Incidence of Postpartum Thrombosis and Preterm Delivery in Women with Antiphospholipid Antibodies and Recurrent Pregnancy Loss

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ABSTRACT. ***Objective.*** To determine the frequency of preterm deliveries and postpartum thrombotic events (TE) in pregnancies resulting in live birth in women with antiphospholipid antibodies (aPL) and a history of recurrent pregnancy loss (RPL) but without prior TE.

Methods. We reviewed the pregnancy outcomes of women referred to our clinic with a history of RPL. Prepregnancy investigation of RPL included history of TE and aPL positivity (anticardiolipin IgG and lupus anticoagulant). We recorded use of anticoagulation therapy during and after pregnancy, obstetric outcome, gestational age at delivery, and postpartum course. Included in our study were women with unexplained RPL with no history of TE attending our clinic who subsequently had pregnancies that resulted in a live birth.

Results. Over a 5-year period, 260 women with RPL and no history of TE had a live birth at our clinic. Eighty-seven (33.5%) were positive for aPL and 173 (66.5%) were negative for aPL. Twenty-four percent of deliveries in the aPL-positive group occurred before 37 weeks' gestation compared to 9.8% of deliveries in the aPL-negative group ($p = 0.004$; 95% CI 0.052–0.234). There were no antepartum TE in either group. One woman in the aPL-positive group (1.1%) had a deep vein thrombosis 3.5 weeks postpartum while receiving prophylactic anticoagulant therapy, compared to none in the aPL-negative group.

Conclusion. A significantly higher proportion of aPL-positive patients had preterm deliveries compared to aPL-negative patients, but pregnancy-related TE was infrequent: 99.0% of aPL-positive women with a history of RPL and no prior TE who had a live birth at our clinic had an uneventful pregnancy, delivery, and postpartum course. (First Release April 1 2007; J Rheumatol 2007;34:992–6)

Key Indexing Terms:
PRETERM DELIVERY POSTPARTUM THROMBOSIS ANTIPHOSPHOLIPID ANTIBODIES
ANTICOAGULATION ANTICARDIOLIPIN LUPUS ANTICOAGULANT

Women with antiphospholipid antibodies (aPL) are considered at increased risk for recurrent pregnancy loss (RPL), intrauterine growth restriction, stillbirth, prematurity, and thrombotic events (TE)[1-3]. Despite continuing debate regarding appropriate therapy due to a dearth of well designed, appropriately powered studies[4,5], the standard of care for women with aPL and a history of RPL but not TE continues to include prophylactic anticoagulant therapy during pregnancy[5-7].

Studies investigating treatment regimens for aPL-positive pregnancy usually identify live birth rate as the primary outcome and the incidence of intrauterine growth restriction, placental infarction, prematurity, and preeclampsia as secondary outcomes. There is only limited literature available about the incidence of postpartum TE in this population[8-10].

The TERM Programme (Treatment and Evaluation of Recurrent Miscarriage), established in 1996, investigates about 300 new patients per year with a history of RPL. Those identified with hormonal, genetic, or anatomic abnormalities that might account for reproductive failures are referred for appropriate treatment or counseling. Those with immunologic and coagulation abnormalities are prospectively followed at our clinic from the prepregnancy to postpartum period.

We initiated this investigation because the necessity for postpartum anticoagulation in aPL-positive pregnancies (in the absence of prior TE) has not been determined and yet this regimen is becoming entrenched. We report our experience

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Accepted for publication January 12, 2007.

over a 5-year period comparing outcomes of aPL-positive and negative women without a history of TE whose pregnancies resulted in a live birth. We wanted to observe the frequency of pregnancy-related thrombosis in women with aPL but without a history of TE compared to women with a similar obstetric history, but no aPL, and also to evaluate the association between aPL positivity and preterm delivery.

MATERIALS AND METHODS

Study design. Patients with a history of RPL referred to our clinic over a 5-year period were prospectively followed throughout their pregnancies. We subsequently performed a chart review and collected demographic, clinical, and obstetric outcome data on patients whose pregnancies had progressed to at least 27 weeks. We restricted our study in this manner because we wanted to confine our analysis to pregnancies with a significant likelihood of live birth. Further, women in early pregnancy are less likely to experience any pregnancy-related TE[11]. We recorded anticoagulation use throughout pregnancy and the postpartum period.

Patients with significant comorbidity, including systemic lupus erythematosus and diabetes, were excluded from the study.

Definition of RPL. Patients were classified with RPL defined as at least 2 consecutive losses in the absence of anatomic (assessed by hysterosalpingogram or sonohysterogram), genetic (karyotype analysis of both partners), or hormonal (luteal-phase biopsy or mid-luteal-phase progesterone level) abnormalities. Early losses were defined as those occurring at < 14 weeks' gestation, late losses as those at ≥ 14 weeks' gestation.

Laboratory evaluation. Prenatal serum and plasma specimens were collected from each patient and stored at –80°C as part of routine investigation. Those with a positive aPL result were recalled to the clinic a minimum of 6 weeks later for collection of a second sample for confirmation purposes. The lupus anticoagulant (LAC) was measured using a panel of tests to optimize detection as described[12], including Russell's viper venom time (DRVVT), dilute prothrombin time, a lupus-sensitive partial thromboplastin time, and the kaolin-cephalin clotting time. Factor deficiencies were ruled out by repeat testing of prolonged results with 1:1 and 4:1 mixing with normal plasma. IgG anticardiolipin (aCL) levels were measured using INOVA Quantalite kits (Intermedico, Mississauga, ON, Canada). Results were derived from a standard curve, and values > 15 GPL units were considered positive based upon the mean + 2 standard deviation of the results of 162 normal sera. We did not include aCL IgM in our study because not all women were tested for that isotype.

aPL-positive group. This group comprised patients with a history of RPL who were positive for aCL IgG and/or LAC on at least 2 occasions, 6 weeks apart, but negative for anatomic, hormonal, or genetic investigations, and an index pregnancy that progressed to at least 27 weeks' gestation.

Comparator group. This group included aPL-negative women with a history of RPL with no anatomic, hormonal, or genetic abnormalities, and no history of TE, with at least one documented pregnancy (subsequent to the last spontaneous loss) that progressed to at least 27 weeks' gestation.

Statistical analysis. We used SigmaStat Version 3.0 software (SPSS Inc., Chicago, IL, USA) for statistical analysis. Proportions were compared using the z test (for population prevalence statistics) with Yates' correction factor. A p value < 0.05 was considered significant and 95% confidence intervals (CI) were calculated for differences and odds ratios. Where appropriate, Fisher's exact test was used for comparisons of proportions with expected cell values of less than 5.

RESULTS

Patients. The 2 comparator groups included 87 aPL-positive and 173 aPL-negative women; all had a history of RPL as defined above and none had a history of TE. There was no difference in the obstetric histories of women in each group (Table 1) with the following exception: significantly more women in the aPL-negative group had a history of at least one live birth compared to the aPL-positive group (72.8% vs 41.4%; p > 0.001, 95% CI 0.189–0.439), indicating that more women in the aPL-positive group had primary rather than secondary RPL. There was no difference in the proportion of each group with 2 or > 2 pregnancy losses (Table 1). There was no difference in the mean ages of the women in each group (32.0 vs 33.3 yrs; p = not significant).

Distribution of aPL. In the aPL-positive group, 54.0% of women were positive for LAC only; 28.7% were positive for aCL only; 17.2% were positive for both LAC and aCL. The LAC-specific partial thromboplastin time (PTT-LAC) was the most frequently seen LAC measured (74.2% of women with an LAC had a prolonged PTT-LAC), followed by the DRVVT (40.9%; Table 2).

Table 1. Obstetric histories of women with a history of recurrent pregnancy loss but not thrombotic events, with and without antiphospholipid antibodies (aPL). There was no difference between the 2 groups with the exception of live births: more aPL-negative women had at least 1 live birth prior to the index pregnancy.

Obstetric History	aPL-Positive, n = 87	aPL-Negative, n = 173	p
Pregnancies, mean ± SD, median (range)	3.5 ± 1.4, 3 (2–8)	3.9 ± 1.3, 4 (2–8)	NS
2 Early losses (%)	34 (39.1)	52 (31.0)	NS
≥ 3 Early losses (%)	45 (51.7)	105 (62.5)	NS
Early and late losses (%)	9 (10.3)	10 (6.0)	NS
Late losses only (%)	2 (2.3)	1 (0.6)	NS
Live birth ever (%)	36 (41.4)	126 (72.8)	< 0.001*

NS: not significantly different. * Power with α = 0.05: 0.998; 95% CI of the difference 0.189–0.439.

Table 2. Frequency and distribution of anticardiolipin (aCL) titers and specific lupus anticoagulant (LAC) tests in the aPL-positive group (n = 87). 15 women in the group were positive for both aCL and LAC. Nine patients in the LAC positive group (13.6%) had prolonged results for all 4 LAC tests.

Phospholipid Antibody	n Positive (%)
aCL IgG (all titers)	48/87 (55.2)
Frequency of titer ranges among aCL-positive results (n = 48)	
Low (15–25 GPL)	28 (58.3)
Moderate (26–50 GPL)	10 (20.8)
High (> 51 GPL)	10 (20.8)
LAC (≥ 1 test in panel)	66/87 (75.9)
Frequency of specific tests among LAC-positive results* (n = 66)	
Dilute PT	15 (22.7)
PTT-LAC	49 (74.2)
DRVVT	27 (40.9)
KCT	15 (22.7)

* Percentages do not sum to 100 because many patients were positive for more than one LAC test. Dilute PT: dilute prothrombin time; PTT-LAC: lupus anticoagulant-specific partial thromboplastin time; DRVVT: dilute Russell's viper venom time; KCT: kaolin-cephalin clotting time; GPL: IgG anticardiolipin units (negative: ≤ 15).

Women fulfilling criteria for the antiphospholipid syndrome (APS). Forty-five women in the aPL-positive group had ≥ 3 early losses and 11 had at least one late loss. Of those 56 women, 45 also had repeated moderate to high levels of aCL IgG and/or prolonged LAC. This latter group thereby satisfied obstetric and laboratory classification criteria for APS.

Anticoagulation therapy during and/or after pregnancy. Prenatal and/or postpartum anticoagulation therapy was given at the discretion of the attending physician. Prophylactic anticoagulation therapy was given during pregnancy to 71/87 aPL-positive patients: 44 received prophylactic doses of low molecular weight heparin (LMWH; dalteparin at 5000 IU once daily or a weight-adjusted equivalent) with low-dose aspirin (ASA, 81 mg/day); ASA only at a dose of 81 mg/day was taken by 27 women; 16 women received no treatment. Only 4 women in the aPL-positive group and none in the aPL-negative group received anticoagulation postpartum. ASA was discontinued at 35 weeks' gestation and not given postpartum, according to clinic policy.

Pregnancy-related TE. There were no episodes of thrombosis during any of the 260 pregnancies observed. There were no postpartum TE in the aPL-negative group. One (1.1%) woman in the aPL-positive group had a deep vein thrombosis 3.5 weeks postpartum while receiving prophylactic LMWH. She had a history of 2 early losses and was positive for high levels of both aCL IgG and LAC (PTT-LAC, dilute prothrombin time, and DRVVT). At 28 weeks' gestation, she developed high blood pressure, decreased platelets, and proteinuria, and was diagnosed with HELLP syndrome (hemolysis, elevated liver enzymes, and low platelets). Due to her deteriorating condition, a nonelective cesarean section was performed at 31 weeks' gestation. She developed hypertensive retinopathy postpartum; she had been receiving 5000 IU/day fractionated heparin throughout pregnancy and after delivery. This treatment was to continue until 6 weeks' postpartum. She was discharged from hospital 10 days after delivery and one week later, she reported leg pain. A deep vein thrombosis was confirmed by venogram 3 weeks' postpartum.

Preterm deliveries. Twenty-four percent of deliveries in the aPL-positive group occurred before 37 weeks' gestation compared to 9.8% of deliveries in the aPL-negative group ($p = 0.004$; 95% CI 0.052–0.234; Figure 1). There was no difference in the frequency of preterm deliveries in the aPL group between women with a history of 2 compared to > 2 prior pregnancy losses (30.4% vs 30.7%, respectively).

Within the 3 treatment groups in the aPL-positive group, preterm and term deliveries were differentially distributed (Table 2): in the group receiving ASA, 13/27 (48.1%) had preterm deliveries compared to 7/44 (15.9%) of women receiving LMWH/ASA ($p = 0.003$, power with $\alpha = 0.05$, 0.843; 95% CI for the difference 0.141–0.579) and 1/15 (6.3%) receiving no treatment ($p = 0.012$, power with $\alpha = 0.05$, 0.758; 95% CI for the difference 0.129–0.709). There was no difference in the frequency of term deliveries among untreated aPL-positive and aPL-negative women (93.8% vs 91.4%, respectively).

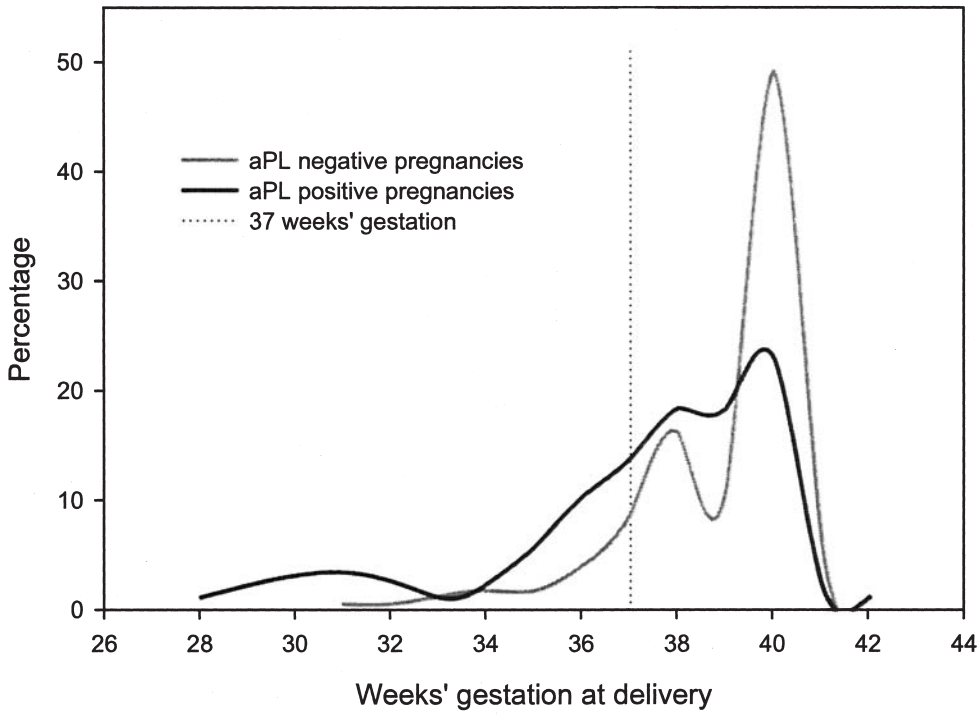

Figure 1. Comparison of preterm deliveries in aPL-positive versus aPL-negative pregnancies. There were significantly more preterm deliveries in the aPL-positive group (24.1% vs 9.8%; $p = 0.004$).

DISCUSSION

Management of TE in women with aPL outside the context of pregnancy is well described[13-15]. Several investigators have attempted to establish guidelines for the treatment of pregnant women with confirmed previous or current thromboembolism regardless of aPL status[16]. As Empson, *et al* and Derksen, *et al* have shown[4-6], there is also a large if disparate body of literature regarding management of pregnancy in women with aPL, although the primary outcome measure of experimental treatment protocols for this population is usually live birth rate and not reduction in TE during pregnancy or postpartum[5,7,17,18]. Despite the lack of evidence-based treatment guidelines[16] particularly for women with aPL in the postpartum period, anticoagulation during and after pregnancy is frequently described as the standard of practice[19-21]. However, as we have reported, management of patients with RPL with or without aPL and with or without a history of TE varies considerably from specialty to specialty[22], and cannot yet be considered either standardized or evidence-based.

In our RPL clinic over 5 years, we observed 260 pregnancies that resulted in a live birth in women with a history of at least 2 prior losses. One woman with aPL in the context of RPL with no prior thrombotic history had a postpartum TE compared to none in the group without aPL. An association between aPL positivity and postpartum TE in this population of women was not found. Postnatal anticoagulation did not eliminate the occurrence of a postpartum TE in our patient. Others have also found that TE can occur despite thromboprophylaxis during pregnancy in women with a history of prior events[23,24]. Of interest, in a prospective study of 125 pregnant women with a history of TE in the absence of known aPL or other prothrombotic conditions, Brill-Edwards, *et al*[25] found that antepartum thromboprophylaxis was unwarranted as the risk of recurrent thromboembolism was so low.

Although there was no difference in the number of prior spontaneous abortions between our 2 groups, more than 60% of our aPL-negative group with RPL had a history of at least one live birth compared to 40% of our aPL-positive group, suggesting an association between primary RPL and aPL positivity. We were also able to confirm an association between aPL positivity and prematurity, as there was a significant increase in preterm deliveries in our aPL-positive group compared to the aPL-negative group. This has been noted by ourselves and others regarding aPL in the context of systemic lupus erythematosus[26].

Table 3. Distribution of preterm deliveries among treatment groups in our aPL-positive population of women (n = 87) with a history of RPL. Results are expressed as percentages in each treatment group with either term or preterm deliveries. In the aPL-negative group, 17 (9.8%) women had preterm deliveries.

Treatment During Pregnancy	Term Deliveries, n (%)	Preterm Deliveries, n (%)
LMWH + ASA	37 (84.1)	7 (15.9)
ASA only	14 (51.9)	13 (48.1)
No treatment	15 (93.8)	1 (6.3)
All treatment groups	66 (75.9)	21 (24.1)

LMWH: low molecular weight heparin.

We noted a modest treatment effect among our patients that has not been previously reported. Of 16 aPL-positive patients who received no anticoagulation during pregnancy at the discretion of their physicians, 15 (93.8%) had term deliveries. A similar if slightly lower percentage (85%) receiving LMWH/ASA also had term deliveries. In contrast, only 14 of 27 (51.9%) women receiving only ASA had term deliveries. These sample sizes are small but the difference between the ASA and no-treatment groups was statistically significant. However, this observation should be considered with caution: this was not a randomized clinical trial comparing treatment effects. The differences we observed in preterm delivery rates may simply have been an epiphenomenon, and our observation is not in agreement with a metaanalysis of ASA consumption during pregnancy in which Kozer, *et al* concluded that ASA seemed to have a small but significant effect on reducing the rate of preterm deliveries in moderate to high-risk pregnancies[27].

Our study has limitations that should be noted. Our population was highly selected and thus our results are probably not widely generalizable. Second, although our population was large in comparison to many studies, it was still too small to establish an association or lack thereof between aPL and postpartum thrombosis. Finally, pre- and postpartum thromboprophylaxis was not protocolized, thus limiting our ability to comment on the efficacy of individual thromboprophylaxis regimens.

Defining RPL as ≥ 2 rather than the more commonly accepted ≥ 3 consecutive pregnancy losses may also be considered a weakness of our study by some. While rigid inclusion and exclusion criteria are required for randomized clinical trials evaluating therapeutic regimens, in our routine clinical practice with this population, many referrals involve women with only 2 losses, and we do not withhold evaluation or treatment until they have had a further loss. As noted recently by Petrozza, *et al*[28], controversy exists regarding how many pregnancy losses should occur before a diagnostic evaluation is considered. In addition, if we are to assume that it is the presence of aPL that influences the development of pregnancy-associated TE in women with RPL, rather than their history of pregnancy loss, then the number of prior losses, whether 2 or 3, is immaterial. Indeed, the only patient with a postpartum event in our prospective, observational study had a history of only 2 losses and did not satisfy classification criteria for APS.

We confirmed an association between aPL positivity and prematurity, and observed a very low rate of postpartum thrombosis in patients with RPL, aPL, and no history of TE. Only one (1.2%) of our aPL-positive patients had a TE during

or after pregnancy, and this occurred despite concurrent prophylactic anticoagulant therapy. We agree with Gates, *et al*[29], who stated that there is still insufficient evidence on which to base recommendations for thromboprophylaxis during pregnancy and the early postnatal period for women with aPL and no history of non-pregnancy-related TE. Our findings suggest that randomized clinical trials of anticoagulant therapy are urgently needed to establish evidence-based standard of care for patients with RPL, and in particular, for patients with RPL and aPL.

ACKNOWLEDGMENT

We thank Dr. Jeff Ginsberg for his thoughtful and constructive reviews of this manuscript.

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