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Recurrent miscarriage and antiphospholipid antibodies: prognosis of subsequent pregnancy

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SUMMARY.

Background: Although women with antiphospholipid antibodies (APLAs) are at increased risk of recurrent miscarriage, the outcome of a subsequent pregnancy is not clearly elucidated. Objectives: To assess the pregnancy outcome of a subsequent pregnancy in women with APLAs and compare this outcome with women with unexplained recurrent miscarriage. Methods:We performed a cohort study among all women who attended the Miscarriage Clinic at Liverpool Women's Hospital between 1987 and 2006 after being referred due to recurrent miscarriage (≥ 2 consecutive pregnancy losses). All women underwent a standardized investigation sequence. Women with other reasons for recurrent miscarriage were excluded. Results:A total of 693 women fulfilled the selection criteria, of whom 176 (25%) had APLAs. One hundred and twenty-two (69%) women with APLAs had a subsequent live birth compared with 324 (63%) women with unexplained recurrent miscarriage (OR 1.3, 95% CI 0.9–1.9). No differences were found for birth weight, gestational age, and intra-uterine growth restriction. When treatment was analyzed, 53/67 (79%) of women with APLAs who had received aspirin and heparin during their pregnancy had a live birth, compared with 64/104 (62%) of women with APLAs who received aspirin only (adjusted OR 2.7, 95% CI 1.3–5.8). In unexplained recurrent miscarriage, stratification for treatment showed no differences in outcome. Conclusion: The prognosis of a subsequent pregnancy in women with APLAs is good. Although this was not a randomized clinical trial, combined treatment of aspirin and heparin seemed associated with a better outcome in women with APLAs, but not in women with unexplained recurrent miscarriage.

INTRODUCTUION

Recurrent miscarriage is common, with an incidence of 0.4–2% amongst couples who try to conceive (depending on the definition of two or three consecutive miscarriages) [1,2]. Major determinants of the prognosis following recurrent miscarriage are maternal age, the number of preceding miscarriages, and whether or not an underlying cause is found. Therefore, diagnosing an underlying cause is essential for appropriate counseling of couples with recurrent miscarriage. Known risk factors for recurrent miscarriage

include anatomical, hormonal or chromosomal abnormalities and the antiphospholipid syndrome (APS) [3]. However, the cause of recurrent miscarriage remains unexplained in more than 50% of couples with recurrent miscarriage [4,5].

APS is an acquired condition, defined as the presence of thrombosis or pregnancy loss or maternal morbidity and persistent circulating antiphospholipid antibodies in plasma [6,7]. The prognosis of a subsequent pregnancy in women with antiphospholipid antibodies (APLAs) and recurrent miscarriage is not clearly elucidated. Most descriptions stem from randomized trials that have assessed the efficacy of aspirin, with or without heparin, to improve the live birth rate in women with APLAs after recurrent miscarriage [8]. Because participants in trials do not necessarily reflect the general population, these results are not easily translated to daily practise.

We aimed to assess the outcome of a subsequent pregnancy in a large cohort of women with recurrent miscarriage and APLAs and compared this with women with unexplained recurrent miscarriage.

PATIENTS/METHODS

We performed a cohort study including all women with recurrent miscarriage (defined as miscarriage < 24 weeks of gestation) who attended the Miscarriage Clinic at Liverpool Women's Hospital, Liverpool, UK, between 1986 and 2006. We compared women with APLAs with women in whom no APLAs were present (for diagnostic criteria see Table 1). The diagnostic criteria for APLAs have been applied in previously reported studies from the same centre [9–13]. IgG and IgM anticardiolipin were quantified in serum using a previously validated ELISA calibrated against an international standard. The upper limit of the normal range was determined from the log-transformed mean plus two standard deviations (SDs) of results in 50 healthy adults (11 IgG phospholipid units (GPU) mL−1 IgG and 6 IgM phospholipid units (MPU) per mL IgM anticardiolipin). Screening for lupus anticoagulant was by the Kaolin Cephalin Clotting Time (KCCT) utilizing sensitive reagents and by the Dilute Russell's Viper Venom Time (DRVVT) with a neutralization procedure using frozen-thawed platelets. Based on results in 50 healthy non-pregnant subjects a positive result was considered to be a DRVVT ratio to normal of ≥ 1.10 with ≥ 20% correction in the platelet neutralization step. This study was approved by the local research ethics committee (LREC reference number: 08/H1017/72).

[TABLE 1.]

All women underwent a standardized investigation sequence, as previously reported [9,10]. This included testing for thrombophilia (APLAs and acquired activated protein C resistance (APCR)), chromosome abnormalities (in both partners), thyroid dysfunction, diabetes mellitus, bacterial vaginosis and uterine abnormalities. All patients were seen as soon as possible after a positive urine pregnancy test performed at home. Viability ultrasound scanning was provided every 2 weeks after 6 weeks gestation until 12 weeks for maternal reassurance and pregnancy surveillance. By hospital protocol, all women with APLAs received aspirin from the time of a positive urine pregnancy test. Heparin was administered as low-molecular-weight heparin (dalteparin 5000 IU o.d.) and was prescribed in women with APLAs according to the pregnancy loss type (pregnancy loss between 12 and 24 weeks). In women with unexplained recurrent miscarriage who suffered consecutive pregnancy losses between 12 and 24 weeks of gestation, dalteparin was offered as empirical treatment. There were no strict criteria for empirical prescription of aspirin to women with unexplained recurrent miscarriage.

The primary outcome measure was the live birth rate in the first index pregnancy subsequent to the referral and investigation visit to the clinic. Secondary outcome measures were miscarriage rate within 13 weeks of gestation, rate of miscarriage between 13 and 24 weeks of gestation, stillbirth (loss > 24 weeks of gestation), and obstetric complications: intrauterine growth restriction (IUGR) (birth weight < 10th percentile) and premature delivery (prior to the 36th week of gestation).

To calculate differences in distribution of the data, independent sample t-tests (two tailed) were used for continuous variables in the case of two groups and one-way anova-tests were performed for comparison between more than two groups. To adjust for potential confounders, we performed binary logistic regression analysis. Covariates that showed a linear relationship were entered as a continuous variable. Mean differences and 95% confidence intervals were calculated for continuous data, and odds ratios (ORs) and 95% confidence intervals were calculated for categorical data. Baseline characteristics were stratified for therapy, to identify differences in prognostic variables between treatment groups. For the primary

outcome measure, we calculated crude odds ratios, as well as ORs adjusted for maternal age and number of previous miscarriages. We also stratified the primary outcome measure for therapy (aspirin, combined treatment of aspirin and heparin or none), in which women who had unexplained recurrent miscarriage and had received no treatment were the reference group. For all secondary outcome measures, we calculated crude ORs (only for miscarriage did we also calculate ORs adjusted for age and number of previous miscarriages).

All data entries were double checked by a second independent investigator. In addition, random validation checks were performed. Missing or inconsistent data were assessed for random distribution by comparison of baseline characteristics and primary and secondary outcomes with those for women in whom the respective data were not missing. Random distribution was assumed if this comparison did not demonstrate a difference. Subsequently, we excluded participants with missing or inconsistent data from the particular analysis. All data were analyzed with spss software (version 16.0.2; SPSS Inc., Chicago, IL, USA).

RESULTS

A total of 693 women met the selection criteria, of whom 176 (25%) were diagnosed with APLAs (for exclusions, see Fig. 1). Baseline characteristics are listed in Table 2 and were similar in women with APLAs and women with unexplained recurrent miscarriage. Live birth was observed in 122/176 (69%) women with treated APLAs and in 324/517 (63%) women with unexplained recurrent miscarriage (OR adjusted for number of previous miscarriages and maternal age 1.4, 95% confidence interval (CI) 0.9–2.0), as shown in Table 3.

[TABLE 2, 3, FIGURE 1]

Late pregnancy loss (13–24 weeks) occurred in 3/176 women with APLAs (2%) and in 15/517 women with unexplained recurrent miscarriage (3%), OR 0.6 (95% CI 0.2–2.0), and stillbirth (> 24 weeks) occurred in 2/176 women with APLAs (1.1%) and in 2/517 women with unexplained recurrent miscarriage (0.4%), OR 3.0 (95% CI 0.4–21) (Table 4).

[TABLE 4]

No differences were found for birthweight or gestational age between the study groups (Table 4). IUGR was observed in 7 (7%) women with APLAs, as compared with 29 (10%) women with unexplained recurrent miscarriage, OR 0.6 (95% CI 0.3–1.5). Premature delivery occurred in 8 (7%) women with APLAs and 25 (8%) women with unexplained recurrent miscarriage, OR 0.9 (95% CI 0.4–2.0).

Determinants for heparin therapy were a history of late miscarriage as well as patient preference. Women with a history of two or more late pregnancy losses were approximately four times more likely to receive heparin treatment as compared with women with a history of no or one late pregnancy loss ($P = 0.014$ for women with APLAs and $P = 0.003$ for women with unexplained recurrent miscarriage). Women with unexplained recurrent miscarriage who received no treatment were significantly younger than women with unexplained recurrent miscarriage who received treatment with aspirin, either or not combined with heparin (mean age 31 vs. 33 years, respectively) (Table 2). Stratification for therapy showed that the combination of low-dose aspirin and heparin was associated with a higher chance of live birth in women with APLAs (53/67; 79%) as compared with women with APLAs who were treated with aspirin only (live birth 64/104; 62%), adjusted OR 2.7 (95% CI 1.3–5.8) (Table 3). Accordingly, combined use of aspirin and heparin in women with APLAs was associated with a lower occurrence of first trimester miscarriage (11/67; 16%) as compared with women with APLAs who received aspirin only (38/104; 37%), adjusted OR 0.4 (95% CI 0.2–0.7). Treatment was not associated with higher live birth rates in women with unexplained recurrent miscarriage as compared with women with unexplained recurrent miscarriage who received no treatment (see Table 3).

DISCUSSION

In this large cohort study, performed in a tertiary referral centre, we observed that the prognosis of a subsequent pregnancy following recurrent miscarriage was similar in women with APLAs and women with unexplained recurrent miscarriage. Live births were observed in 69% of 176 women with APLAs and in 63% of 517 women with unexplained recurrent miscarriage. Previously reported live birth rates in women

with APS varied between 42% and 100% [9,14–24]. However, comparison between these studies requires comment.

The applied cut-off levels in our study are lower as compared with the cut-off levels defined in the APS diagnostic criteria [6,7]. Although the APS criteria have primarily been defined for research purposes, they are also frequently applied in clinical practise because clinical diagnostic criteria are lacking. Nevertheless, the criteria are still the subject of ongoing debate [25]. Because circulating APLAs may elicit pregnancy loss due to impaired trophoblast differentiation, proliferation and migration, lower concentrations of APLAs might also be pathological [26,27]. Although the observed live birth rates between our study and trials including women with established APS are similar, comparison should be performed with caution.

This study was an observational cohort study, whereas most other studies were randomized controlled trials, allocating patients with established APS to either one or more of the following treatments: aspirin [9,14–24], prednisone [18], heparin [9,15,19–21,24], IVIG [23], placebo [16–18] or usual care [14]. Trials applied various diagnostic criteria for positivity for APLAs (single or repetitive positivity for IgM/IgG anticardiolipin antibodies only and/or lupus anticoagulant) and for recurrent miscarriage (two or three miscarriages, consecutive or non-consecutive miscarriages). Notably, the few studies with the smallest sample sizes reported the highest successful pregnancy rates [14,16,22,23]. This may be the result of publication, referral or selection bias, or lack of concealed allocation bias of small trials with positive results. When the studies are confined to those with more than 50 participants, the successful pregnancy rates vary between 42% and 80%, which is more in line with our findings [9,18–20,24]. The observed live birth rates in women with unexplained recurrent miscarriage in this study are similar to the observed live birth rates as reported in other studies [24,28–30].

Indeed, in this study, a minority of women had a history of only two miscarriages. However, because live birth rate was similar in women with a history of two miscarriages as compared with women with three miscarriages in both groups (data not shown), we did not perform separate analyses for these two groups, but adjusted for the numbers of pregnancy losses instead.

We observed that combined treatment of aspirin and heparin was associated with a higher live birth incidence in women with APLAs as compared with women with APLAs who received aspirin only. This supports findings from previous trials that showed a beneficial effect of combined treatment with aspirin and unfractionated heparin over aspirin alone in women with APS and recurrent miscarriage [19,20]. The observed live birth rates in our study are in line with the largest reported prospective RCT from the same centre as the present study, in which treatment with aspirin was compared with treatment with aspirin combined with low-molecular-weight heparin [9]. The benefit of combined treatment in this study was, however, not significant (78% in women with aspirin and heparin vs. 72% in women with aspirin only, OR live birth 1.39, 95% CI 0.5–3.47]. Age and obstetric history were equally comparable between the study participants of this trial and our study. The most recent trial including women with APS and recurrent miscarriage in whom treatment with aspirin and heparin was compared with aspirin alone, reported no difference in live birth incidence [24]. However, only a small subset of women in this trial had APS (n = 42).

Treatment with aspirin or aspirin and heparin was not associated with an increased chance of live births in women with unexplained recurrent miscarriage. This finding is in line with two recent, partially placebo-controlled, trials in women with unexplained recurrent miscarriage, in which no effect of treatment was found [30,31].

Our study has several strengths. First, the large number of women with recurrent miscarriage and APLAs in our study enabled us to perform clinically relevant subgroup analyses, such as stratification for therapy. Furthermore, the observational design provides a good reflection of the course of a subsequent pregnancy in women with APLAs and recurrent miscarriage. Third, the measurements of APLAs in all participants were performed in the same laboratory, thereby ensuring homogeneity of our patient population.

Some limitations warrant comment. First, although the combined treatment of aspirin and heparin was associated with a higher rate of live births in women with APLAs and recurrent miscarriage, our observational study design (grade 2 level of evidence) does not rule out that this observation is confounded by indication. Indeed, heparin treatment was prescribed four times more often in women with a history of two or more late pregnancy losses. However, the presence of more known and unknown unfavorable prognostic variables in women who have received heparin is likely to underestimate, not overestimate, the association between treatment and live birth. We are aware that evidence for prescription of heparin only to

women with a history of late pregnancy loss is lacking. Nevertheless, because the occurrence of late pregnancy loss is experienced more dramatically as compared with early miscarriage, this treatment was offered empirically.

Second, the retrospective design of the study posed us with a number of missing data. However, comparison of baseline characteristics of women with and without missing data showed random distribution, thus making us confident that this has not affected our results.

Third, the cut-off values of the APLA parameters were lower as compared with other studies [14,15,19,24]. Including women who have been misclassified as having APLAs based on low titers would lead to an underestimation of an association between APLAs and treatment. Still, we observed that combined treatment of aspirin and heparin was associated with an increased live birth rate only in women with APLAs. Future trials should assess whether women with high cut-off levels would benefit even more from aspirin and heparin treatment.

Finally, we only tested for the APLAs as stated in the 1999 Sapporo criteria to diagnose APS [6]. These criteria have been adapted since the initiation of this study [7]. Thus, our findings may not apply to women testing for positive APLAs based on exclusive positivity for anti-β2-glycoprotein-1 antibodies. The extension of the time between initial and repeated testing for APLAs from 6 to 12 weeks possibly has attenuated our findings, as we may have included women with assumed APLAs who had only transient antiphospholipid antibodies.

In conclusion, our large cohort study showed that the overall prognosis of a successful pregnancy in women with recurrent miscarriage and APLAs treated with heparin and aspirin is good.

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DISCLOSURE OF CONFLICTS OF INTEREST

The authors state that they have no conflict of interest.

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[TABLES AND FIGURES]

Table 1 Inclusion and exclusion criteria

Inclusion criteria	
Greater than or equal to two consecutive miscarriages < 24 weeks gestational age, delivery at Liverpool Women's Hospital, presence of APLAs	
IgM anticardiolipin antibodies ≥ 6 U mL^{-1}	tests positive on two different occasions with an interval of 6 or more weeks
IgG anticardiolipin antibodies ≥ 11 U mL^{-1}	
Diluted Russell venom viper test (DRVVT) ≥ 1.10 with a neutralization procedure using frozen-thawed platelets	
Exclusion criteria	
Other causes for recurrent miscarriage	
Chromosomal abnormalities in the participant or in the male partner	
Major (congenital) uterine abnormalities	
Endocrine disorders at the time of previous miscarriages (including diabetes mellitus, thyroid dysfunction)	
Pregnancy losses due to documented fetal formation or autoimmune disorders (e.g. SLE and thrombophilia)	
Incomplete data sets (including outcome of tests for other causes of recurrent miscarriage)	

APLAs, antiphospholipid antibodies; SLE, systemic lupus erythematosus.

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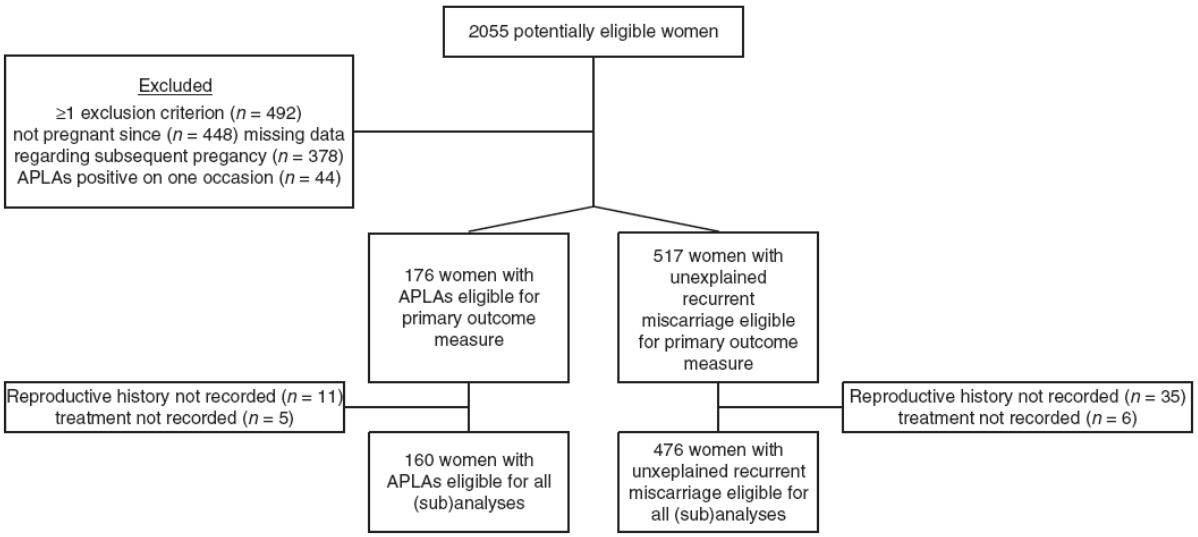

Fig. 1. Flow chart of patient selection. APLAs, antiphospholipid antibodies.

Table 2 Baseline characteristics of women with recurrent miscarriage

	All women (n = 693)	APLAs (n = 165)*	Unexplained recurrent miscarriage (n = 482)*	APLAs, aspirin only (n = 98)†	APLAs, aspirin and heparin (n = 62)†	Unexplained recurrent miscarriage, aspirin only (n = 146)†	Unexplained recurrent miscarriage, aspirin and heparin (n = 36)†	Unexplained recurrent miscarriage, no treatment (n = 294)†
Mean age, years (SD)	32 (5.6)	32 (5.3)	32 (5.7)	32 (5.9)	32 (4.2)	33 (5.6)	33 (5.6)	31 (5.5)
Number of previous miscarriages‡								
2	196 (30%)	46 (28%)	150 (31%)	26 (27%)	20 (32%)	42 (29%)	9 (25%)	98 (33%)
3	263 (41%)	75 (46%)	188 (39%)	46 (47%)	25 (40%)	60 (40%)	13 (36%)	113 (39%)
4	99 (15%)	24 (14%)	75 (15%)	17 (17%)	7 (11%)	22 (15%)	8 (22%)	45 (15%)
5	46 (7%)	9 (5%)	37 (8%)	7 (7%)	1 (2%)	8 (6%)	4 (11%)	23 (8%)
>5	43 (7%)	11 (7%)	32 (7%)	2 (2%)	9 (15%)	14 (10%)	2 (6%)	15 (5%)

APLAs, antiphospholipid antibodies; SD, standard deviation. *Reproductive history was not recorded in 11 women with APLAs and 35 women with unexplained recurrent miscarriage. †Treatment was not recorded in five women with APLAs and six women with unexplained recurrent miscarriage. ‡Miscarriage within 24 weeks of gestation.

Table 3 Pregnancy outcome in women with recurrent miscarriage

	All women (n = 693)	APLAs (n = 176)	Unexplained recurrent miscarriage (n = 517)	APLAs, aspirin only (n = 104)*	APLAs, aspirin and heparin (n = 67)*	Unexplained recurrent miscarriage, aspirin only (n = 163)*	Unexplained recurrent miscarriage, aspirin and heparin (n = 43)*	Unexplained recurrent miscarriage, no treatment (n = 305)*
Live birth, n (%)	446 (64%)	122 (69%)	324 (63%)	64 (62%)	53 (79%)	93 (57%)	25 (58%)	204 (67%)
OR live birth (95% CI)		1.3 (0.9–1.9)	1 (ref)					
OR live birth adjusted (95% CI)†		1.4 (0.9–2.0)	1 (ref)					
OR live birth (95% CI)				1 (ref)	2.4 (1.2–4.8)			
OR live birth adjusted (95% CI)†				1 (ref)	2.7 (1.3–5.8)			
OR live birth (95% CI)						0.7 (0.4–1.0)	0.7 (0.4–1.3)	1 (ref)
OR live birth adjusted (95% CI)†						0.8 (0.5–1.1)	0.7 (0.4–1.4)	1 (ref)

APLAs, antiphospholipid antibodies; OR, odds ratio; CI, confidence interval. *Treatment was not recorded in five women with APLAs and six women with unexplained recurrent miscarriage. †Adjusted for age and number of previous miscarriages.

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Table 4 Secondary outcomes in women with recurrent miscarriage

	All women (n = 693)	APLAs (n = 176)	Unexplained recurrent miscarriage (n = 517)
First trimester miscarriage (loss < 13 weeks), n (%)	225 (33%)	49 (28%)	176 (34%)
OR miscarriage (95% CI)	–	0.7 (0.5–1.1)	1 (ref)
OR miscarriage adjusted (95% CI)*	–	0.7 (0.5–1.1)	1 (ref)
Late miscarriage (loss between 13 and 24 weeks), n (%)	18 (3%)	3 (2%)	15 (3%)
OR late pregnancy loss (95% CI)	–	0.6 (0.2–2.0)	1 (ref)
Stillbirth (pregnancy loss > 24 weeks), n (%)	4 (0.6%)	2 (1.1%)	2 (0.4%)
OR stillbirth	–	3.0 (0.4–21)	1 (ref)
Mean birth weight, grams (SD)	3211 (692)	3168 (603)	3265 (665)
Mean difference, grams (95% CI)	–	−96 (−240–48)	
Mean gestational age, weeks (SD)	39 (2.6)	39 (2.4)	39 (2.8)
Mean difference, weeks (95% CI)	–	−0.3 (−0.9–0.3)	
IUGR, n (%)	36 (9%)	7 (7%)	29 (10%)
OR IUGR	–	0.6 (0.3–1.5)	1 (ref)
Premature delivery, n (%)	33 (8%)	8 (7%)	25 (8%)
OR premature delivery	–	0.9 (0.4–2.0)	1 (ref)

APLAs, antiphospholipid antibodies; IUGR, intrauterine growth restriction; OR, odds ratio; CI, confidence interval. *Adjusted for age and number of previous miscarriages.