Thrombophilia ad dies vitae

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Chapter 11

Recurrent miscarriage in women with and without antiphospholipid syndrome: prognosis for the next pregnancy outcome

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Abstract

Background

Antiphospholipid syndrome (APS) is frequently diagnosed in women with recurrent miscarriage. Nevertheless, the outcome of a subsequent pregnancy in these women is not clearly established.

Objective

To assess the outcome of a subsequent pregnancy in women with APS and 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 referred with recurrent miscarriage (≥2 consecutive pregnancy losses). We compared the pregnancy outcome (live birth rate, miscarriage rate, birth weight, gestational age and intra-uterine growth restriction) of the subsequent index pregnancy in women with APS with the outcome of women with unexplained recurrent miscarriage. Furthermore, the influence of treatment on live birth rate was assessed.

Results

A total of 693 women fulfilled the selection criteria, of whom 176 (25%) had APS. 122 (69%) women with APS had a subsequent live birth compared to 324 (63%) women with unexplained recurrent miscarriage (OR 1.3, 95%CI 0.9 to 1.9). No differences were found for birth weight, gestational age, and intra-uterine growth restriction between these two groups. When treatment choice was analyzed, 53/67 (79%) of women with APS who had received aspirin and heparin during their pregnancy had a live birth, compared to 64/104 (62%) of women with APS who received aspirin only (adjusted OR 2.7, 95%CI 1.3 to 5.8) and compared to 204/305 (67%) of women with unexplained miscarriage who received no treatment (adjusted OR 2.2, 95%CI 1.1 to 4.2).

Conclusion

Live birth rate between women with recurrent miscarriage and APS and women with unexplained recurrent miscarriage was comparable. In women with APS, combined use of aspirin and heparin was associated with a higher live birth rate as compared to women with APS who were treated with aspirin only and as compared to women with unexplained recurrent miscarriage without treatment.

Introduction

Recurrent miscarriage is fairly common with a prevalence of 0.4-2% amongst couples who try to conceive (depending on the definition of 2 or 3 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 an essential part of investigation and for appropriate counselling 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]

Antiphospholipid syndrome (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 APS and recurrent miscarriage is not clearly established. Most estimates are based on a few small randomised trials that have assessed the efficacy of aspirin, with or without heparin, to improve the live birth in women with APS after recurrent miscarriage, mostly without a no treatment arm.[8] Since participants of trials do not necessarily reflect the general APS population, these results are not easily translated to daily practice.

Treatment guidelines vary with regard to the administration of heparin for APS and recurrent miscarriage. The American College of Chest Physicians (ACCP) guidelines recommend the combination of low-dose aspirin *and* a low dose of either unfractionated or low molecular weight heparin (LMWH) (level of evidence: 1B),[9] whereas the European Society for Human Reproduction and Embryology (ESHRE) guidelines recommend the prescription of aspirin *with* or *without* LMWH (level of evidence: 2B).[10]

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

Material and Methods

We performed a cohort study including all women with recurrent miscarriages (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 established APS to women in whom APS was excluded (for diagnostic criteria see Table 1).

Table 1. Selection criteria of the study participants

Inclusion criteria	
≥2 consecutive miscarriages < 24 weeks gestational age	
delivery at Liverpool Women's Hospital	
APS definition according to Sapporo criteria[6]	tests positive on two different occasions with an interval of 6 or more weeks
IgM anticardiolipin antibodies ≥ 6 U/mL	
IgG anticardiolipin antibodies ≥ 11 U/mL	
diluted Russell venom viper test (DRVVT) ≥ 1.10	
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 auto-immune disorders (e.g. SLE and thrombophilia)	
incomplete data sets (including outcome of tests for other causes for recurrent miscarriages)	

This study was approved by the Local Research Ethics Committee (LREC reference number: 08/H1017/72).

All women underwent a standardised investigation sequence, as previously reported.[11,12] This included testing for thrombophilia (APS and acquired activated protein C resistance (APCR)), chromosome abnormalities (in both partners), thyroid dysfunction, diabetes mellitus, bacterial vaginosis and uterine abnormalities. By hospital protocol, all women with APS received aspirin. Heparin was prescribed according to the pregnancy loss type and patient choice. From 1988 onward, heparin was administered as low-molecular-weight heparin and was offered as a choice to women with a history of late pregnancy loss.

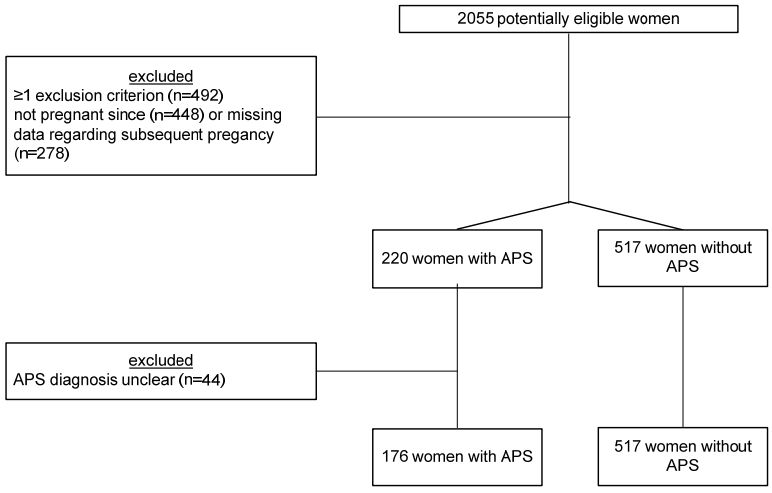
The primary outcome measure was the live birth rate in the first index pregnancy subsequent to the referral and investigation visit to the clinic. Secondary outcome measures were miscarriage rate within 13 weeks of gestation, rate of miscarriage between 13 and 24 weeks of gestation, stillbirth (loss > 24 weeks of gestation), and APS related obstetric complications: intra uterine 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 case of two groups and one-way ANOVA-tests were performed for comparison between more than two groups. χ^2-tests were used in case of categorical variables. To adjust for potential confounders, we performed binary logistic regression analysis. Covariates which showed a linear relationship were entered as a continuous variable. Mean differences and 95% confidence intervals were calculated for continuous data, and odds ratios (OR) 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 (OR), 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 we also calculated 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, primary and secondary outcomes with those in 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 analysed with SPSS software (version 16.0.2).

Figure. Flow chart of patient selection



APS = antiphospholipid syndrome

Results

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

Miscarriage (<13 weeks) occurred in 49/176 women with APS (28%) and in 176/517 women with unexplained recurrent miscarriage (34%), OR 0.7 (95%CI 0.5 to 1.1) (Table 4).

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

No differences were found for birth weight or gestational age between both study groups (Table 4). IUGR was observed in 7 (7%) women with APS as compared to 29 (10%) women with unexplained recurrent miscarriage OR 0.6 (95%CI 0.3 to 1.5). Premature delivery occurred in 8 (7%) women with APS and 25 (8%) women with unexplained recurrent miscarriage, OR 0.9 (95%CI 0.4 to 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 to women with a history of no or one late pregnancy loss (p=0.014 for women with APS 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 APS (53/67; 79%) as compared to women with APS who were treated with aspirin only (live birth 64/104; 62%), adjusted OR 2.7 (95% CI 1.3 to 5.8), and as compared to women with unexplained recurrent miscarriage who had had no treatment (live birth 204/305; 67%), adjusted OR 2.2 (95%CI 1.1 to 4.2) (Table 3).

Table 2. Baseline characteristics of women with recurrent miscarriage.

	All women N=693	APS N=165*	Unexplained recurrent miscarriage N=482*		APS aspirin only N=98**	APS 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)	p=0.66	32 (5.9)	32 (4.2)	p=0.55	33 (5.6)	33 (5.6)	31 (5.5)	p=0.008
Number of previous miscarriages¹				p=0.62			p=0.013				p=0.54
2 miscarriages	196 (30%)	46 (28%)	150 (31%)		26 (27%)	20 (32%)		42 (29%)	9 (25%)	98 (33%)	
3 miscarriages	263 (41%)	75 (46%)	188 (39%)		46 (47%)	25 (40%)		60 (40%)	13 (36%)	113 (39%)	
4 miscarriages	99 (15%)	24 (14%)	75 (15%)		17 (17%)	7 (11%)		22 (15%)	8 (22%)	45 (15%)	
5 miscarriages	46 (7%)	9 (5%)	37 (8%)		7 (7%)	1 (2%)		8 (6%)	4 (11%)	23 (8%)	
≥ 5 miscarriages	43 (7%)	11 (7%)	32 (7%)		2 (2%)	9 (15%)		14 (10%)	2 (6%)	15 (5%)	

APS = antiphospholipid syndrome, SD= standard deviation; ¹ miscarriage within 24 weeks of gestation. *Reproductive history was not recorded in 11 women with APS and 35 women unexplained recurrent miscarriage **Treatment was not recorded in 5 women with APS and 6 women unexplained recurrent miscarriage.

Table 3. Pregnancy outcome in women with recurrent miscarriage

	All women N=693	APS N=176	Unexplained recurrent miscarriage N=517	APS aspirin only N=104*	APS 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 to 1.9)*	*1(ref)*	*0.8 (0.5 to 1.3)*	*1.9 (1.0 to 3.5)*	*0.7 (0.4 to 1.0)*	*0.7 (0.4 to 1.3)*	*1 (ref)*
OR live birth adjusted (95%CI)**	-	*1.4 (0.9 to 2.0)*	*1 (ref)*	*0.8 (0.5 to 1.3)*	*2.2 (1.1 to 4.2)*	*0.8 (0.5 to 1.1)*	*0.7 (0.4 to 1.4)*	*1 (ref)*

APS = antiphospholipid syndrome, OR = odds ratio, CI = confidence interval. *Treatment was not recorded in 5 women with APS and 6 women unexplained recurrent miscarriage, **Adjusted for age and number of previous miscarriages.

In women with unexplained recurrent miscarriage, treatment was not associated with higher live birth rates: 163 women received aspirin, of whom 93 (57%) had a live birth, adjusted OR 0.8 (95%CI 0.5 to 1.1) and 43 women received aspirin and heparin treatment, of whom 25 (58%) had a live birth, adjusted OR 0.7 (95% CI 0.4 to 1.4).

Table 4. Secondary outcomes in women with recurrent miscarriage

	All women N=693	APS 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 to 1.1)***	***1 (ref)***
OR miscarriage adjusted (95%CI)*	-	***0.7 (0.5 to 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 to 2.0)***	***1 (ref)***
Stillbirth (loss >24 weeks) N (%)	4 (0.6%)	2 (1.1%)	2 (0.4%)
OR IUFD	-	***3.0 (0.4 to 21)***	***1 (ref)***
Mean birth weight, grams (SD)	3211 (692)	3168 (603)	3265 (665)
Mean difference, grams (95%CI)	-		***-96 (-240 to 48)***
Mean gestational age, weeks (SD)	39 (2.6)	39 (2.4)	39 (2.8)
Mean difference, weeks (95%CI)	-		***-0.3 (-0.9 to 0.3)***
IUGR, N (%)	36 (9%)	7 (7%)	29 (10%)
OR IUGR	-	***0.6 (0.3 to 1.5)***	***1 (ref)***
Premature delivery, N (%)	33 (8%)	8 (7%)	25 (8%)
OR premature delivery	-	***0.9 (0.4 to 2.0)***	***1 (ref)***

APS = antiphospholipid syndrome, IUGR = intra-uterine growth restriction, OR = odds ratio, CI = confidence interval. * Adjusted for age and number of previous miscarriages

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 APS and women with unexplained recurrent miscarriage. Live births were observed in 69% of 176 women with APS and in 63% of 517 women with unexplained recurrent miscarriage. Previously reported live birth rates in women with APS varied between 42% and 100%.[11,13-22] However, comparison between studies is difficult for various reasons.

This study was an observational cohort study, whereas all other studies were randomized controlled trials, allocating patients with APS to either one or more of the following treatments: aspirin[11,13-22], prednisone[17], heparin[11,14,18-20], IVIG[22], placebo[15-17] or usual care[13].

These trials applied various diagnostic criteria for APS (single or repetitive positivity for IgM/IgG ACA only and/or LA) and for recurrent miscarriage (2 or 3 miscarriages, consecutive or non consecutive miscarriages), and had relatively small sample sizes ranging from only 16 to 202 participants. It is interesting to note that studies with the smallest sample sizes reported the highest successful pregnancy rates. 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.[11,17-19]

Successful pregnancy outcome in women with *unexplained recurrent miscarriage* occurred less frequently as compared to a previous report from the same clinic (63% vs. 75%).[23] However, the definition of "successful pregnancy outcome" differed between the two studies: live birth in our study versus "survival beyond 24 weeks" in the latter study. Furthermore, in contrast to the latter study, we also included women with a history of late miscarriage which may have accounted for the observed difference in live birth rates. The observed difference is not easily interpreted otherwise, as the most important predictors of a future live birth (i.e. maternal age and obstetric history) were similar in both reports. The observed live birth rates in this study are similar to the observed live birth rates as reported in other studies.[24,25]

We observed that combined treatment of aspirin and heparin was associated with a higher live birth incidence in women with APS as compared to women with APS 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.[18,19] However, these results contrast with level 1B evidence from the largest reported prospective RCT from the same centre as the present study, in which treatment with aspirin was compared to treatment with aspirin combined with low-molecular-weight heparin.[11] Only a small, non significant difference in live birth was observed in the group treated with aspirin and heparin as compared to the group who received aspirin alone (78% vs. 72%, OR live birth 1.39, 95%CI 0.55 to 3.47). Age and obstetric history were equally comparable between the study participants of this trial and our study.

Our study has several strengths. First, the large number of women with recurrent miscarriage and APS 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 APS patients with recurrent miscarriage. Third, the diagnosis of APS in all participants was 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 APS 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. Nevertheless, the presence of more known and unknown unfavourable prognostic variables in women who have received heparin is likely to underestimate, not overestimate, the association between treatment and live birth. 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, we used 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 only positive for anti-β2-glycoprotein-1 antibodies. The extension of the time between initial and repeated testing for APS related antibodies from 6 weeks to 12 weeks possibly has attenuated our findings, as we may have included women with assumed APS 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 APS treated with heparin and aspirin is good.

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