

# Lupus anticoagulant, disease activity and low complement in the first trimester are predictive of pregnancy loss

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## ABSTRACT

**Introduction:** Multiple factors, including proteinuria, antiphospholipid syndrome, thrombocytopenia and hypertension, are predictive of pregnancy loss in systemic lupus erythematosus (SLE). In the PROMISSE study of predictors of pregnancy loss, only a battery of lupus anticoagulant tests was predictive of a composite of adverse pregnancy outcomes. We examined the predictive value of one baseline lupus anticoagulant test (dilute Russell viper venom time) with pregnancy loss in women with SLE.

**Methods:** From the Hopkins Lupus Cohort, there were 202 pregnancies from 175 different women after excluding twin pregnancies and pregnancies for which we did not have a first trimester assessment of lupus anticoagulant. We determined the percentage of women who had a pregnancy loss in groups defined by potential risk factors. The lupus anticoagulant was determined by dilute Russell viper venom time with appropriate mixing and confirmatory testing. Generalised estimating equations were used to calculate p values, accounting for repeated pregnancies in the same woman.

**Results:** The age at pregnancy was <20 years (2%), 20–29 (53%), 30–39 (41%) and >40 (3%). 55% were Caucasian and 34% African-American. Among those with lupus anticoagulant during the first trimester, 6/16 (38%) experienced a pregnancy loss compared with only 16/186 (9%) of other pregnancies (p=0.003). In addition, those with low complement or higher disease activity had a higher rate of pregnancy loss than those without (p=0.049 and 0.005, respectively). In contrast, there was no association between elevated anticardiolipin in the first trimester and pregnancy loss.

**Conclusions:** The strongest predictor of pregnancy loss in SLE in the first trimester is the lupus anticoagulant. In addition, moderate disease activity by the physician global assessment and low complement measured in the first trimester were predictive of pregnancy loss. These data suggest that treatment of the lupus anticoagulant could be considered, even in the absence of history of pregnancy loss.

## INTRODUCTION

Rates of pregnancy loss in systemic lupus erythematosus (SLE) have improved over the

## KEY MESSAGES

- ▶ A positive Lupus anticoagulant in the first trimester, rather than a previous positive result, is predictive of pregnancy loss.
- ▶ High disease activity as well as low complement levels during the first trimester is also predictive of pregnancy loss.

decades. Clark *et al*<sup>1</sup> found a decrease in fetal loss rates from 40% to 17% based on a literature review from 1960 to 2000. More recent cohort studies have reported pregnancy loss rates in the range of 10–25%.<sup>2–10</sup>

Genetic anomalies, chromosomal abnormalities, anatomical defects and hormonal dysfunction all contribute to first trimester fetal loss in patients with SLE just as they do in the general population.<sup>11–14</sup> In SLE, however, other risk factors for poor fetal outcomes from the first trimester to the neonatal period play a major role. We previously reported four factors at the first pregnancy visit to predict pregnancy loss: proteinuria (>500 mg in a 24 h urine collection or urine protein-to-creatinine ratio >0.5), thrombocytopenia (platelet count <150 000) and antiphospholipid syndrome and hypertension (blood pressure >140/90 mm Hg).<sup>9</sup> We have also found high lupus activity as defined by the physician global assessment score >2, on a 0–3 visual analogue scale, a risk factor for fetal loss.<sup>10</sup> Additional risk factors reported in the literature have included positive anti-dsDNA at any time during pregnancy and low complement levels in the second trimester.<sup>2</sup>

Clowse *et al*,<sup>9</sup> in a previous study of the Hopkins Lupus Cohort in 2006, found that patients with SLE with antiphospholipid antibodies, but without secondary antiphospholipid syndrome, had the same miscarriage rate as those patients without antiphospholipid

antibodies (12% vs 15%). Mecacci *et al*,<sup>5</sup> in a study of 58 lupus pregnancies divided into three groups (antiphospholipid syndrome, antiphospholipid antibody positive and antiphospholipid antibody negative), found no differences in the live birth rate. In a prospective study by Lima *et al*<sup>15</sup> in 1995 of 108 pregnancies in patients with SLE, lupus anticoagulant did not predict fetal loss ( $p=0.056$ ). In 1994, Derksen *et al*<sup>16</sup> described 35 pregnancies in 25 patients with SLE and found that there was no difference in the live birth rate between those patients with antiphospholipid antibodies and those without.

In contrast to the previous findings, two studies have found increased rates of fetal loss in patients with antiphospholipid antibodies. In 2002, Moroni *et al*<sup>17</sup> studied 70 pregnancies in 48 patients with lupus nephritis. In both univariate and multivariate analyses, the presence of antiphospholipid antibodies was significantly associated with increased fetal loss. There was, however, no differentiation between the presence of lupus anticoagulant and anticardiolipin antibodies. In the PROMISSE study, Lockshin *et al*<sup>8</sup> studied pregnancies in SLE or in antiphospholipid-positive women versus control pregnancies. Adverse pregnancy outcome was defined as fetal demise after 12 weeks, neonatal death prior to discharge, preterm delivery prior to 34 weeks and small for gestational age. In the PROMISSE study, lupus anticoagulant was considered positive if it was identified by any of three tests: dilute Russell viper venom time (dRVVT), a lupus anticoagulant-sensitive partial thromboplastin time or the dilute prothrombin time.<sup>21</sup> It was found that the lupus anticoagulant predicted adverse pregnancy outcome ( $p<0.0001$ ). In multivariate analysis, but not in bivariate analysis, the presence of SLE conferred a relative risk of 2.16 ( $p=0.005$ ).

In this paper, we report on an updated set of pregnancies from the Hopkins Lupus Cohort. Our goal was to assess the association of lupus anticoagulant detected by the dRVVT in the first trimester with the risk of pregnancy loss in patients with SLE.

## PATIENTS AND METHODS

### Cohort

We performed an analysis of pregnancies among patients in the Hopkins Lupus Cohort for which there was a measure of lupus anticoagulant during the first trimester. The Hopkins Lupus Cohort consists of consecutively enrolled patients with SLE who have been followed by one rheumatologist (MP) from 1987 to 2012 at the Hopkins Lupus Center. Patients were seen at 4-week to 6-week intervals during their pregnancy until delivery.

Pregnancy was confirmed by urine and serum beta human chorionic gonadotrophin tests and fetal ultrasound. Pregnancy losses were defined as any fetal death in utero. Pregnancy outcomes were obtained from obstetric records. Cohort pregnancies were excluded from the analysis if they were not singleton, if there was

uncertainty about the outcome or if the patient was not assessed for lupus anticoagulant in the first trimester.

The physician global assessment score was obtained at each visit. This validated visual analogue scale assesses lupus activity (0, no activity; 1, mild lupus activity; 2, moderate lupus activity; 3, severe lupus activity).<sup>18</sup>

Lupus anticoagulant was screened by the dRVVT and then confirmed by mixing studies and confirmatory tests.<sup>19</sup> Anticardiolipin was determined by ELISA (Inova).

### Statistical analysis

We identified subgroups of pregnancies based on their characteristics during the first trimester and compared them with respect to pregnancy loss rates. Subgroups were defined by age, ethnicity, year of conception, disease activity and serological activity. The statistical significance of each observed difference was determined using a generalised estimating equation approach to adjust for the fact that some women contributed more than one pregnancy. We performed a sensitivity analysis using only the first pregnancy for each woman and compared rates using Fisher's exact test. Analyses were performed using SAS V.9.2.

## RESULTS

This analysis is based on the 202 pregnancies for which there was a first trimester assessment of lupus anticoagulant. These 202 pregnancies were from 175 women. In total, 154 women had one pregnancy, 17 had two pregnancies, 3 had three pregnancies and 1 had five pregnancies.

Fifty-three per cent of pregnancies occurred in women between the ages of 20 and 29; 41% occurred in women between the ages of 30 and 39; 3% in women over >40 and 2% in women younger than 20 years of age (table 1). The ethnic composition of our sample consisted of 55% Caucasian, 34% African-American and 11% other ethnicity.

There were 22 pregnancy losses out of the 202 pregnancies (11%). Of these, 12 (55%) occurred within the first trimester, 9 (40%) occurred during the second trimester and 1 (5%) occurred during the third trimester.

There were no statistically significant differences in frequency of pregnancy losses by age group, ethnicity or year of conception (table 2), although 3/6 pregnancies (50%) among those 40 years of age or older resulted in a pregnancy loss.

First trimester lupus anticoagulant was significantly associated with an increased pregnancy loss rate ( $p=0.0035$ , table 2). In 186 pregnancies with a negative first trimester lupus anticoagulant, the pregnancy loss rate was 9%. In the 16 pregnancies with a positive lupus anticoagulant in the first trimester, there were 6 pregnancy losses (36%). Also, 4 of the 16 pregnancies with first trimester-positive lupus anticoagulant had a history of previous thrombosis; 2 of the 6 pregnancies with pregnancy loss and 2 of the 10 without.

**Table 1** Characteristics of singleton pregnancies in the Hopkins Lupus Cohort

Characteristic	Number (%) of pregnancies (N=202)
Age (years)	
<20	5 (2%)
20–29	108 (53%)
30–39	83 (41%)
40+	6 (3%)
Ethnicity	
Caucasian	112 (55%)
African–American	68 (34%)
Other	22 (11%)
Year of conception	
1986–1999	78 (38%)
2000–2004	42 (21%)
2005+	82 (41%)
Previous clinical manifestations	
Malar rash	(54%)
Discoid rash	(18%)
Photosensitivity	(50%)
Oral ulcers	(46%)
Arthritis	(66%)
Serositis	(41%)
Seizures or psychosis	(9%)
Previous laboratory abnormalities	
Antinuclear antibodies	(97%)
Proteinuria	(42%)
Immunologic (lupus anticoagulant, anticardiolipin, anti-dsDNA, anti-Smith, false positive rapid plasma reagin)	(82%)

A history of lupus anticoagulant prior to pregnancy was not predictive of pregnancy loss (table 2). In fact, of the 25 patients with a history of lupus anticoagulant who did not have lupus anticoagulant during the first trimester, none had a pregnancy loss.

A score of  $\geq 2$  on the physician global assessment (on a 0–3 visual analogue scale) during the first trimester was statistically associated with increased risk of pregnancy loss (29% vs 8%,  $p=0.005$ ). Although the numbers in some of the subgroups were not large enough to perform a complex multivariable analysis, an analysis of the association between lupus anticoagulant in the first trimester, scores of disease activity and pregnancy loss was performed. Of the 11 patients with lupus anticoagulant but without high disease activity during the first trimester, 3 (27%) experienced a pregnancy loss. Of the three with both lupus anticoagulant and high disease activity during the first trimester, two experienced a pregnancy loss. Statistically, the association between lupus anticoagulant and pregnancy loss persisted after adjustment for high physician global assessment ( $p=0.013$ ).

**Table 2** Pregnancy loss rates by characteristics of the patients

Patient characteristic	Proportion (%) with pregnancy loss	p Value*
All	22/202 (11%)	
Age (years)		0.22
<30	9/113 (8%)	
30–39	10/83 (12%)	
40+	3/6 (50%)	
Ethnicity		0.98
Caucasian	12/112 (11%)	
African–American	8/68 (12%)	
Other	2/22 (9%)	
Year of conception		0.069
186–1999	13/78 (17%)	
2000–2004	5/42 (12%)	
2005+	4/82 (5%)	
Lupus anticoagulant measured in first trimester by dilute Russell viper venom time (confirm)		0.0035
Negative	16/186 (9%)	
Positive	6/16 (38%)	
History of lupus anticoagulant by dilute Russell viper venom time prior to pregnancy		0.95
No	18/167 (11%)	
Yes	4/35 (11%)	
Anticardiolipin IgG measured during first trimester†		1.0†
Normal	9/108 (8%)	
High	0/7 (0%)	
Ever positive for anticardiolipin IgG		0.66
No	7/74 (9%)	
Yes	15/128 (12%)	
Physician global assessment $>2$ during pregnancy		0.0046
No	15/180 (8%)	
Yes	6/21 (29%)	
Low complement during first trimester		0.049
No	8/118 (7%)	
Yes	13/83 (16%)	
Anti-dsDNA during first trimester		0.19
No	12/140 (9%)	
Yes	9/61 (15%)	
Mean prednisone dose during first trimester		0.093
<10	12/146 (8%)	
10+	9/55 (16%)	
History of thrombosis prior to pregnancy		0.89
No	20/182 (11%)	
Yes	2/20 (10%)	
History of miscarriage prior to pregnancy		0.28
No	12/132 (9%)	
Yes	10/70 (14%)	
Antiphospholipid syndrome‡ prior to pregnancy		0.58
No	15/148 (10%)	
Yes	7/54 (13%)	

\*Calculated based on a generalised estimating equation model to account for repeated pregnancies from the same woman.

†Calculated with Fisher's exact test.

‡Defined as history of thrombosis or recurrent miscarriage and either history of lupus anticoagulant or elevated anticardiolipin.

Anticardiolipin IgG levels were measured at the first pregnancy visit in 115 pregnancies. Among the seven patients with high IgG titres, none had a miscarriage. Sixty-three per cent of pregnancies had a history of positive anticardiolipin antibodies. There was no significant difference in the pregnancy loss rate between those pregnancies with or without a history of anticardiolipin IgG antibodies (12% vs 9%,  $p=0.66$ ).

Low complement levels occurred in the first trimester in 83 pregnancies (41%). The pregnancy loss rate in this group was 16%. When compared with the 118 pregnancies with normal complement levels in the first trimester, the loss rate was 7% ( $p=0.049$ ). A positive anti-dsDNA was not significantly associated with increased risk of pregnancy loss (15% vs 9%,  $p=0.19$ ). A prednisone dose  $>10$  mg/day at the first pregnancy visit was more frequent in those with pregnancy loss (16% vs 8%,  $p=0.09$ ). Rates of pregnancy loss were somewhat elevated among those with a history of thrombosis or prior miscarriage; however, these differences were not statistically significant in this small sample.

As a sensitivity analysis, we performed the same analyses using only the first pregnancy for each woman. This analysis was based on 175 women. In this analysis, we found that there was still a significant association between pregnancy loss and lupus anticoagulant in the first trimester: pregnancy losses were 5/13 (38%) vs 20/162 (6%) for those with and without lupus anticoagulant ( $p=0.0020$ ). A positive association between pregnancy loss and both high disease activity and low complement was also seen in this smaller sample ( $p=0.016$  and  $0.068$ , respectively).

## DISCUSSION

Our results demonstrate an increased risk of pregnancy loss associated with the presence of lupus anticoagulant by the dRVVT at the first trimester visit; however, a history of positive lupus anticoagulant was not associated. We also found that lupus activity defined by the physician global assessment in the first trimester was significantly associated with increased risk of pregnancy loss. Other variables including age, ethnicity, high titres of anticardiolipin antibody, use of prednisone dose as a surrogate for lupus activity and the presence of anti-dsDNA were not significantly associated with increased risk of pregnancy loss. Lupus anticoagulant remained statistically significant in multiple variable models that included disease activity and low complement.

The impact of antiphospholipid antibodies on pregnancy loss has previously been reported in this cohort.<sup>9</sup> Clowse *et al* found an increased risk of total pregnancy loss in patients with SLE with antiphospholipid syndrome. The presence of either lupus anticoagulant or anticardiolipin antibody, but without the clinical criteria for classification of antiphospholipid syndrome, did not increase the risk of miscarriage. In this study, we looked separately at the contribution of lupus anticoagulant

and anticardiolipin antibody to the risk of pregnancy loss. While lupus anticoagulant was strongly associated with increased pregnancy loss risk, anticardiolipin antibody was not associated with increased risk. Our current results differ from our past report in that we have now looked at each antiphospholipid antibody separately.

Our study looked at the utility of one single lupus anticoagulant test, the dRVVT, at the first pregnancy visit with one outcome (pregnancy loss). Thus, we confirm the PROMISSE finding that only the lupus anticoagulant 'matters' but extend the PROMISSE finding to the most important of the adverse pregnancy outcomes, namely pregnancy loss. Our study differed from PROMISSE in that dRVVT was done as the lupus anticoagulant assay; only first trimester results were used; we excluded PROMISSE patients and a different outcome measure (pregnancy loss) was used.

The PROMISSE study could not evaluate the contribution of high disease activity, as such patients were excluded. High disease activity assessed by physician global assessment score of  $\geq 2$  in our study was significantly associated with an increased risk of pregnancy loss. Prednisone dose as a surrogate for disease activity was higher as well, but did not meet statistical significance. Clowse *et al*,<sup>10</sup> in a previous analysis of our cohort in 2004, demonstrated a significant decrease in the live birth rate (84% vs 57%,  $p=0.04$ ) in pregnancies with high versus low lupus activity in the first trimester defined by the physician global assessment. Chakravarty *et al*<sup>22</sup> defined active disease at conception as the use of 10 mg of prednisone daily. With only six pregnancy losses in the first trimester and none in the second or third trimester, they were unable to demonstrate an increased risk of pregnancy loss. We have extended our previous work to show the independent effect of disease activity in multiple variable models.

Our study found that low complement during the first trimester was associated with an increased risk of pregnancy loss. Between 1992 and 2003, Ramos-Casals *et al*<sup>23</sup> routinely measured complement levels in 530 female patients with SLE. They found similar rates of pregnancy loss in those patients with low complement (14%) compared with those patients with normal complement. This is in contrast to the data published by Cortes-Hernandez *et al*<sup>24</sup> in 2002, in which low complement levels detected at the first visit or at 3-month intervals were significantly associated with a combination of miscarriage and stillbirth. Clowse *et al*<sup>2</sup> previously compared low or normal complement levels and the presence or absence of anti-dsDNA in the Hopkins Lupus Cohort. Neither first trimester hypocomplementemia (18% vs 15%,  $p=0.55$ ) nor the presence of anti-dsDNA (20% vs 13%,  $p=0.29$ ) significantly increased the rate of pregnancy loss. However, low complement levels in the second trimester were associated with a significantly increased risk of fetal loss. The larger number of pregnancies in our updated analysis has allowed us to show the effect of low complement in the first trimester.

Multicentre studies such as PROMISSE are ideal, but our study fills in three important gaps. First, one lupus anticoagulant assay, the dRVVT, with confirmatory testing, is predictive of pregnancy loss. Only the presence of the lupus anticoagulant during the pregnancy matters, as a history of lupus anticoagulant is not predictive. Thus, in clinical practice, a large battery of tests is unnecessary. Prophylactic treatment could be considered in these pregnancies. Second, high disease activity (omitted from PROMISSE) is a risk factor and control of disease activity before conception is essential to successful pregnancy outcome. Third, low complement in the first trimester is also a risk factor. In the non-pregnant patient with SLE, low complement in the absence of disease activity (serologically active, clinically quiescent) is not treated.<sup>25</sup> Although we cannot address treatment, our study indicates the value of low complement for the prediction of pregnancy outcome.

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