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High risk of adverse pregnancy outcomes in women with a persistent lupus anticoagulant

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Key Points

- In this high-risk cohort of persistently LA-positive women, the risk of a pregnancy complication was as high as 70% per pregnancy.
- A higher Rosner index, representing circulating anticoagulant activity, was associated with an increased risk of adverse pregnancy outcomes.

Lupus anticoagulant (LA) has been associated with pregnancy complications and pregnancy loss. Identification of predictive factors could aid in deciding on therapeutic management. To identify risk factors for adverse pregnancy outcomes in high-risk women with persistently positive LA, we prospectively followed 82 women of childbearing age, of whom 23 had 40 pregnancies within the Vienna Lupus Anticoagulant and Thrombosis Study. Pregnancy complications occurred in 28/40 (70%) pregnancies, including 22 (55%) spontaneous abortions (<10th week of gestation [WOG]: n = 12, 10th to 24th WOG: n = 10) and 6 deliveries <34th WOG (15%, 3 due to severe preeclampsia/HELLP [hemolysis, elevated liver enzymes, and a low platelet count] syndrome, 3 due to placental insufficiency). One abortion was followed by catastrophic antiphospholipid syndrome. Neither a history of pregnancy complications nor of thrombosis, or prepregnancy antiphospholipid antibody levels were associated with adverse pregnancy outcomes. In logistic regression analysis, higher age was associated with a lower risk of adverse pregnancy outcome (per 5 years' increase: odds ratio [OR] = 0.41, 95% confidence interval [CI]: 0.19-0.87), a high Rosner index (index of circulating anticoagulant) predicted an increased risk (OR = 4.51, 95% CI: 1.08-18.93). Live birth rate was 15/28 (54%) in women on the combination of low-molecular-weight heparin and low-dose aspirin and 3/12 (25%) in those with no treatment or a single agent. We conclude that the risk of severe, even life-threatening pregnancy complications and adverse pregnancy outcomes is very high in women with persistent LA. A high Rosner index indicates an increased risk. Improved treatment options for women with persistently positive LA are urgently needed.

Introduction

The lupus anticoagulant (LA), anti–β-2-glycoprotein I (aß2GPI), and anticardiolipin (aCL) antibodies represent a heterogeneous group of autoantibodies directed against anionic phospholipids or affiliated plasma proteins and are collectively referred to as antiphospholipid antibodies (APLAs). The presence of APLAs entails a prothrombotic state and an increased risk of pregnancy complications. The diagnosis of the antiphospholipid syndrome (APS) is established in case of persistent positivity of at least one of the APLAs and the occurrence of clinical manifestations like arterial or venous thrombosis or pregnancy morbidity.[1] Adverse pregnancy outcomes considered as a clinical criterion for the diagnosis of APS include recurrent early abortions, fetal death, and premature birth due to preeclampsia (PE) and other placenta-mediated complications.[1]

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The link between different APLA patterns and the clinical occurrence of pregnancy morbidity is ambiguous, and the body of evidence is as yet limited and contradictory.[2-4] These uncertainties mostly result from inappropriate design and outcome reporting of available studies, the limited availability of prospective studies, the heterogeneity of investigated patient cohorts, and the large variation in definition and diagnosis of APLAs. Especially the causal association of APLAs and recurrent embryonic loss are often questioned, whereas the association, especially of LA, triple APLA positivity, and aCL antibody positivity, with late fetal death seems to be more evident.[4] On the other hand, placenta-mediated complications and intrauterine growth restriction have been associated with all APLAs, although especially here data are limited. According to available data, the association between LA and fetal death seems to be most consistently reported.[2,4] Also, clinical factors, like a positive history for thrombosis and/or pregnancy morbidity, and concomitant autoimmune rheumatic diseases, among others, have been inconsistently linked to adverse pregnancy outcomes.[3,5-14]

The Vienna Lupus Anticoagulant and Thrombosis Study (LATS) is an observational single-center cohort study including patients who repeatedly tested positive for LA. Patients with and without clinical manifestations of APS in terms of thrombosis and/or pregnancy complications are included. In the current analysis, we evaluated the occurrence of adverse pregnancy outcomes in our prospectively followed cohort of patients with persistent LA positivity. Levels of APLAs and related laboratory parameters before every pregnancy and clinical factors were analyzed to identify risk factors for adverse pregnancy outcomes in LA-positive patients.

Patients and methods

The Vienna LATS is conducted as an ongoing, biobank-based, prospective observational, single-center cohort study. Details on the LATS have been reported previously.[15,16] Adult patients with persistent LA positivity diagnosed according to current recommendations, with or without previous clinical manifestation of APS as thrombosis and/or pregnancy complications, were enrolled.[17-19] Follow-up visits were performed every 6 months during the first 5 years and then once a year. Follow-up visits included the recording of the patients' clinical history, the performance of coagulation tests, and the assessment of antiphospholipid antibodies. All patients gave written informed consent before study inclusion. The ethics committee of the Medical University of Vienna in accordance with the Declaration of Helsinki approved the conduct of the study (Ethics Committee no. 068/2001 and 1268/2014).

Determination of LA and antiphospholipid antibody positivity

Blood samples were drawn with a 21-gauge butterfly needle (Greiner Bio-One) into Vacuette tubes (Greiner Bio-One). All samples were processed within 3 hours after venipuncture. The determination of LA followed the recommendations of the Scientific and Standardization Committee[20]/International Society on Thrombosis and Hemostasis.[18,21] A lupus-sensitive activated partial thromboplastin time (aPTT-LA; Diagnostica Stago, Asniere-sur-Seine, France) and a diluted Russell's viper venom time were used as screening tests. During treatment with vitamin K antagonists, screening was performed only using the aPTT. Confirmatory tests were performed as described in the case of prolongations of 1 or both screening tests.[22] The StaClot LA (Diagnostica Stago) and the diluted Russell's viper venom time–LA Confirm (Life Diagnostics, Clarkston, GA) were applied as confirmatory tests. In the case of a not definitely positive confirmatory test during the follow-up period, the patient was still regarded as LA positive if the Rosner index, calculated as 100 × (clotting times of the 1:1 mixture-normal plasma)/patient's plasma, was ≥15.[23] In the current study, the Rosner index (index of circulating anticoagulant, %) was analyzed as a continuous parameter.

For the determination of aCL and aß2GPI, immunoglobulin G (IgG) and IgM antibodies commercially available indirect solid-phase enzyme immunoassays were used following the manufacturers' instructions. For the determination of aCL, the Varelisa Cardiolipin test (Pharmacia [Phadia AB], Uppsala, Sweden) was performed semiautomatically with a Tecan Genesis liquid handling system (Tecan Group Ltd, Maennedorf, Switzerland) between 2001 and September 2005. Anti-β2GPI IgG and IgM antibodies were determined using the QUANTA Lite β2GPI (Inova Diagnostics) from 2001 to September 2006. From October 2005, the Orgentec Cardiolipin and, from October 2006, the Orgentec β2GPI tests (both from Orgentec, Mainz, Germany) were performed on a fully automated BEP2000 Advance System (Siemens Healthcare Diagnostics, Marburg, Germany). In the current analysis, aCL and aß2GPI antibodies were used as continuous variables. For the definition of triple antibody positivity, the following cutoffs were applied: aCLs were regarded as positive if >40 IgG phospholipid units (GPL)/IgM phospholipid units (MPL) U/mL (Varelisa Cardiolipin and Orgentec Cardiolipin test), according to the recommendations,[1] and positivity for aß2GPI IgG and IgM was defined as results >8 GPL/MPL U/mL, corresponding to the 99th percentile of healthy controls (Orgentec β2GPI test). For the analysis of prepregnancy laboratory parameters as risk factors for pregnancy complications, the last available measurement before the respective pregnancy was used.

Definition of adverse pregnancy outcomes

Pregnancy complications were categorized as follows: Spontaneous abortion <10th week of gestation (WOG), unexplained fetal death ≥10th WOG, and premature birth <34th WOG due to eclampsia or severe PE or other features of placental insufficiency. Definitions of pregnancy complications are based on the current recommendations by Miyakis et al.[1] In detail, diagnosis of PE was based on new onset of both hypertension (systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg) and proteinuria (≥300 mg of protein per 24-hour urine collection, or protein to creatinine ratio ≥30 mg/mmol) after gestational week 20, and severe PE was defined by the presence of sustained severe hypertension (2 or more recordings of systolic pressure of ≥170 mm Hg or diastolic pressure of ≥110 mm Hg), or evidence of multisystem disorder. The diagnostic criteria for placental insufficiency included (1) intrauterine growth restriction = estimated fetal weight <5th percentile, (combined with) (2) abnormal Doppler flow velocimetry waveform analysis suggestive of fetal hypoxemia (eg, absent end-diastolic flow in the umbilical artery), or (3) new onset of oligohydramnios (amniotic fluid index ≤10th percentile).

Statistical methods

All statistical analyses were performed using Stata 14.0 (Stata Corp, Houston, TX). Continuous variables were summarized as medians (25th to 75th percentile), whereas count data were reported as absolute frequencies (%). Median follow-up was estimated with a reverse Kaplan-Meier estimator according to Schemper and Smith. The risk of pregnancy complications was

computed with a generalized linear model with a normal link function. Importantly, confidence intervals (CIs) and *P* values were adjusted to account for dependency structure of the data (ie, that 1 woman could contribute >1 pregnancy). Uni- and multivariable logistic regression models, again with adjustment for dependency, were used for quantifying associations between prepregnancy covariates and the odds of pregnancy complications.

Results

Occurrence of pregnancies and pregnancy complications

At the time of analysis, 165 patients were included in LATS, of whom 136 (82%) were women. Eighty-two (60%) of the 136 women were of childbearing age (≤45 years) at study inclusion and were followed up for a median interval of 9.0 years (25th to 75th percentile: 3.5-13.5) and 580 study visits. During this follow-up period, 24 (29%) of the 82 women of childbearing age had at least 1 pregnancy. In detail, we observed 42 pregnancies in these 24 patients, of which 40 were singleton and 2 were twin pregnancies. The median number of pregnancies per woman during the observation period was 1 (25th to 75th percentile: 1-2) and ranged from 1 pregnancy to a maximum of 4 pregnancies: (n = 13 [54%] with 1 pregnancy, n = 6 [25%] with 2 pregnancies, n = 3 [13%] with 3 pregnancies, and n = 2 [8%] with 4 pregnancies), respectively. One termination of pregnancy and 1 tubular pregnancy were excluded from data analysis, as they are not antiphospholipid antibody-related pregnancy complications by definition. Finally, 40 pregnancies (38 singleton, 2 twin pregnancies) in 23 LA-positive individuals were analyzed (Figure 1).

The primary endpoint of a pregnancy complication occurred in 28 out of 40 pregnancies. This corresponded to an overall pregnancy complication risk of 70% per pregnancy (95% CI: 56-84).

Individual pregnancy complications included 22 spontaneous abortions (<10th WOG: n = 12, 10th to 24th WOG: n = 10 [n = 1 associated with catastrophic antiphospholipid syndrome], and 6 deliveries <34th WOG [3 due to severe PE/HELLP (hemolysis, elevated liver enzymes, and a low platelet count) syndrome, and 3 due to placental insufficiency]), respectively. Twelve pregnancies ended with births ≥34th WOG, of which 11 were uneventful and one was associated with mild PE. No fetal deaths were observed in the 6 deliveries <34th WOG (caesarian section, n = 6), or the 12 deliveries ≥34th WOG (caesarian section, n = 8; vaginal delivery, n = 4). The birth weight, available for all but 1 uneventful pregnancy, was significantly lower in the 6 children born alive <34th WOG in comparison with these born ≥34th WOG (1345 g [1110-2330] and 2970 g [2750-3130], *P* = .002). The calculated birth weight percentiles by gestational age were lower but not significantly different between these 2 groups (21 [10-45] and 32 [21-58], *P* = .314). In the 6 deliveries <34th WOG, the birth weight by gestational age was below the 5th percentile in 1 out of 6 and below the 10th percentile in 3 out of 6 newborns, whereas only 1 out of 11 newborns ≥34th WOG was below the 10th percentile.

Among the 23 women with at least 1 pregnancy, only 5 did not experience a pregnancy complication, which constituted a pregnancy complication risk per woman with at least 1 pregnancy of 78% (95% CI: 61-95).

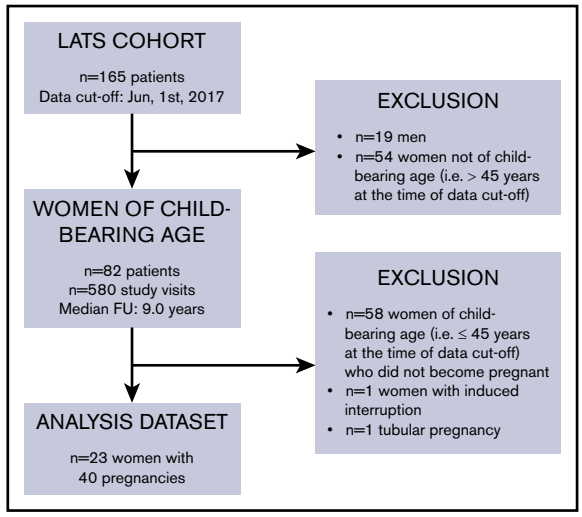

Figure 1. Patient inclusion flowchart. FU, follow-up.

Association of clinical factors and prepregnancy antibody profile with pregnancy complications

No statistically significant differences in the distribution of prepregnancy covariates were observed between uneventful pregnancies and pregnancies with complications, except for the Rosner index, indicating the strength of circulating anticoagulant activity, which was significantly higher in pregnancies that resulted in complications (dependency-adjusted *P* = .043; Table 1). The median aPTT-LA, an in vivo biomarker of LA potency, was 15 seconds longer in complicated pregnancies, although this was only borderline statistically significant with the small numbers we had (dependency-adjusted *P* = .056). Similarly, without reaching statistical significance, triple antibody positivity was more common in patients with than without pregnancy complications (61% and 36%, dependency-adjusted *P* = .182; Table 1), and pregnancy complications were less frequent in women exposed to a combination therapy of LDA and low-molecular-weight heparin (LMWH) during pregnancy (dependency-adjusted *P* = .285; Table 1).

In univariable logistic regression, higher age at pregnancy was associated with lower odds of pregnancy complications (odds ratio [OR] per 5 years' increase in age = 0.41, 95% CI: 0.19-0.87, *P* = .013), which did not prevail after adjustment for the Rosner index (supplemental Table 1). Autoimmune rheumatic disease status did not emerge as a predictor of pregnancy complication risk in our analysis (Table 2; supplemental Table 1). The odds of experiencing a pregnancy complication were lower in number but not in statistical significance in patients exposed to LDA/LMWH combination therapy in comparison with other types of or no anticoagulant treatment.

Among antiphospholipid laboratory characteristics, a higher Rosner index was univariably associated with a higher risk of pregnancy complications (OR per doubling = 4.51, 95% CI: 1.08-18.93, *P* = .039). A numeric association between a prolonged aPTT-LA and a higher risk of pregnancy complications did not reach statistical significance, similarly to the results for triple antibody positivity. IgM- and IgG-isotype antibodies against Cardiolipin or β2GPI did not appear to harbor information on the pregnancy

Table 1. Distribution of prepregnancy clinical and laboratory variables according to pregnancy complication status (n = 40 pregnancies)

Variable	No pregnancy complication (n = 12 pregnancies, N = 6 women)	Pregnancy complication (n = 28 pregnancies, N = 17 women)	P*
Demographic and clinical variables			
Age at pregnancy onset (range), y	33 (31-37)	31 (28-35)	.055
Prior history of venous thrombosis	10 (83)	21 (75)	.563
Number of women with a prior history of venous thrombosis	5 (83)	12 (71)	.541
Number of women with a prior history of arterial thrombosis	0 (0)	0 (0)	N/A
Prior history of pregnancy complications†	6 (50)	17 (61)	.530
Number of women with a prior history of pregnancy complications†	4 (67)	9 (53)	.560
Autoimmune rheumatic disease‡	4 (33)	6 (21)	.435
LDA alone	0 (0)	2 (7)	.485
LMWH alone	0 (0)	5 (18)	.298
LDA+LMWH	10 (83)	18 (64)	.285
Laboratory variables			
Rosner index	34 (26-42)	36 (33-47)	.043
aPTT-LA, s	81 (75-100)	96 (82-113)	.056
aCL IgM	6.2 (1.9-23.0)	5.3 (2.9-9.8)	.243
aCL IgG, GPL	25.8 (15.0-106.1)	51.8 (26.3-120.0)	.198
aβ2GPI IgM§	5.0 (2.3-44.1)	2.9 (1.4-8.5)	.229
aβ2GPI IgG, GPL§	41.0 (11.4-97.1)	44.8 (10.1-100.0)	.788
Triple antibody positivity§	4 (36)	17 (61)	.182

Data represent either a median (25th-75th) for continuous variables or an absolute frequency (%) for count data. Data are reported for individual pregnancies, except for "Number of women with a prior history of thrombosis" and "Number of women with a prior history of pregnancy complications," which report data for individual women.

N/A, not applicable.

*P value for a difference between pregnancies with and without complications from a linear or generalized linear regression model taking into account the dependent data structure (ie, that women could have >1 pregnancy).

†Pregnancy complications were defined according to revised Sapporo criteria.[1]

‡Autoimmune rheumatic disease was defined as 4 cases of systemic lupus erythematosus and 1 case of lupus-like disease.

§aß2GPI IgG/IgM antibodies missing in 1 pregnancy. Cutoffs for triple antibody positivity were defined as follows: aCL >40 GPL/MPL U/mL; aβ2GPI IgG >8 GPL/MPL U/mL.

complication risk. In the multivariable logistic regression models provided in supplemental Table 1, the prognostic association of the Rosner index for an increased risk of pregnancy complications prevailed after adjustment for a history of thrombosis or a history of prior pregnancy complications, or after adjustment for the diagnosis of an autoimmune rheumatic disease or treatment with low-dose aspirin (LDA) and LMWH. Nonetheless, after adjustment for age, the association lost statistical significance. This is due to the fact that higher age was associated with a lower Rosner index as well as lower odds of pregnancy complications. In the multivariable models, including each laboratory variable, the association between the Rosner index and pregnancy morbidity lost statistical significance after adjustment for aPTT-LA, aCL IgG, aß2GPI IgG or IgM, or triple antibody positivity due to confounding and collinearity of these factors.

Association of previous clinical history of thrombosis and/or pregnancy complications with pregnancy complications

Prior history of thrombosis or pregnancy complications did not emerge as predictors of future pregnancy complication risk (Table 2). In detail, 16 (74%) of the 23 women had a prior history of 24 thrombotic events at study inclusion (isolated deep vein thrombosis: n = 19, isolated pulmonary embolism n = 4, deep vein thrombosis + pulmonary embolism, n = 1). All of these 24 events occurred in the venous vasculature. A prior history of venous thrombosis was not associated with future risk of pregnancy complications (χ^2 test, $P = .563$; Table 1; Table 2).

Sixteen of the 23 women (70%) had 33 pregnancies prior to study inclusion. Thirteen of those 16 women had had a history of 24 pregnancy complications. Of the 33 pregnancies before study inclusion, 24 had been complicated (spontaneous abortion <10th WOG: n = 11, 10th to 24th WOG: n = 13), and 9 uncomplicated pregnancies had occurred. A prior history of pregnancy complications did not predict future pregnancy complications (χ^2 test, $P = .530$; Table 1; Table 2).

Regarding their index presentation at study inclusion, 8 patients (35%) could be considered as having a history of thrombotic APS only (n = 1 patient with a history of thrombosis and pregnancy but no history of pregnancy complications, and n = 7 patients with a history of thrombosis but no prior pregnancy). Four patients (17%) can be regarded as obstetric APS only (history of pregnancy complications, no history of thrombosis). Nine patients (39%) had both, a previous history of thrombosis and pregnancy complications. Two patients (9%) were LA positive without a clinical manifestation of APS (no prior history of thrombosis

Table 2. Univariable logistic regression models of pregnancy complication risk (n = 40 pregnancies)

Variable	OR	95% CI
Demographic and clinical variables		
Mean age (per 5-y increase)	0.41	0.19-0.87
Prior history of thrombosis	0.60	0.10-3.50
Prior history of pregnancy complications*	1.55	0.39-6.14
Autoimmune rheumatic disease†	0.55	0.12-2.5
LDA alone	N/E	N/E
LMWH (any dose level) alone	N/E	N/E
LDA+LMWH	0.36	0.06-2.02
Laboratory variables‡		
Rosner index (per doubling)	4.51	1.08-18.93
aPTT-LA (per doubling)	5.21	0.80-33.87
aCL IgM (per doubling)	0.93	0.55-1.57
aCL IgG (per doubling)	1.42	0.90-2.23
aß2GPI IgM (per doubling)§	0.74	0.49-1.12
aß2GPI IgG (per doubling) §	1.08	0.74-1.57
Triple antibody positivity§	2.70	0.63-11.68

CIs were adjusted for the dependent data structure (ie, that women could have >1 pregnancy).

N/E, not evaluated.

*Pregnancy complications were defined according to revised Sapporo criteria.[1]

†Autoimmune rheumatic disease was defined as 4 cases of systemic lupus erythematosus and 1 case of lupus-like disease.

‡Laboratory variables were log2-transformed to stabilize skewed distributions. Corresponding ORs represent the relative increase in the odds of a pregnancy complication per doubling of the respective laboratory parameter.

§aß2GPI IgG/IgM antibodies missing in 1 pregnancy. Cutoffs for triple antibody positivity were defined as follows: aCL >40 GPL/MPL U/mL, aß2GPI IgG >8 GPL/MPL U/mL.

or pregnancy complication). Interestingly, in an exploratory analysis, a prior history of only obstetric APS predicted future pregnancy complication risk, with all 4 women developing a future pregnancy complication in all of their 5 future pregnancies. No association of future pregnancy complication risk was seen for the other 3 subgroup variables (data not shown).

Anticoagulant and additional treatment during pregnancy

Anticoagulants were given during 35/40 pregnancies (Table 3). In the majority of pregnancies (n = 28), a combination of LDA and LMWH was given. Of these 28 pregnancies, 15 (53.6%) ended in live births, whereas only 1 out of 5 pregnancies with LMWH alone and 0 out of 2 pregnancies with LDA alone led to deliveries of a live infant. During 5 pregnancies in 3 patients, no anticoagulant treatment was administered, resulting in 3 abortions (<10th WOG: n = 2, ≥10th WOG: n = 1), and 2 uneventful pregnancies with deliveries ≥34th WOG (Table 3). Doses of LMWH are reported in Table 4 according to the pregnancy outcome and the index APS presentation at study inclusion.

Immunosuppressive agents were given during 6 pregnancies in 3 women with systemic lupus erythematosus. One of these patients with 2 abortions (<10th WOG: n = 1, 10th to 24th WOG: n = 1) and 1 uneventful pregnancy (delivery ≥34th WOG) were treated with low-dose corticosteroids only. Two patients took hydroxychloroquine: 1 patient additionally to LDA alone in 1 pregnancy, resulting in an early pregnancy loss <10th WOG, and 1 further patient in combination with LDA and LMWH during 2 pregnancies, resulting in an early delivery <34th WOG due to HELLP (hemolysis, elevated liver enzymes, and a low platelet count) syndrome, and 1 delivery ≥34th WOG.

Discussion

In our cohort of persistently LA-positive patients, we observed a very high rate of pregnancy complications, severely affecting the fetuses as well as the mothers. The Rosner index, as a proxy variable for lupus inhibitor potency, was identified as a prognostic parameter for adverse pregnancy outcomes in a univariable regression model. Higher age was univariably associated with lower odds for adverse pregnancy outcomes in our cohort. Neither a previous history of thrombosis or pregnancy complications nor the diagnosis of a concomitant autoimmune rheumatic disease was associated with an increased risk of pregnancy morbidity in our patients.

The rate of pregnancy complications in our prospective study in persistent LA-positive patients was 70% despite the initiation of anticoagulant treatment with LMWH and LDA in the majority of pregnancies. LA positivity was identified as the major risk factor for pregnancy complications in the prospective PROMISSE study, investigating pregnant patients with APLA and/or systemic lupus erythematosus.[8,24] In the subgroup analyses of LA-positive patients only, adverse pregnancy outcomes occurred in 25/64 (39%) and 9/17 (53%) of pregnancies.[8,24] These rates are lower than the rate of 70% in our study, which might be explained by the fact that, in contrast to our study, PROMISSE only included pregnancy complications after the 12th WOG. As the most common pregnancy complication in our cohort was early abortion <10th WOG, this might explain our comparatively high complication rate. Our data and the cohort of the PROMISSE study underline the relevance of LA positivity as the strongest laboratory determinant of pregnancy complication risk in the APS spectrum disorder.[2,7,8,24,25] Clinical factors, which had been associated with poor pregnancy

Table 3. Pregnancy outcomes according to anticoagulant treatment during pregnancy

	No anticoagulation (n = 5)	LMWH alone (n = 5)	LDA alone (n = 2)	LMWH+LDA (n = 28)
Abortion <10 WOG	2	2	2	6
Late abortion 10-24 WOG	1	2	0	7
Birth <34 WOG	0	1	0	5
Birth ≥34 WOG	2	0	0	10
Live birth rate	2/5	1/5	0/2	15/28

Table 4. Number of pregnancies in each LMWH dose category according to pregnancy outcomes during the observation period and the individual index APS presentation at study inclusion

	No LMWH	LMWH prophylactic dose*	LMWH half-therapeutic dose†	LMWH therapeutic dose‡
Pregnancy complication	5	4	7	12
Early abortion <10th WOG	4	2	1	5
Late abortion 10th to 24th WOG	1	1	3	5
Delivery <34th WOG	0	1	3	2
Uncomplicated pregnancy	2	1	4	5
Thrombotic APS	2	2	5	4
Obstetric APS	1	1	1	2
Thrombotic/obstetric APS	0	2	5	11
LA positivity only	4	0	0	0

*Enoxaparin-natrium 40 mg or dalteparin-natrium 5000 IU once daily, not adjusted to body weight.
†Enoxaparin-natrium 40 mg or dalteparin-natrium 5000 IU twice daily or adjusted to body weight (1 mg/kg body weight once daily for enoxaparin-natrium or equivalent).
‡Adjusted to body weight (1 mg/kg body weight twice daily or 1.5 mg/kg once daily for enoxaparin-natrium or equivalent).

outcomes in other studies on patients with APS, did not emerge as prognostic factors for adverse pregnancy outcomes in our study.[24,26,27] However, prior manifestation as only obstetric APS before study inclusion and not only thrombotic or both, obstetric and thrombotic APS, seems to yield a higher risk for future pregnancy complications. An effect of more intense treatment in pregnancies of patients with a history of thrombotic or both, thrombotic and obstetric manifestations in comparison with patients with prior obstetric manifestations only, cannot be excluded.

A higher Rosner index (index of circulating anticoagulant, %) was identified as a risk factor for adverse pregnancy outcomes in our cohort of LA-positive individuals. The reported association might represent a more severe LA phenotype and underlines the relevance of LA as the major risk factor for pregnancy complications.

In the current study, anticoagulant treatment during pregnancy was performed according to the treating physician, and thus our study was not designed to evaluate the causal effect of anticoagulant treatment strategies for prevention of LA-associated pregnancy complications. During all but 5 pregnancies, anticoagulant treatment was given, with the majority receiving a combination therapy of LDA and LMWH. The live birth rate was 54% in the group treated with LDA and LMWH and only 25% in the group receiving LDA or LMWH alone or no treatment. Nevertheless, these data have to be interpreted with caution due to the low patient numbers, especially in the group with LDA or LMWH alone or no treatment.

Due to the lack of evidence from large randomized controlled trials, there are no clear recommendations on the indication, type, and dosage of anticoagulant treatment in pregnancies of LA-positive women with or without previous thrombosis and/or pregnancy complications.[28] Few randomized controlled trials have been performed in APLA-positive women with recurrent pregnancy loss and report conflicting results. In 2 of these randomized trials, a superiority of treatment with LDA plus heparin vs LDA alone with regard to the live birth rate was shown,[29,30] with live birth rates of 71% and 80% in the group treated with LDA plus heparin and only 42% and 44% in the group with LDA alone, whereas there was no difference in a further 2 studies with live birth rates of ~80% in both treatment arms.[31,32] Nevertheless, these latter studies are controversial due to weaknesses in the study design, patient selection, and unmet laboratory criteria for APS diagnosis.[33-36] Furthermore, the FRUIT-RCT trial did not show a difference in the recurrence of APLA-associated pregnancy complications in a small group of 32 pregnant women who were aCL antibody positive (>10 GPL/MPL) and/or LA positive, had a history of pregnancy complications, and were randomized to LDA+LWMH or LDA only.[37] In 3 meta-analyses, the combination therapy with unfractionated heparin and LDA was reported to have a beneficial effect on pregnancy outcomes in patients with APS and recurrent pregnancy loss.[38-40] However, comparability of the data is limited due to small trial sizes and varying selection of included patients and clinical heterogeneity concerning the antiphospholipid antibody status and previous pregnancy morbidity. The live birth rates in the abovementioned interventional studies were far better than those in our cohort. The low live birth rate in our study in comparison with the previously reported rates is most probably attributed to the selection of a high-risk cohort in this analysis, as all had persistently positive LA. This low live birth rate also necessitates further studies to allow for an improved stratification of patients according to their individual risk for pregnancy loss in order to apply tailored treatment strategies. Furthermore, the high-risk situation of LA-positive pregnant women requires a close interdisciplinary cooperation between LA specialists, obstetricians, and rheumatologists.

The main limitation of the current study is the small number of pregnant women in the observed cohort. However, women with persistent LA according to the strict criteria of Miyakis et al are indeed very rare.[1] The major consequence of the small sample size of our study is the inherent risk for "false negative" results (ie, not detecting an association with the numbers we have when in fact there is an association). This appears to be particularly the case for the lupus-sensitive aPTT. The OR for association with pregnancy complications was high, and its CI was strongly "leaning to the right" of unity, which suggests an effect. A confirmation of our results in a larger cohort of high-risk APLA patients would be important. Second, our data report results of a very selected group of high-risk LA-positive women. Therefore, the results cannot be generalized to apply to other patient groups

included in the APS spectrum disorder, such as patients with isolated aCL or aβ2GPI-positive antibody profile. However, we report on a rigorously prospectively followed cohort of high-risk LA-positive women. The strict inclusion criteria and the long observation period of a median of 9 years are further strengths of the Vienna LATS.

We conclude that the risk for adverse pregnancy outcomes in patients with persistent positivity for LA is extremely high, especially in patients with a more severe LA phenotype. In addition to the high rate of fetal complications, mothers also frequently experienced severe and life-threatening pregnancy complications. This finding reveals an unmet need for improved therapies for these patients in order to raise the yet dismal live birth rate and underscores the importance of LA as the strongest laboratory risk factor for pregnancy complications in patients with an APS spectrum disorder.

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Authorship

Contribution: J.G., C.A., and I.P. designed the study; J.G., S.K., L.K., C.A., and I.P. contributed patients; S.K., T.P., and P.Q. performed laboratory analyses; S.K. and F.P. supported data storage; J.G., F.P., S.K., L.K., and I.P. collected and interpreted the data; F.P. analyzed the data; J.G., F.P., and I.P. wrote the manuscript; and all authors had access to the study data, proofread the manuscript, agreed with the content, and approved its submission.

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