The impact of positive acquired thrombophilia serology on ultrasound, obstetric outcome and the placenta in a low-risk primigravid population

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Summary: Our aim was to determine the prevalence and sequelae of positive acquired thrombophilia serology in the asymptomatic low-risk primigravid population. We undertook a prospective blinded study of 1011 primigravid patients screening for lupus anticoagulant, anticardiolipin antibody, anti- β_2 glycoprotein-1 and antinuclear antibody assessment at booking and 36 weeks gestation. Serial ultrasounds of the fetus with uterine and umbilical Dopplers and placental evaluation were performed at 24 and 36 weeks gestation. Antenatal course, labour and delivery outcome and placental histology were reviewed. The incidence of positive acquired thrombophilia serology was 27.4%. Overall, there was no difference in rates of fetal loss or maternal disease between women with positive acquired thrombophilia serology and the control population. Routine testing for acquired thrombophilic traits is therefore not warranted.

Keywords: acquired thrombophilia, primigravid, obstetric outcome, placenta

INTRODUCTION

Antiphospholipid antibodies (APAs) are non-specific antibodies and are present in healthy patients and those with disease.¹ Increased levels of anticardiolipin antibody (ACA) in pregnancy predispose to pregnancy complications; however, the acquisition of APAs *de novo* in pregnancy is of indeterminate significance.^{2,3}

Published outcome data on APAs relate to women with antiphospholipid syndrome (APLS). There are minimal cross-sectional data on ultrasound, outcome and placental histology in women with positive APA tests in the absence of APLS.

Our aim was to ascertain the impact of positive acquired thrombophilia serology in the absence of APLS on antenatal course, ultrasound, labour, delivery, perinatal outcome and placental histology.

METHODS

Study sample and size

Ethical approval was obtained from the Ethics Committee of the Rotunda Hospital with written informed consent from all participants. Sample size was calculated based on detection of the prevalence of acquired thrombophilia.

A number of inclusion and exclusion criteria were agreed upon. All participants were Caucasian primips, aged 15–41

years, with no personal or family history of thrombosis, no chronic medical diseases and booking between 16 and 20 weeks gestation. All investigators were blinded to the serology results until following delivery and following placental analysis.

Procedures and interventions

Anticardiolipin and anti- β_2 GP-1 testing

Orgentec Diagnostika GmbH ORG515 immunometric enzyme immunoassay was performed for the quantitative determination of anticardiolipin immunoglobulin G (IgG) and immunoglobulin M (IgM). A positive ACA test was IgG in excess of 10 U/ml or IgM in excess of 7 U/ml. A positive anti- β_2 glycoprotein-1 test was IgG or IgM in excess of 10 U/ml.

β_2 -glycoprotein I testing involves horseradish peroxidase (HRP) conjugated anti-human IgG and IgM immunologically binding to bound patient antibodies forming a conjugate/antibody/antigen complex in microwells. An enzyme substrate in the presence of bound conjugate hydrolyzes to form a blue colour. The addition of an acid stops the reaction forming a yellow end-product. The intensity of this yellow colour is measured photometrically at 450 nm. The amount of colour is directly proportional to the concentration of antibodies present in the original sample.

Lupus anticoagulant testing

Lupus anticoagulant is diagnosed by using two tests. Test plasmas are identified by the Stago Diagnostika[®] Analyser (STA[®]) Analyser (Diagnostica Stago Incorporated, New Jersey, United States). DVVconfirm was performed if the DVVtest

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was positive. The original dilute Russel Viper Venom Test (dRVVT) showed greater sensitivity toward Lupus anticoagulant (LA) than the activated partial thromboplastin time (aPTT) owing to a reduced phospholipid concentration, and it provided the option to add excess platelets as a confirmatory procedure. Further development of this technique resulted in the single vial of DVVtest and DVVconfirm. The higher phospholipid concentration in DVVconfirm allows for the correction of the prolonged result of the DVVtest if LA is present. The use of a confirmatory reagent provides the means for a diagnosis of LA as phospholipid interfering antibodies. Any DVVtest result that is greater than 46.4 seconds is considered positive.

Antinuclear antibody testing

Antinuclear antibody (ANA) testing involved the addition of 40 µl of a 1/80 diluted sample or control to a human epithelial (Hep-2) cell slide which is then incubated for 25 minutes and sequentially washed with Phosphate Buffered Saline (PBS). All slides are read by two experienced readers. The slides are examined using ultraviolet (UV) light microscopy. Negative results show no fluorescence or a generalized pale green non-specific staining of the cell. Positive results show bright apple-green fluorescence of the cell nucleus with a specific pattern.

Fetal assessment

Fetal growth parameters, umbilical artery Dopplers, uterine artery Dopplers and placental architecture were assessed at 22–24 weeks and 36 weeks gestation. The presence of reduced, absent or reversed end-diastolic flow, and raised resistance and pulsatility indices above the 95th centile for gestation was recorded. A notch was defined as an obvious upward deflection of the uterine artery waveform in the early diastolic phase. The subjective quantity of amniotic fluid present at the time of examination was also recorded.

Placental architecture was assessed ultrasonographically at each of the study ultrasounds. The presence of a low-lying placenta or anomalous cord insertion was recorded.

The presence of placental calcification, lakes and infarcts was noted. Placental length and thickness were measured in the cross-section involving cord insertion. Placental length was measured in linear segments and recorded in millimeters.

We recorded the incidence of Grannum grade 3 on ultrasound at 32–36 weeks.⁴

A placental infarct was defined as an echo-poor lesion with a characteristic halo. The incidence of placental lakes and calcification was recorded.

Outcome measures

Evaluation of antenatal course, labour and delivery

Primary outcome measures comprised the presence of maternal or fetal antenatal complications or disease, operative delivery or perinatal complications. Secondary outcome measures reviewed the impact of positive serology on antenatal ultrasound or placental histology. Infant birthweight was measured in the first 60 minutes of life using standard approved Marsden scales® (Marsden, London, UK), and expressed in kilograms and centiles calculated.⁵

Perinatal morbidity was defined in this study as any baby delivering before 37 weeks gestation, birthweight less than the ninth centile and/or admission to the neonatal unit.⁶

The antenatal course, labour and delivery outcome variables were analysed separately for each of our test cohorts.

Placental histology

The placenta was weighed on the delivery suite and the weight recorded to the nearest 5 g. The specimen was temporarily stored at 4°C, prior to transfer to the laboratory. Microbiological sampling was performed as clinically indicated, and the specimen was then placed in 10% buffered formalin for 24 hours fixation and examined according to the standard method as prescribed by Fox.⁷

Statistical analysis

Data analysis was undertaken using the Statistical Package for the Social Sciences (SPSS), Version 15.0 (SPSS Incorporated, Chicago, Illinois, United States). Frequencies, ranges and means were utilized to describe the findings. chi-squared analysis was employed to compare proportions. The comparison of means between groups was carried out using *t*-tests and *f*-tests as appropriate. The Mann-Whitney and Kruskal-Wallis tests were used in place of the *t*-test and *f*-test, respectively, for non-parametric variables.

The sample size was determined allowing for the detection of the prevalence of acquired thrombophilia of 7.5% with an 80% power and at a 5% significance level.

RESULTS

All eligible participants attending the hospital during the study period (15 April 2003 to 19 May 2004) were approached. The recruitment rate was 90% (*n* = 1011). Complete data pertaining to serology, ultrasound, antenatal course, labour, delivery and placental histology were available for 810 women (80%). Table 1 lists the serology results for the cohort. A total of 588 women had negative acquired thrombophilia tests and were our control population for this analysis.

Ultrasound results are produced in tabular form in Table 2. The maternal age range was 15.6–40.4 years with a mean maternal age of 26.3 years. Table 3 outlines the incidence and indication for emergency room review for the groups. The labour, delivery and perinatal outcome are outlined in Table 4. Table 5 lists the placental histology findings for the groups.

The mean gestation at delivery was not significantly different in any of the test groups with a mean gestation at delivery of 39.6 weeks (range 25.2 to 42.0 weeks) for the control population and a mean of 39.4 weeks (range 27.0 to 41.7 weeks) in those patients with negative acquired thrombophilia or ANA serology.

Table 1 Serology subgroups (*n* = 810)

Test groups		Study groups (<i>n</i> = 810)	
		No.	%
Control	Acquired thrombophilia and ANA negative	588	72.6
1	Acquired thrombophilia test positive	222	27.4
2	ACA and anti-β ₂ GP-1	57	7.0
3	Lupus anticoagulant positive	102	12.6
4	Antinuclear antibody positive	63	7.8

ACA = anticardiolipin antibody; GP-1 = glycoprotein-1

Table 2 Doppler studies and placental findings at the second and third trimester scan ($n = 810$)

Study ultrasound	Control		ACA or Anti- β_2 GP-1 positive				LA positive				ANA positive			
	First	Second	First	P	Second	P	First	P	Second	P	First	P	Second	P
Umbilical artery (Mean (SD))	1.32 (0.2)	1.04 (0.23)	1.29 (0.28)	0.108	0.98 (0.23)	0.42	1.37 (0.24)	0.52	1.06 (0.26)	0.47	1.23 (0.21)	0.68	0.96 (0.19)	0.21
PI > 2 SD (%)	2.7	2.8	1.7	0.50	1.7	0.50	1.2	0.53	4.8	0.41	3.7	0.41	0	0.44
Right uterine artery														
PI > 2 SD (%)	4.6	4.8	0	0.81	7.0	0.71	6.0	0.59	7.2	0.43	0	0.55	11.1	0.29
RI > 2 SD (%)	2.8	4.1	0	0.69	2.6	0.48	4.8	0.33	3.6	0.31	0	0.54	3.7	0.55
Left uterine artery														
PI > 2 SD (%)	4.3	4.9	6.5	0.21	7.0	0.28	3.6	0.35	3.6	0.62	0	0.11	7.4	0.12
RI > 2 SD (%)	3.0	3.6	3.2	0.55	2.1	0.88	1.2	0.51	2.4	0.52	0	0.19	7.4	0.25
Unilateral notch (%)	3.1	1.9	3.2	0.80	1.8	0.77	4.7	0.23	4.8	0.10	0	0.50	3.7	0.55
Bilateral notches (%)	0.1	0	0	0.89	0	0.90	0	0.77	0	0.77	0	0.85	0	0.82
Decreased liquor volume (%)	0.1	0.3	0	0.70	0	0.65	0	0.60	0	0.61	0	0.74	0	0.72
Placenta low-lying	12.5	1	3.3	0.12	0	0.10	10.7	0.75	1.2	0.58	11.1	0.41	3.7	0.32
Central cord insertion	95.9	98.4	96.7	0.80	98.2	0.85	95.2	0.79	98.8	0.75	100.0	0.45	95.7	0.60
Placental infarcts	2.2	22.5	0	0.52	20.0	0.54	0	0.60	31.0	0.03*	0	0.73	26.1	0.60
Placental lakes	6.2	3.2	12.9	0.20	1.8	0.51	5.9	0.23	7.1	0.56	11.1	0.25	3.7	0.88
Placental calcification	1.5	0.7	0	0.90	0	0.95	0	0.85	0	0.80	0	0.94	0	0.80
Grannum grade 3	NA	12.0	NA	NA	9.4	0.76	NA	NA	15.7	0.61	NA	NA	3.7	0.14
Mean placental length (cm) (SD)	14.5 (2.3)	16.6 (3.0)	13.5 (4.2)	0.25	15.8 (4.8)	0.53	14.7 (2.2)	0.55	16.0 (2.5)	0.54	14.5 (2.8)	0.43	16.9 (3.7)	0.41
Mean placental thickness (cm) (SD)	3.1 (0.9)	4.3 (1.4)	2.9 (1.1)	0.84	4.1 (1.7)	0.74	2.8 (0.7)	0.72	4.4 (1.3)	0.66	3.2 (0.9)	0.61	4.2 (1.3)	0.55

ACA = anticardiolipin antibody; GP-1 = glycoprotein-1; LA = lupus anticoagulant; ANA = antinuclear antibody; PI = pulsatility index; RI = resistance index; SD = standard deviation; * = statistically significant $p < 0.05$

Group 1. ACA, anti- β_2 GP-1 antibody, lupus anticoagulant or antinuclear antibody-positive participants

In all, 27.4% ($n = 222$) of our low-risk study population had one or more positive ACA, anti- β_2 glycoprotein-1 (GP-1), lupus anticoagulant (LA) or antinuclear antibody (ANA). A higher diastolic BP was observed in Group 1 at the time of the first study ultrasound when compared to the control thrombophilia test negative population (68.8 mm Hg versus 66.8 mm Hg; $P = 0.002$); however, there was no statistically significant difference in the incidence of hypertensive disease.

A higher incidence of placental infarction that was noted on ultrasound was also identified in this group, when compared with those patients with negative thrombophilia serology

with higher rates of histological placental infarction also (26.4% versus 19.7%; $P = 0.026$).

Women with positive acquired thrombophilia serology had higher rates of emergency room review (44.8% versus 29.0%; $P = 0.001$) and a statistically higher incidence of vaginal bleeding in the first trimester (20.7% versus 9.9%; $P = 0.001$) when compared to those women with negative thrombophilia serology.

Group 2: ACA or anti- β_2 GP-1 antibody test positive participants

Seven percent ($n = 57$) of our study population were positive for either ACA, or anti- β_2 GP-1 antibody. Significantly more

Table 3 Antenatal complications and emergency room review ($n = 810$)

	Control		ACA or Anti- β_2 GP-1 positive			LA positive			ANA positive		
	No.	%	No.	%	P	No.	%	P	No.	%	P
Emergency room review	263	32.5	19	33.3	0.81	46	44.7	0.10	30	47.6	0.62
Antenatal admission	110	13.6	9	15.8	0.54	16	15.3	0.12	8	13.3	0.64
Pregnancy complications											
Vaginal bleeding (first trimester)	77	9.5	6	10.5	0.51	26	25.4	0.02*	14	1.7	0.54
Vaginal bleeding (second trimester)	27	3.3	0	0	0.91	4	4.2	0.29	5	8.7	0.44
Antepartum haemorrhage	41	5.1	1	1.7	0.85	7	7.1	0.36	3	4.3	0.60
Abruption	6	0.7	0	0	0.82	0	0	0.79	0	0	0.61
Maternal disease											
Diabetes	6	0.7	1	1.7	0.25	1	1.4	0.51	4	6.4	0.53
Pregnancy-induced hypertension	17	2.1	2	3.4	0.21	1	1.4	0.21	3	4.3	0.90
Preeclampsia	26	3.2	3	5.1	0.33	8	7.5	0.11	3	4.3	0.77
Fetal complications											
Threatened preterm labour	9	1.1	1	1.7	0.59	0	0	0.77	0	0	0.75
Fetal growth restriction	8	1	1	1.7	0.66	2	2.8	0.45	0	0	0.81
Abnormal biophysical profile	10	1.2	1	1.7	0.71	1	1.4	0.50	0	0	0.81
Preterm rupture of membranes	12	1.5	1	1.7	0.64	0	0	0.54	0	0	0.83

ACA = anticardiolipin antibody; GP-1 = glycoprotein-1; LA = lupus anticoagulant; ANA = antinuclear antibody; * = statistically significant $p < 0.05$

Table 4 Labour and delivery variables ($n = 810$)

	Control %	ACA or Anti- β_2 GP-1 positive %	<i>P</i>	LA positive %	<i>P</i>	ANA positive %	<i>P</i>
Pre-labour emergency caesarean section	1.1	2.0	0.23	0	0.45	0	0.48
Reason for induction /planned caesarean section							
Fetal reason	19.2	5.2	0.11	7.1	0.21	0	0.09
Maternal reason	22.4	1.7	0.20	8.2	0.11	14.8	0.56
Mode of delivery							
Emergency caesarean section	22.8	33.3	0.56	28.2	0.56	40.1	0.44
Perinatal outcome							
Second trimester fetal loss	0.7	0	0.92	0	0.88	0	0.82
Preterm delivery <37 weeks	5.9	10.5	0.58	1.2	0.26	7.4	0.29
Preterm delivery < 28 weeks	0.6	1.7	0.61	24.7	0.12	0	0.23
Birthweight $\leq$ 9th centile	19.3	19.3	0.88	5.9	0.90	18.5	0.55
Birthweight $\leq$ 2nd centile	4.2	28.6	0.00*	0	0.77	7.4	0.84
Intrauterine growth restriction	1.0	1.7	0.45	2.4	0.59	0	0.55
NICU admission rate	4.5	7.3	0.26	5.1	0.69	7.4	0.79

ACA = anticardiolipin antibody; GP-1 = glycoprotein-1; LA = lupus anticoagulant; ANA = antinuclear antibody; NICU = neonatal intensive care unit; * = statistically significant $p < 0.05$

infants were born with birthweights less than the second centile in this group (28.6% versus 4.2%; $P = 0.003$). No other perinatal parameters were significantly affected. A statistically higher incidence of placental infarction was also identified in this group (35.5% versus 19.7%; $P = 0.041$).

Group 3: Lupus anticoagulant-positive participants

Positive LA tests occurred in 12.6% ($n = 102$). Positive lupus serology was associated with statistically higher rates of vaginal bleeding in the first trimester (25.4% versus 9.5%; $P = 0.02$). Estimated blood loss at delivery was also statistically higher in Group 3 (405 mL versus 274 mL; $P = 0.009$), despite similar operative delivery and assisted delivery rates between the control and test populations. A statistically higher incidence of placental

infarction on ultrasound in the third trimester was also seen in the LA test positive group (31.0% versus 22.5%; $P = 0.03$).

Group 4: ANA-positive participants

In all, 7.7% ($n = 63$) of our study population were positive for ANA. Overall, there were no statistically significant differences in primary or secondary outcome measures in Group 4. However, women with positive ANA serology had statistically higher rates of mild villous dysmaturity (50.0% versus 27.8%; $P = 0.006$), and yet the overall rate of dysmaturity in this group was not statistically different from control.

DISCUSSION

Acquired thrombophilic traits have been implicated in the pathogenesis of a range of adverse pregnancy outcomes including early pregnancy loss, fetal death, antepartum haemorrhage (APH), intrauterine growth restriction (IUGR), pre-eclampsia (PET) and venous thromboembolism (VTE).^{8,9} The risk of thromboembolism among APA-positive patients is highly variable, with the incidence in pregnancy between 5% and 24%.^{9,10}

However, APAs may also be found in normal asymptomatic individuals. We found an overall incidence of positive acquired thrombophilia serology of 27.4%, with the largest contribution being those women with a single positive LA test.

The majority of the current data in the literature refer to multiparous women with APLS.^{11,12} Our study was restricted to the healthy primiparous population.

In our study, a statistically higher incidence of placental infarction was identified antenatally by ultrasound in those women with positive acquired thrombophilia serology. This was confirmed by histological examination of the placenta in the early postnatal period. Vasculopathy of the placental and maternal vasculature is assumed to be the key pathogenic step in many of the disorders associated with APAs.

Placental infarcts are a common histopathological finding. They are one of a spectrum of placental features proven to result from maternal hypoperfusion of the placenta.¹³ Thrombophilia is known to produce an array of placental lesions.¹⁴ However, in our study the presence of placental disease did not impact significantly on overall rates of maternal or fetal disease. This may reflect our sample size and requires further study.

Table 5 Placental histology for the study ($n = 810$)

	Control %	ACA or Anti- β_2 GP-1 positive %	<i>P</i>	LA positive %	<i>P</i>	ANA positive %	<i>P</i>
Placental weight (kg) (SD)	0.609 (0.134)	0.601(0.115)	0.44	0.607(0.140)	0.45	0.650(0.128)	0.52
Normal villi	57.7	63.2	0.56	60.0	0.56	63.0	0.88
CUPI	11.2	10.5	0.74	9.4	0.48	22.2	0.41
Villous dysmaturity	27.8	24.6	0.82	27.1	0.57	11.1	0.26
Vascular features							
Retroplacental haemorrhage	2.6	7.0	0.26	1.2	0.21	0	0.88
Infarction	19.7	35.5	0.04*	24.7	0.26	22.2	0.53
Intervillous thrombus	8.8	14.0	0.59	3.5	0.18	14.8	0.91
Features of infection							
Ascending infection	26.5	21.1	0.69	21.2	0.89	33.3	0.41
Chorioamnionitis	2.0	1.8	0.57	2.4	0.62	7.4	0.33
Villitis	3.5	1.8	0.63	3.5	0.55	3.7	0.58

ACA = anticardiolipin antibody; LA = lupus anticoagulant; ANA = antinuclear antibody; CUPI = chronic uteroplacental insufficiency; SD = standard deviation; * = statistically significant $p < 0.05$

The incidence of preeclampsia in our study is lower than rates reported in other studies.¹⁵ This may reflect our low risk population.

The overall risk of spontaneous miscarriage after 15 weeks is estimated at 0.6% and all women with second trimester losses in our study were negative for acquired thrombophilia.

The association between acquired thrombophilia and IUGR is controversial. One small prospective study by Polzin *et al.*¹² in 1991 demonstrated the presence of APAs in 27% of cases with IUGR. The high prevalence of ACA in this population suggested a significant association between the presence of circulating maternal ACAs and fetal growth restriction.

We found no difference in the antenatal detection rates of small for gestational age (SGA) in our control and test populations. Women with positive ACA or Anti- β_2 GP-1 antibody tests had a statistically higher incidence of infants born with birthweight less than the second centile.

Abruptio occurs in 0.4–1% of all pregnancies, and may result in intrauterine death (IUD). However, all cases of abruptio and perinatal death in our study had negative acquired thrombophilia tests.

Preterm birth was included in our analysis as abruptio, IUGR and PET are known contributing factors to both idiopathic and iatrogenic preterm birth (PTB). No difference in PTB rates was identified between the test and control populations.

In this study ANA was associated with a statistically higher incidence of mild villous dysmaturity. Villous dysmaturity accounts for intrauterine death in three in 1000 pregnancies. As yet, there are no means available to us to detect villous dysmaturity antenatally, and it may recur in subsequent pregnancies.¹⁶ Mild villous dysmaturity was evident in this group which is of dubious clinical significance.

Uterine and umbilical artery indices have been shown to be higher in the presence of acquired thrombophilia. Studies suggest that the presence of multiple prothrombotic factors further increase arterial indices.¹⁷ In high-risk pregnancies, uterine artery Doppler at 22–24 weeks has been shown to be a useful screening test in predicting the pathogenesis of PET and IUGR. We found no association between prothrombotic substances and the development of PET or IUGR in this population.

We therefore conclude that routine antenatal screening for acquired thrombophilia or ANA of the low-risk primigravid population is not warranted. While the overall incidence of acquired thrombophilia or ANA in our low-risk cohort was 27.4%, this did not translate into a higher overall incidence of maternal complications antenatally, during labour or problems for the infant in the immediate neonatal period. This may reflect the sample size.

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