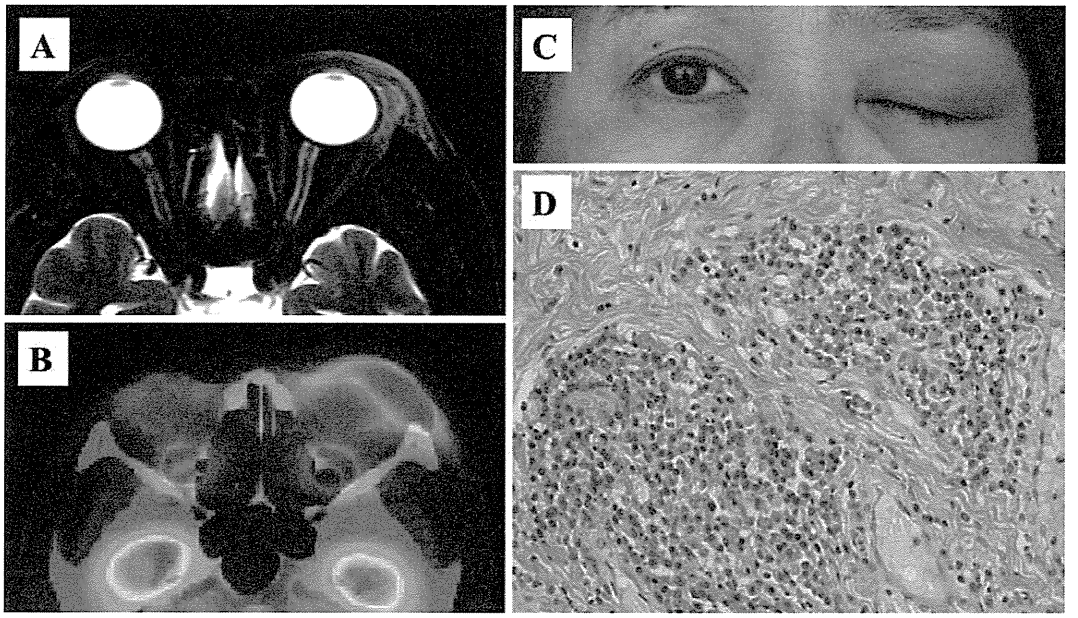


**Figure 2. The findings indicated orbital inflammation in patient 2. A: An orbital enhanced magnetic resonance (T2WI) image showing a diffuse enlargement of the left lacrimal gland and subcutaneous tissue swelling in the eyelid. B: An axial fluorodeoxyglucose positron emission tomography image showing an oblong anterio-posterior enlargement of the left lacrimal gland with the highest contrast enhancement. C: The patient presented with left ptosis and pain, as well as erythema with edema in the lateral upper eyelid. D: A histological evaluation of the lacrimal gland specimen revealed lymphocytes and plasma cells with neutrophils infiltrating the region around the small vessels along with fibroconnective tissue, suggesting post-inflammatory changes (Hematoxylin and Eosin staining, 400×).**

detect IgG4-positive plasmacytes. Extensive investigations, including a repeat blood culture and bone marrow aspiration, failed to disclose a specific infectious or neoplastic disease. AOSD was diagnosed, and an apparent resolution of her ocular and systemic symptoms was achieved after administering 35 mg of prednisolone (body weight 70.4 kg) daily. She has continued receiving prednisolone (3 mg/day) without any flare-ups.

## Discussion

AOSD/Juvenile idiopathic arthritis (JIA) can be complicated with a clinical and radiographic finding of idiopathic orbital inflammation and may involve any structures in the orbit and clinical symptoms include proptosis, ptosis, extraocular motility disturbance, pain, erythema, and chemosis. Five cases of orbital inflammation associated with AOSD/JIA have been reported since the initial report on a peripheral orbital inflammatory pseudotumor at the onset of AOSD/JIA with serositis (1). Subsequently, a postseptal pseudotumor was described, which was rarely complicated with lytic bone lesions, uveitis, or keratopathy (2). Trochleitis, an unusual form of orbital inflammation localized to the superior oblique tendon and trochlea complex, was also described (3, 4). Additionally, preseptal cellulitis was also found to be involved (5). In the five previous cases, the female-to-male ratio was 2:3, and the ages ranged from 2 to 23 years. Furthermore, 2 cases were AOSD (1, 5) and the remaining 3 (2-4) were JIA. In three cases, the orbital disease simultaneously occurred with AOSD/JIA, whereas in the other cases, the ocular symptoms emerged with an AOSD/JIA flare-up. Three cases presented with symptoms in both eyes; however, these symptoms may also occur unilaterally. A histopathological evaluation in one case indicated non-granulomatous chronic inflammation. In all the cases, prednisolone was administered to control the symptoms, however, the dose ranged from 10 mg on alternate days to 1 g of methylprednisolone pulse per day.

Dacryoadenitis, which is the most common form of idiopathic orbital inflammation, has thus far never been reported in association with AOSD. In the absence of definite causes, localized inflammation in the first case and generalized inflammation which presented as dacryoadenitis in the second case were found to be associated with AOSD.

The diagnostic biopsy results indicated no granuloma or necrotic and leukocytoclastic vasculitis, or fibrotic degeneration, thus ruling out sarcoidosis and vasculitis, including granulomatosis with polyangiitis and eosinophilic granulomatosis with polyangiitis. No IgG4-positive plasma cells were found, ruling out a role for IgG4-mediated fibroinflammatory disease. Tuberculous and syphilitic dacryoadenitis typically occur concomitantly with periostitis of the palpebral orbital bony rim and lead to osteolysis, which was not diagnosed in either cases (6). Furthermore, other infections

of the lacrimal gland, such as those caused by bacilli and *Aspergillus*, or mucormycosis do not usually occur simultaneously with the bilateral symptoms or as an acute onset.

Imaging plays an important role in elucidating the involved structures and gives indications about the underlying etiology behind orbital inflammation. It is not easy to differentiate from neoplasm or malignant lymphoma, whereas a previous report has stated that lacrimal enlargement in both the orbital and palpebral lobes is a feature of inflammatory disease in contrast with an epithelial neoplasm, which typically involves only the orbital lobes. Furthermore, a compressed oblong shape of the enlarged lacrimal glands suggests an inflammatory process, as opposed to rounded enlargements typical of an epithelial neoplasm or lymphoma (7). Nevertheless, a diagnostic biopsy should be performed positively as other pathologies affecting the orbit must be ruled out.

Our patients promptly responded to corticosteroid therapy, as did the patients in the previous reports. Spontaneous resolution or supportive treatment with acetylsalicylic acid alone has been shown to arrest the disease in some patients. Thus, an initial observation with supportive treatment for the pain should also be considered (8, 9). However, a more intensive regimen including biological agents for recalcitrant disease may be required to control recurrence in the course of reducing corticosteroids. Gutmark et al. reported the effective treatment with anakinra to an AOSD patient with recurring trochleitis (4), and we succeeded in administering TCZ in the second case in the present study. In recalcitrant conditions, corticosteroids alone cannot control the exacerbations, and biological agents may be curative.

The reason dacryoadenitis occurs in AOSD remains ambiguous, whereas in Crohn's disease, for instance, it is speculated to be due to antigenic overlaps between the bowel and lacrimal tissues (10). Alternatively, some antigens may hematogenously localize to the lacrimal gland and incite a T-cell response that follows a granulomatous reaction pattern (11).

In conclusion, the lacrimal gland may be an inflammatory target and is affected before the full manifestations of AOSD due to systemic inflammation. Therefore, a careful follow-up is necessary if a patient with AOSD develops symptoms which suggest the presence of an orbital lesion, even if in remission. The accumulation of such cases will reveal the etiology of AOSD and thus lead to the establishment of optical therapy for this form of AOSD.

**The authors state that they have no Conflict of Interest (COI).**

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# Second-to-fourth Digit Ratio in Systemic Lupus Erythematosus

Kentaro Doe, Kazuhisa Nozawa, Takuya Hirai, Hiroshi Tsushima, Eri Hayashi, Kaori Hiruma, Seiichiro Ando, Soichiro Nakano, Takayuki Kon, Hirofumi Amano, Ken Yamaji, Naoto Tamura, and Yoshinari Takasaki

*ABSTRACT.* ***Objective.*** Systemic lupus erythematosus (SLE) occurs predominantly in women, and sex hormones play an important role in SLE. Variation in the second-to-fourth digit ratio (2D4D ratio) is attributed to sex hormone exposure. Therefore, we evaluated the relationship between sex hormones and SLE by measuring 2D4D ratios.

***Methods.*** We measured 2D4D ratios in 100 patients with SLE and 200 normal healthy controls (NHC).

***Results.*** Patients with SLE had a lower 2D4D ratio than NHC.

***Conclusion.*** Our study suggests that patients with SLE have experienced high prenatal testosterone and low prenatal estrogen. To our knowledge, this is the first study evaluating the association between 2D4D ratio and SLE. (First Release March 1 2015; J Rheumatol 2015;42:826–8; doi:10.3899/jrheum.140974)

*Key Indexing Terms:*
SYSTEMIC LUPUS ERYTHEMATOSUS SEX HORMONE DIGIT RATIO 2D4D

In human hands, the relative lengths of index and ring fingers differ between men and women, such that men have a lower second-to-fourth digit ratio (2D4D ratio) than women. Baker reported this characteristic in 1888[1]; however, the reason for this difference was unknown at that time. In 1998, Manning, *et al* reported that the 2D4D ratio was linked to sex hormones[2]. Many reports about the 2D4D ratio have been published since then.

The 2D4D ratio is considered stable over time[3]. Interestingly, a low 2D4D ratio may reflect prenatal exposure to high testosterone and low estrogen levels[2]. Moreover, 2D4D ratio depends on the androgen receptors and estrogen receptors situated in the index and ring fingers[4].

Accumulating reports have indicated an association between the 2D4D ratio and the etiology of sex-biased diseases, including Klinefelter syndrome[5], schizophrenia[6], amyotrophic lateral sclerosis[7], myocardial infarctions[8], gastric cancer[9], prostate cancer[10], breast cancer[11], and oral squamous cell carcinoma[12].

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Systemic lupus erythematosus (SLE) is a systemic autoimmune disease that affects multiple organs. The etiology of SLE is still unknown, but SLE occurs predominantly in women, and sex hormones are believed to play an important role in the pathogenesis of this disease. Patients with SLE are reported to have high estrogen levels[13], and 17β-estradiol (E2) increases the production of immunoglobulin G (IgG) and anti-dsDNA antibodies from peripheral blood mononuclear cells (PBMC) in patients with SLE[14]. However, to date, there are no reports concerning the 2D4D ratio in patients with SLE or other connective tissue diseases. Therefore, we conducted this study to investigate the association between the 2D4D ratio and the etiology of SLE disease onset.

## MATERIALS AND METHODS

Our study was approved by our local ethics committee in Juntendo University. Ambulatory patients with SLE were recruited at the Juntendo University hospital and its satellite hospitals, and these patients provided informed consent. All patients fulfilled the American College of Rheumatology criteria for SLE[15]. The normal healthy controls (NHC) were matched as closely as possible for age and sex, and they lacked any family history of autoimmune diseases. A total of 100 patients with SLE (50 men, 50 women) and 200 NHC (100 men, 100 women) participated in the present study. The samples were divided into 4 groups: male SLE group (SLE-M), female SLE group (SLE-W), male NHC group (NHC-M), and female NHC group (NHC-W). A digital camera was used to collect the images of both hands with a cross-section sheet, and digital length was measured from the proximal crease of the digit to the tip using the measurement tool in Adobe Photoshop (Adobe Systems Inc.). The lengths of the index and ring fingers were measured 3 times, and the average was used. The 2D4D ratio was calculated as the length of the index finger divided by that of the ring finger. The 2D4D ratios in both the right and left hands were analyzed. Statistical analysis was performed in the 4 groups

using the Mann-Whitney U test, and to investigate the association between the 2D4D ratio and SLE, simple and multivariate analyses were used. Intraclass correlation (ICC) of the repeated measures of the 2D4D ratio was performed to investigate the repeatability. A p value < 0.05 was considered statistically significant.

## RESULTS

Three hundred images of the subjects were collected (SLE-M: 50, SLE-W: 50, NHC-M: 100, NHC-W: 100). The mean ± SD age (yrs) was 41.16 ± 13.93, 42.44 ± 14.58, 38.36 ± 8.37, and 31.46 ± 8.69 in the SLE-M, SLE-W, NHC-M, and NHC-W groups, respectively. ICC was 0.989, 0.989, 0.991, and 0.990 for the 2D in the right and left hands and the 4D in the right and left hands, respectively. This indicated strong similarity and high reliability in our measurements. The calculated 2D4D ratios for the 4 groups are shown in Table 1. Generally, the 2D4D ratio is believed to be lower in men than in women. As expected, our data indicated that the 2D4D ratio in the NHC-W group was significantly higher than that of the NHC-M group on both the right ($p = 0.0051$) and left hands ($p = 0.0024$). Interestingly, when evaluating the right hand, the 2D4D ratio in the SLE-M group was significantly lower than that of the NHC-M ($p < 0.0001$) and NHC-W groups ($p < 0.0001$); however, no significant difference was found between the SLE-M group and the NHC-M when evaluating the left hand ($p = 0.3929$). In addition to the SLE-M group, the 2D4D ratio in the SLE-W group was significantly lower than that in the NHC-W group when evaluating both the right and left hands ($p = 0.014$ and 0.0179, respectively). The results of simple and multivariate regression analyses are shown in Table 2. For the right hand, the 2D4D ratios of the SLE groups were statistically significantly lower when compared to that of NHC groups (β –0.025, 95% CI –0.035 to –0.015). Coefficient (β) of the SLE groups remained significantly lower even after adjusting for sex (β –0.025, 95% CI –0.034 to –0.015). For the left hand, however, significant difference was not observed between the SLE and NHC groups.

## DISCUSSION

Manning, *et al* reported that the 2D4D ratio is associated with sex hormones, and that a lower 2D4D ratio reflects a high exposure of prenatal serum to testosterone and a low exposure to estrogen[2]. Thereafter, several papers have reported on the 2D4D ratio in sex-biased diseases[5,6,7,8,9,10,11,12]. However, to our knowledge, there have been no reports concerning the 2D4D ratio in connective tissue diseases, including SLE. We believe that this is the first report on the 2D4D ratio in patients with SLE.

In our present study, we clarified that both men and women with SLE have a lower 2D4D ratio than NHC of the same sex. Therefore, all patients with SLE are expected to have been exposed to high testosterone and low estrogen levels at birth. However, Folomeev, *et al* reported elevation of serum estrogen levels in patients with SLE[13]. Kanda, *et al* also reported that E2 increased the production of IgG, including anti-dsDNA antibodies in the PBMC of patients with SLE[14]. Moreover, on the contrary, testosterone has been reported to suppress anti-dsDNA antibody production[16]. Roubinian, *et al* also reported that estrogen levels increased IgG anti-dsDNA antibody production and testosterone reduced the serum anti-DNA antibody level in SLE-prone (New Zealand black × New Zealand white) F1 mice[17]. These reports have indicated the protective effects of testosterone and the deleterious effects of estrogen in SLE. However, our data indicated that exposure to high levels of testosterone and low levels of estrogen in the prenatal period was associated with SLE pathogenesis. This contradiction was reported in myocardial infarction (MI). Men have greater rates of MI than women, and it was expected that the patients with MI have low 2D4D ratio. However, men with low 2D4D ratio were protected against early MI[8]. This contradiction may be explained by the hypothesis that the amount of change in the exposure to estrogen plays an important role in the etiology of SLE onset. Aromatase is a cytochrome P-450 enzyme that catalyzes the conversion of sex hormones from androgens to estrogens. Folomeev, *et al* reported an increase in aromatase activity in patients with SLE compared with that in control subjects, and the aromatase activity in patients with SLE was significantly and directly correlated with estrogen levels[13]. Greenstein, *et al* reported the efficacy of the aromatase inhibitor in female MRL/MP-lpr/lpr mice with lupus nephritis[18]. The hypothesis suggested by our results is that patients with SLE have high levels of testosterone and low levels of estrogen in the early prenatal period. As a

*Table 1.* Comparison of the 2D4D ratios between the 4 groups.

| Sex | Group | Right Hand | | | Left Hand | | |
|---|---|---|---|---|---|---|---|
| | | Mean | SD | 95% CI | Mean | SD | 95% CI |
| Males | NHC | 0.947 | 0.044 | 0.938–0.956 | 0.958 | 0.042 | 0.950–0.967 |
| | SLE | 0.914* | 0.041 | 0.902–0.925 | 0.955 | 0.043 | 0.943–0.968 |
| Females | NHC | 0.963 | 0.031 | 0.956–0.969 | 0.977 | 0.037 | 0.970–0.984 |
| | SLE | 0.946* | 0.043 | 0.934–0.958 | 0.963* | 0.046 | 0.950–0.976 |

* Statistically significant ($p < 0.05$) versus NHC. 2D4D ratio: second-to-fourth digit ratio; NHC: normal healthy controls; SLE: systemic lupus erythematosus.

*Table 2.* Association between the 2D4D ratio and SLE by sex and hand.

| Hand | Group | Sex | Coefficient | 95% CI | p | Coefficient Adjusted by Other | 95% CI | p |
|---|---|---|---|---|---|---|---|---|
| Right | SLE negative | | 1 | — | — | 1 | — | — |
| | SLE positive | | –0.025 | –0.035 to –0.015 | < 0.001 | –0.025 | –0.034 to –0.015 | < 0.001 |
| | | Males | 1 | — | — | 1 | — | — |
| | | Females | 0.021 | 0.012–0.030 | < 0.001 | 0.021 | 0.012–0.030 | < 0.001 |
| Left | SLE negative | | 1 | — | — | 1 | — | — |
| | SLE positive | | –0.085 | –0.019 to –0.015 | 0.096 | –0.009 | –0.019 to –0.0013 | 0.088 |
| | | Males | 1 | — | — | 1 | — | — |
| | | Females | 0.0151 | 0.0058–0.0244 | < 0.01 | 0.015 | 0.0058–0.0245 | < 0.01 |

2D4D ratio: second-to-fourth digit ratio; SLE: systemic lupus erythematosus.

result, an increase in aromatase activity leads to high estrogen levels, which triggers later SLE disease onset.

Our study had some limitations. First, the 4 groups were not age-matched. However, this may be irrelevant because the 2D4D ratio stabilizes over time[3]. Second, the sample size was small. Further comparative studies with larger patient groups are needed to confirm our findings. Third, the 2D4D ratio on the left hand was not significantly different between the SLE-M and NHC-M groups. However, this may be irrelevant because several studies evaluated 1 hand only[6,9,11,19]. Moreover, Zheng and Cohn reported that the 2D4D ratio on the right hand is more sensitive to prenatal sex hormones than that on the left hand[4].

We demonstrated that patients with SLE have a lower 2D4D ratio than NHC of the same sex. This is the first report, to our knowledge, concerning the association between the 2D4D ratio and the etiology of SLE. The amount of change in sex hormone levels during the fetal period may be important in the pathogenesis of SLE.

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RESEARCH ARTICLE

# Prognostic Significance of Anti-Aminoacyl-tRNA Synthetase Antibodies in Polymyositis/Dermatomyositis-Associated Interstitial Lung Disease: A Retrospective Case Control Study

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## Abstract

### Background

In polymyositis/dermatomyositis (PM/DM), anti-aminoacyl-tRNA synthetase (ARS) antibodies are closely associated with interstitial lung disease (ILD), a frequent pulmonary complication. However, the clinical significance of anti-ARS antibodies is not well established.

### Objective

We aimed to evaluate the clinical significance of anti-ARS antibodies in PM/DM-ILD patients.

### Methods

Forty-eight consecutive PM/DM-ILD patients were studied retrospectively. Anti-ARS antibodies were screened by ELISA and confirmed by RNA immunoprecipitation test. Medical records, high-resolution computed tomography images, and surgical lung biopsy specimens were compared between ARS-positive (ARS group) and ARS-negative patients (non-ARS group).

### Results

Anti-ARS antibodies were detected in 23 of 48 patients (48%). Radiologically, nonspecific interstitial pneumonia (NSIP) pattern was observed more frequently in the ARS group than in the non-ARS group (73.9% vs. 40%, $P = 0.02$). Pathologically, NSIP was the most frequent in both groups. Ten-year survival rate was also significantly higher in the ARS group