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Concise report

Persistent antiphospholipid antibodies do not contribute to adverse pregnancy outcomes

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Abstract

Objective. To determine whether women with persistent aPL (>12 weeks apart on at least two separate occasions) without a history of thrombosis or adverse pregnancy outcome had the same adverse pregnancy outcomes as those with obstetric APS or unmatched controls.

Methods. This was a case–control study between 2005 and 2011 where we identified 73 women with persistent aPL and coincidentally the same number with obstetric APS. Unmatched controls were identified from low-risk clinics (ratio 1:4). Women with multiple pregnancies, fetal anomalies, SLE, thrombotic APS and other thrombophilias were excluded.

Results. Cases and controls were demographically similar, with the exception of younger controls with fewer medical comorbidities. aPL profiles were similar between aPL and APS. In women with aPL, risk of APS-type complications (odds ratio 1.3; 95% CI 0.6, 2.9) and birthweight distribution (median birthweight on a customized centile was 50.8, interquartile range 26.4–68.9; $P < 0.05$) were similar to controls. These findings persisted even after adjustment for maternal age and medical comorbidities.

Conclusion. Women with persistent aPL on aspirin had pregnancy outcomes that were similar to controls. These data suggest that in the absence of other risk factors, women with aPL do not need intense antenatal surveillance or modified management in pregnancy.

Key words: anti-phospholipid antibodies, antiphospholipid syndrome, pregnancy outcomes, placental insufficiency, pre-eclampsia, small for gestational age, adverse outcomes, intrauterine death, fetal growth, pregnancy loss.

CLINICAL SCIENCE

Introduction

The role of aPLs in obstetrics is controversial [1, 2]. aPLs can be transient, present in 8–10% of the normal population and up to 40% of patients with SLE [3]. In the absence of a defining history of thrombosis or adverse pregnancy outcomes as outlined in the classification criteria [4], the clinical significance of persistent aPL in the obstetric setting is poorly understood [5]. It is often assumed that they have similar risks of adverse pregnancy outcomes as women with obstetric APS. Not infrequently, women undergoing assisted reproductive therapy (ART) or those who have suffered pregnancy losses for other reasons (i.e. painless cervical dilatation in the mid-trimester or preterm rupture of membranes) are being tested and misdiagnosed as having APS [6, 7]. The primary aim of our study was to determine whether women with persistent aPL shared the same adverse obstetric outcomes as those with obstetric APS.

Patients and methods

This was a case–control study of women attending the Obstetric Medicine clinic at Guy's & St Thomas' Hospital with known aPL between January 2005 and July 2011. The Women's Health Department review board for observational studies and clinical audits at our institution approved our study. Notes were reviewed by a single individual (M.C.S.) and classified according to the 2006 criteria as to whether they had obstetric APS (i.e. three

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or more consecutive ⩽10-week miscarriages, one or more >10-week miscarriage for which no cause was found or a preterm delivery ⩽34 weeks gestation from placental insufficiency) and persistent aPL. Women were included if they had aPL demonstrated on two or more occasions, ⩾12 weeks apart; singleton pregnancy; antenatal care and delivery at our hospital. Exclusion criteria were pre-existing factors associated with similar adverse outcomes to obstetric APS such as concurrent SLE, other connective tissue disorders, thrombotic APS (i.e. venous, capillary or arterial thrombosis without vessel wall inflammation) or presence of other thrombophilias or any congenital anomalies in the fetus. Pregnancy losses at ⩽10 weeks gestation were excluded because of differential case ascertainment between the cases and controls based on referral practice. Unmatched controls were from community antenatal clinics (i.e. low-risk pregnancies) over the same booking interval as the women with aPL at a ratio of 1:4.

Data collected included baseline characteristics, demographic data, type of aPL as well as other factors that could affect pregnancy outcomes such as maternal age, height, weight, parity, nicotine use, obstetric history, ART, cervical insufficiency and underlying medical comorbidities (e.g. hypertension, renal disease and diabetes), pregnancy outcomes and any complications that arose during the pregnancy.

Aspirin was prescribed for all women with aPL and APS and women deemed to be at high risk of pre-eclampsia (PET). Low-molecular-weight heparin (LMWH) was prescribed only for women at high risk of venous thromboembolism, obstetric APS with late pregnancy complications or previous APS pregnancies with adverse outcomes despite aspirin use. Many women with aPL had already been commenced on LMWH following ART; where appropriate, we encouraged them to discontinue.

aPL positivity was determined by the presence of either LA and/or aCL antibodies IgG or IgM in our own laboratory, which follows standard guidelines [4]. β2-glycoprotein I levels were not included as they were not routinely tested in our hospital.

Outcomes of interest and obstetric definitions

Outcomes of interest were late obstetric APS-related complications such as PET, preterm delivery (<34 weeks gestation) from placental insufficiency, fetal loss at >10 weeks gestation and small for gestational age. Placental insufficiency is when there is abnormal development of the placenta from various pathophysiological processes, including obstetric APS, with resultant poor fetal growth and PET.

Obstetric definitions were as follows:

(i) Pregnancy-induced hypertension (PIH) was raised blood pressure developing after 20 weeks gestation.
(ii) PET was PIH with proteinuria >0.3 g/24 h.
(iii) Preterm rupture of membranes was rupture of membranes before 37 weeks of gestation; it has a high risk of recurrence in subsequent pregnancies.
(iv) Cervical insufficiency was the painless dilatation of the cervix in the absence of contractions leading to pregnancy loss [8].
(v) Fetal loss included all pregnancy losses from >10 weeks gestation or intrauterine deaths from any reason.

Small for gestational age (SGA) was a customized birth weight <10th centile for the population. Customized birthweight centiles are centiles corrected for maternal and fetal factors that affect growth and are more strongly associated with adverse outcome related to growth restriction [9] (GROW-Centile Gestation Network, www.gestation.net (v 6.5): bulk centiles_uk_exp31Oct13).

Composite APS-related outcomes include fetal loss, preterm deliveries <34 weeks from PET or placental insufficiency as defined by the updated classification criteria for APS [4].

Data analysis

We used medians and interquartile ranges to summarize continuous variables and the Mann–Whitney *U* test for comparisons between groups. We used Fisher's exact test or the χ^2 test as appropriate for univariate comparisons of dichotomous data. The risk of an event was modelled with logistic regression on a complete dataset. Univariate analysis was performed on each outcome of interest. However, due to small number of events, multivariate analysis adjusting for maternal age and medical comorbidities was only performed on a composite APS-related outcome. All *P*-values were two-sided and the significance was set at $P < 0.05$ for all hypotheses tested. Data were analysed using Stata-IC 11.0.

Results

Demographics and baseline characteristics

There were 73 pregnancies in women with persistent aPL and coincidentally exactly the same number of pregnancies in women with obstetric APS and 292 controls. More than half our cases (63.0% APS and 64.4% aPL) were LA positive. The distribution of aPL subtypes was statistically similar between women with aPL and obstetric APS (Table 1).

Compared with controls, more women with aPL conceived using ART. Women in this group were more likely to cervical insufficiency and minor medical comorbidities. Women with APS were more likely to have previous adverse pregnancy outcomes and were multiparous. Collectively women with APS and aPL were older and had more medical comorbidities compared with controls (Table 1). Most women (>95%) with aPL and APS were prescribed aspirin. Women with obstetric APS had significantly higher rates of LMWH use throughout pregnancy compared with women with aPL (Table 1). None of the women developed thromboses antenatally or in the 6-week postnatal period.

Table 1 Baseline characteristics and demographic details of all groups

Variable	Controls ($n = 292$)	aPL ($n = 73$)	APS ($n = 73$)
Age, median (IQR)	32 (27–35)	36 (32–40)*	36 (31–39)*
Ethnicity, *n* (%)			
Caucasian	161 (55.1)	47 (64.4)	38 (52.1)
Indian subcontinent	20 (6.9)	4 (5.5)	8 (11.0)
African	87 (29.8)	18 (24.7)	23 (31.5)
Others	24 (8.2)	4 (5.5)	4 (5.5)
Type of aPL, *n* (%)	NA		
aCL IgG[a]		11 (15.1)	2 (2.7)
aCL IgM[a]		5 (6.8)	2 (2.7)
LA		47 (64.4)	46 (63.0)
aCL and LA		14 (19.2)	23 (31.5)
BMI, median (IQR)	24 (22–27)	24 (22–27)	25 (21–29)
Nicotine use, *n* (%)	32 (11.3)	7 (9.6)	9 (12.3)
ART, *n* (%)	17 (5.8)	17 (23.3)*	9 (12.3)
Medical comorbidities, *n* (%)			
Hypertension	8 (2.7)	4 (5.5)	8 (11.0)*
Renal disease	2 (0.7)	1 (1.4)	3 (4.1)*
Diabetes—type 1 and type 2	4 (1.4)	0	2 (2.74)
Minor medical problems[b]	62 (21.3)	25 (34.3)*	27 (37.0)*
No medical comorbidities	216 (74.0)	43 (59.0)*	33 (45.2)*
Previous pregnancy morbidity, *n* (%)			
None	274 (93.8)	68 (93.2)	0*,**
Recurrent <10-week miscarriage	3 (1.0)	1 (1.4)	19 (26.0)*,**
Pregnancy loss at ⩾10 weeks	9 (3.1)	5 (6.9)	10 (13.7)*
Delivery <34 weeks from severe pre-eclampsia	0	0	7 (9.6)*,**
Delivery <34 weeks from severe placental insufficiency or intrauterine growth restriction	1 (0.3)	0	5 (6.9)*,**
Structural anomalies, *n* (%)			
Cervical insufficiency	16 (11.0)	15 (20.5)*,**	6 (8.2)
Structural anomalies of the uterus	17 (11.6)	10 (13.7)*	4 (5.5)
Parity, *n* (%)			
Nulliparity	173 (59.3)	39 (53.4)	27 (37.0)*,**
Aspirin use, *n* (%)	18 (6.2)	70 (95.9)*	71 (97.3)*
LMWH use, *n* (%)	5 (1.7)	47 (64.4)*	59 (80.8)*,**
LMWH continued throughout pregnancy	1 (20.0)	9 (19.1)*	25 (42.4)*,**

IQR: interquartile range. [a]aCL > 40 GPL or MPL. [b]Minor medical problems included thyroid disease, recurrent headache, asthma, etc., medical conditions that were not thought to affect fetal growth and pregnancy outcomes in the long term. *$P < 0.05$ when comparing either aPL or obstetric APS and controls. **$P < 0.05$ when comparing aPL and obstetric APS.

Obstetric outcomes according to groups

Women with APS were four times more likely than controls to have PIH or PET. Their live birth rates were the lowest (86.3%), with comparable rates between women with aPL (93.2%) and controls (96.9%). The rate of pregnancy loss was five times higher in women with APS and this risk persisted despite adjustment for maternal age and medical comorbidities (Table 2). Rates of fetal loss were not significantly higher in women with aPL compared with controls. Complications unrelated to APS which also increase the risk of pregnancy loss or affect fetal growth such as preterm rupture of membranes and gestational diabetes were similar between aPL and APS.

Of the five fetal losses in women with aPL, four had underlying structural anomalies of the cervix or uterus with prior pregnancy losses and one was undergoing ART (Table 2). Four of the losses were attributed to cervical insufficiency, only one was from placental abruption and a resultant intrauterine death at 22 weeks gestation.

Among live births, the median gestation was the same across all groups, median birthweight was lowest in the APS group with corresponding significantly lower birthweight customized centiles. The rate of SGA by customized centiles was three times higher in women with APS compared with controls. There were no significant differences in birthweight distribution and rate of SGA between women with aPL and controls.

The composite APS-related complications were five times higher in women with APS compared with controls. Adjusting for the higher maternal age and medical comorbidities in this group was without effect (Table 2).

Compared with women with aPL, women with APS had four times higher risk of composite APS-related outcomes

Table 2 Maternal and fetal obstetric outcomes

Variable	Controls	aPL	APS
Maternal outcome			
Maternal complications			
Essential hypertension and PIH, *n* (%)	7 (2.4)	4 (5.5)	7 (9.6)*
Unadjusted OR (95% CI)	1.0	2.4 (0.7, 8.3)	4.3 (1.5, 12.7)
All pre-eclampsia (PET), *n* (%)	13 (4.5)	2 (2.7)	3 (4.1)
Unadjusted OR (95% CI)	1.0	0.6 (0.1, 2.7)	0.9 (0.3, 3.3)
Early PET—delivery <34 weeks, *n* (%)	2 (0.7)	0	2 (2.7)
Unadjusted OR (95% CI)	1.0	—	4.1 (0.6, 29.5)
Preterm rupture of membranes, *n* (%)	7 (2.4)	2 (2.7)	3 (4.1)
Unadjusted OR (95% CI)	1.0	1.1 (0.2, 5.7)	1.7 (0.4, 6.9)
Gestational diabetes, *n* (%)	11 (3.8)	4 (5.5)	2 (2.7)
Unadjusted OR (95% CI)	1.0	1.5 (0.5, 4.8)	0.7 (0.2, 3.3)
Fetal outcome			
Fetal loss, *n* (%)	9 (3.1)	5 (6.9)	10 (13.7)*
Unadjusted OR (95% CI)	1.0	2.3 (0.8, 7.1)	5.0 (1.9, 12.8)
Birthweight, median (IQR)	3400 (1760–4580)	3445 (3110–3685)	3100*,** (2710–3380)
Customized birthweight centile, median (IQR)	44.4 (22.3–68.9)	50.8 (26.4–68.9)	29.0*,** (9.3–50.8)
Small for gestational age, median (%)	31 (11.0)	4 (5.9)	17 (27.0)*,**
Unadjusted OR (95% CI)	1.0	0.5 (0.2, 1.4)	3.1 (1.7, 5.8)
Adjusted OR[a] (95% CI)	1.0	0.5 (0.2, 1.4)	2.9 (1.5, 5.7)
All APS-type complications[b], *n* (%)	31 (10.6)	9 (12.3)**	28 (38.4)*
Unadjusted OR (95% CI)	1.0	1.2 (0.5, 2.6)	5.2 (2.7, 9.6)
Adjusted OR[a] (95% CI)	1.0	1.3 (0.6, 2.9)	5.7 (3.0, 10.9)

IQR: interquartile range. [a]Adjusted for maternal age and medical comorbidities. [b]All APS-type complications include fetal loss >10 weeks gestation, early-onset PET with <34-week deliveries, small for gestational age infants, intrauterine death from placental abruption. *$P < 0.05$ when comparing either aPL or obstetric APS and controls. **$P < 0.05$ when comparing aPL and obstetric APS.

[unadjusted odds ratio (OR) 4.4, 95% CI 1.9, 10.3]. This association was not explained by maternal age and a higher incidence of medical comorbidities in women with APS (adjusted OR 5.5, 95% CI 2.2, 13.7). Among women with aPL and APS, the use LMWH was not associated with a lower risk of all APS-related complications (unadjusted OR 0.6, 95% CI 0.3, 1.4). However, in the multivariate model comparing women with APS to women with aPL, the risk of APS-related complications was further increased in women with APS following adjustment for use of LMWH (adjusted OR 6.9, 95% CI 2.6, 18.1).

Discussion

Our data show that women with persistent aPL, without a diagnosis of APS, have similar obstetric outcomes as our controls. Most strikingly, the rates of SGA, a reflection of placental insufficiency (characteristic of obstetric APS), are low in women with aPL and similar to controls.

As most of the controversy arises from the classification of obstetric APS and persistent aPL in the absence of a clinical history of adverse pregnancy outcomes, our study adopted stringent inclusion criteria for aPL and APS to capture the purest possible cohorts of patients to ensure that obstetric outcomes would not be biased by underlying connective tissues diseases or other thrombotic disorders. We believe that to date, this is the largest—and perhaps the only—case–control study of women with aPL and obstetric APS without concurrent SLE. Anecdotally, we had noted that women with aPL (but without APS) had excellent pregnancy outcomes; as there is a dearth of published data in this area, we compared their outcomes with unselected low-risk controls from our community antenatal clinics.

Despite clear classification criteria for APS [4] and longitudinal studies showing an absence of increased risk of thrombosis or propensity to developing autoimmune diseases in the long term [10, 11], many studies classify women with aPL as having APS [12], making interpretation of outcome data difficult. Even different phenotypes, i.e. thrombotic and obstetric APS, have different pregnancy outcomes, with the former having much higher rates of SGA and preterm delivery compared with the latter [13, 14].

Previous literature has been inconclusive about the role aPLs play in contributing to adverse pregnancy outcomes. Studies have attempted to address this issue by prospectively testing women for aPLs in pregnancy [15–18]. However, despite the large numbers of women tested, actual study subjects were very small [17]. One study specifically picked high-risk women with previous pregnancy loss, but even that study failed to establish a link between aPL and miscarriage [15]. The older studies did not adhere

to the currently accepted guidelines for aPL testing and often only a single positive sample for the presence of aPL was necessary for inclusion in the study [15–17]. Given that up to 10% of the general population may test positive for aPL, it is unsurprising that these studies have failed to establish a correlation between adverse pregnancy outcomes and isolated aPL [15–17].

Despite the high rate of LA (>60%) in the group with aPL, this did not appear to contribute to adverse pregnancy outcomes as suggested by work published by Lockshin *et al.* [12]. The possible explanation for this is the inclusion of women with SLE—a disorder also known to contribute to adverse pregnancy outcomes—in his study, and among other similar studies, thereby further complicating the interpretation of the results from some of these studies [12, 14].

As this was a retrospective study, the exact duration of LMWH use was not always clearly documented; when unavailable, it was assumed that LMWH was continued throughout pregnancy. When compared with women with aPL, women with APS appeared to derive benefit from LMWH use as reflected by the increase in OR in all APS-related complications in the multivariate analysis. However, our study was not designed to evaluate the effectiveness of LMWH. Furthermore, there is a growing body of evidence that LMWH is of no benefit in RPL in APS [1, 9, 20]. Aspirin was used in >95% of women with aPL and APS, hence it is possible that the low rates of PET in women with aPL could be in part attributed to aspirin use.

A limitation of this study was the exclusion of early pregnancy losses at <10 weeks gestation, as these data could not be reliably collected. We concentrated on later losses that are less common and likely to be placentally mediated events more typical of APS. It is possible that cervical insufficiency and the need for ART may have contributed to higher rates of fetal loss in the aPL group, but our study was not powered to address this issue.

Our findings suggest that women with persistent aPL on aspirin had very similar maternal and fetal obstetric outcomes to the control population. aPL in isolation do not appear to contribute to placentally mediated adverse obstetric outcomes. In light of our current findings, we now urge women with aPL that they do not require LMWH for obstetric indications and if LMWH is started by fertility or miscarriage services we advice them to discontinue this at the time of booking with our service—before 13 weeks gestation. If they have other risk factors for VTE, then they may be offered LMWH for thromboprophylaxis. Aspirin is a safe drug commonly used in pregnancy to lower the risk of PET, and it is likely that we will continue to recommend its use in women with aPL until further evidence to the contrary comes to light.

We submit that, in the absence of other risk factors, pregnant women with persistent aPL on aspirin could be managed as normal, without intense antenatal surveillance. We would caution against the overdiagnosis of APS in women with persistent aPL without a history of thrombosis or poor pregnancy outcomes. A future prospective study would be useful to confirm these findings, particularly if there is any role for LMWH or even aspirin use in these women.

Rheumatology key messages

- Without a supporting history, aPL alone do not equate to the diagnosis of APS.
- Women with isolated persistent aPL on aspirin have pregnancy outcomes similar to the normal population.
- Women with aPL could potentially be managed as normal without intense antenatal surveillance or intervention.

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