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AMONG PREGNANT WOMEN IN SOUTHWESTERN NIGERIA**

PREVALENCE AND CLINICAL CORRELATES OF ANTIPHOSPHOLIPID SYNDROME AMONG PREGNANT WOMEN IN SOUTHWESTERN NIGERIA

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ABSTRACT

Introduction: This study aimed to utilize triple auto-antibodies to determine the prevalence of antiphospholipid syndrome (APS) among pregnant women in Ogbomosho, Oyo State, Nigeria.

Methods: The longitudinal descriptive study involved a hundred and sixty pregnant women with pregnancy complications and control. Participants were tested for APS by assaying Anti β 2, ACA and LAC at first contact and for persistent positivity after twelve weeks using the ELISA method with blood specimens. Data were analyzed using SPSS version 21.

Results: The prevalence of persistent positivity to anti-phospholipid antibodies in this study is 28.8% and 2.5% among the subjects and control respectively. Persistent positivity to ACA was observed in 26.3%, β 2-GP1 in 21.1% and LAC in 16.8% of participants in the study group and 2.5%, 1.3% and 2.5% in the control group. Persistent positivity to anti-phospholipid antibodies was associated with hypertension and recurrent miscarriage (≥ 3).

Conclusion: Hypertension and recurrent miscarriage are associated with APS among pregnant women in this study area. Triple auto-antibodies are suggested as routine

pregnancy tests among pregnant women with previous history of these complications.

Keywords: Antiphospholipid syndrome, pregnancy, Ogbomosho, Nigeria

INTRODUCTION

Antiphospholipid Syndrome (APS) is an autoimmune disease characterized by clinical thrombotic events which may be arterial or venous-vasculature associated with the presence of antiphospholipid antibodies in the individual's plasma.^{1,2} It was first described as an acquired thrombophilic disorder in which autoantibodies are produced by a variety of phospholipids and phospholipid-binding proteins.^{3,4} The core features associated with this syndrome include arterial and venous thromboses, recurrent spontaneous miscarriages, preeclampsia, intra-uterine growth restriction (IUGR), thrombocytopenia and the presence of high titers of antiphospholipid antibodies (aPLs) in the blood of the subjects.⁵

The precise mechanism whereby haemostasis is altered to induce a hypercoagulable state in APS is unclear and several mechanisms are responsible for clinical manifestations in

patients with this syndrome.^{6,7} In young healthy subjects, the prevalence for both primary and secondary APS is about 1% to 5%.^{8,9} The prevalence increases with age and obstetric complications are believed to result from different mechanisms acting on the placental cells and the endometrial tissues. Thrombosis, inflammation and immunomodulation are also thought to play a role.^{10,11} The antiphospholipids implicated include anticardiolipin, beta2 glycoprotein and lupus anticoagulant, but there are also clinical conditions with sero-negativity for them.¹²

Like other autoimmune disorders, APS does not have a known etiology; however, several hypotheses explain the probable cause: these include the passive transfer of maternal autoantibodies to the fetus, and familial occurrence of antiphospholipid with a genetic association like HLA-DR4, DR7, DRw53 and C4 null allele.^{3,13}

The Clinical spectrum ranges from no symptom to imminent life-threatening, catastrophic APS (CAPS). It is more common in women than men and its diagnosis is made with the presence of at least one of the clinical criteria and of the laboratory criteria using revised Sidney classification criteria for (APS).^{14,15} APS occurs in isolation as a primary APS in more than 50% of the cases, but may be associated with other autoimmune diseases, most often with systemic lupus erythematosus (SLE).⁵ Twenty to 35% of women with SLE develop APS and it occurs mostly in young women of reproductive age.¹⁶ It occurs rarely in children and only 12% of all APS occur after 50 years of age.¹⁷ The study of triple antibodies in this environment therefore will help in identifying symptomatic and asymptomatic patients who could later

develop one or more complications during late pregnancy.

Antiphospholipid syndrome is an acquired systemic autoimmune disease that is sometimes overlooked.¹⁸ The most commonly detected antiphospholipid antibodies are lupus anticoagulant (LAC), anticardiolipin (ACA) and anti-beta 2 GPI (β 2-GPI) antibodies which are detected by immunoassays that measure the immunogenic reactivity to a phospholipid or a phospholipid-binding protein. The prevalence and isotype distribution of all the antibodies in different populations of patients with APS occur with high variability and IgG isotype is associated with about 2.4 fold increase in developing pregnancy morbidity.^{3,19} Several multicenter studies in other parts of the world had shown that prevention with prophylactic anticoagulant in patients with persistent positivity to triple antiphospholipid antibodies reduces the risk of pregnancy complication by about 50%.²⁰

Therefore, due to the paucity of reports in this study area, this study utilized triple auto-antibodies to determine the prevalence of antiphospholipid syndrome among pregnant women in LAUTECH Teaching Hospital, Ogbomoso, Nigeria.

MATERIALS AND METHODS

Study Area

This study was carried out at LAUTECH Teaching Hospital, Ogbomoso, in March 2005. Ogbomoso is located on Latitude 8° 08' 00" East and Longitude 4° 16' 00" North of the Equator. It is the second largest city in Oyo State with a population of 645,000 in 1991.

Study Population

This study was conducted in 2016 on pregnant women who attended the Booking

Clinic, Antenatal Clinic, and Gynaecological Emergency Unit and whose pregnancies have been confirmed by serum human chorionic gonadotropin assay or by ultrasonography with a past history of at least two consecutive spontaneous abortions, past history of previous unexplained intrauterine fetal death, history of previous preterm delivery and hypertension in pregnancy after obtaining informed consents. The same number of controls without a history of pregnancy complications and who did not have any autoimmune or medical disease, history of thromboembolism, and having at least one live birth were recruited. The cases and controls were matched for age.

Study Design

This was a longitudinal descriptive study.

Sample Size

The sample size was calculated based on the prevalence of APS in Nigeria which is 5% using Fisher's formula.[Click or tap here to enter text.](#)^{21,22} Therefore, for the purpose of this study a sample size of 80 was considered for subjects and 80 healthy pregnant women were recruited as control.

Sampling Method

Eighty eligible consented pregnant women were consecutively recruited from the Booking Clinic, Antenatal Clinic, Gynaecological Emergency Unit and Labour Ward of the hospital with eighty age-matched eligible and consented healthy pregnant women as controls. Written informed consent was obtained from each participant.

Research Instrument

A modified semi-structured questionnaire of the Medical Research Council/Royal College of Obstetricians and Gynecologists was used. Other information obtained included socio-demographic characteristics, pregnancy history, risk factor for antiphospholipid syndrome, previous pregnancy history and previous history of complications in pregnancy.

Sample Collection

10mls of venous blood sample was collected from each participant on two occasions (12 weeks interval) into trisodium citrate plain specimen bottle. Serum was extracted and stored at -20°C till analysis. IgG Anti-cardiolipin, IgM Anti-cardiolipin, IgG Anti-beta 2glycoprotein, IgM Anti-beta 2glycoprotein, and Lupus Anticoagulant were assayed with the respective ELISA Kits using Labtech LT-4000 microplate Reader.

Statistical Analysis

The data obtained were analyzed using Statistical Package for Social Sciences (SPSS) version 21.0. Frequency distribution tables and/or charts were generated from variables. Level of significance was set at p-value less than or equal to 0.05. Binary logistic regression model was used to examine the effect of clinical factor on the distribution and levels of the antibodies.

Ethical Considerations

Ethical clearance for the study was obtained from the Ethical Review Committee of LAUTECH Teaching Hospital, Ogbomoso.

RESULTS

As detailed in Table 1, participants were aged between 30-34 years (mean = 29.7 ± 5.2). 62(77.5%) of the study group were Christians and all were married. More than two-thirds were of the Yoruba tribe with tertiary level of education.

The obstetric history of the participants is set out in Table 2: The minimum gestational period of participants in the study group was 15 weeks and the maximum 30 weeks. The mean gestational age of participants was statistically higher in subject (mean = 22.7 ± 4.7), compared to the control group (mean = 19.86 ± 5.1), $t = 3.605$, $p\text{-value} = 0.001$. Forty (52.6%) of the participants in the study group had at least one child alive and 7(9.2%) had at least a premature birth.

36(45%) of the participants in the study group had one to two miscarriages.

The Anthropometric measurements and clinical parameters of the subjects are in Table 3. More than one-third (37.5%) of participants in the study group had at least a systolic blood pressure of ≥ 140 mmHg and blood pressure was associated with the group ($\chi^2 = 36.9$, p-value = 0.001). Also, there was

a statistically significant difference in the mean systolic blood pressure of participants between the study group (mean = 130.9 ± 30.2) and the control group (mean = 109.5 ± 10.5). Thirty-three participants (41.2%) had their diastolic BP ≥ 90 mmHg. None of the participants in the control group was hypertensive while the prevalence of hypertension in the study group was 41.2%.

Table 1: Socio-demographic profile of participants (*p-value <0.05 indicates significance, χ^2 = chi-square)

CHARACTERISTICS	CONTROL	STUDY	Test statistic	p-value
Age groups				
15-19 years	7 (8.7)	5 (6.3)		
20-24 years	20 (25)	19 (23.8)		
25-29 years	14 (17.5)	17 (21.3)		
30-34 years	22 (27.5)	21 (26.3)	$\chi^2 = 1.473$	0.916
35-39 years	11 (13.8)	9 (11.3)		
40-44 years	6 (7.5)	9 (11.3)		
Mean age \pm SD	29.7 ± 5.2	29.9 ± 4.9	t-statistic=-0.25	0.803
Religion				
Islam	29 (36.2)	17 (21.2)	5.76	0.124
Christianity	51 (63.8)	62 (77.5)		
Traditional	-	1 (1.2)		
Marital Status				
Married	77 (96.2)	80 (100)	3.057	0.08
Single Mother	3 (3.8)	-		
Years of Marriage				
1- 5 years	55 (68.8)	58 (72.5)		
6- 10 years	24 (30)	17 (21.1)	4.075	0.254
11 – 15 years	1 (1.2)	4 (5)		
Above 15 years	-	1 (1.2)		
Ethnic group				
Yoruba	75 (93.8)	74 (92.5)		
Igbo	2 (2.5)	5 (6.2)	2.292	0.318
Hausa	-	-		
Others	3 (3.8)	1 (1.2)		
Highest level of education				
Primary	3 (3.8)	1 (1.2)		
Secondary	28 (35)	12 (15)	10.194	*0.017
Post-Secondary	3 (3.8)	4 (5)		
Tertiary	46 (57.5)	63 (78.8)		
Occupation				
Civil Servant	30 (37.5)	51 (63.8)		
Trading	22 (27.5)	14 (17.5)	26.617	*0.001
Artisan	20 (25)	1 (1.2)		
Student	8 (10)	14 (17.5)		

Table 2: Obstetric history of participants

VARIABLES	Study group n = 80	Control group n = 80	Test statistic	p-value
Gestational Age				
Minimum	13	13		
Maximum	30	29		
Mean \pm SD	22.65 \pm 4.67	20.25 \pm 4.48	t = 3.318	*0.001
Miscarriages				
0	28 (35.0)	0 (0.0)		
1 - 2	36 (45.0)	0 (0.0)	NA	NA
≥ 3	14 (17.5)	0 (0.0)		
Foetal death				
Yes	2 (2.5)	0	NA	NA
No	78 (97.5)	80 (100)		
Past history of fetal growth retardation				
Yes	1 (1.2)	0 (0)	NA	NA
No	79 (98.8)	80 (100)		
Premature Birth				
≥ 1	7 (9.2)	0 (0)	NA	NA
Eclampsia or pre-eclampsia during pregnancy				
Yes	4 (5)	0 (0)	NA	NA
No	76 (75)	80 (100)		
Number of children full term				
≥ 1	40 (52.6)	37 (46.2)	NA	NA

*p-value < 0.05 indicates significance, NA = Not applicable

Table 3: Anthropometric measurements and clinical parameters. (*p-value < 0.05 indicates significance)

VARIABLES	n (%)	Study group n = 80	Control group n = 80	Test statistics	p-value
Height (meters)					
Mean \pm SD		1.60 \pm 0.6	1.61 \pm 0.6	t = -1.220	0.224
Weight (Kg)					
Mean \pm SD		70.32 \pm 11.5	65.63 \pm 12.51	t = 2.467	*0.015
Systolic BP (mmHg)					
<140	50 (62.5)		80 (100)	X ² = 36.9	*0.001
≥ 140	30 (37.5)		0 (0.0)		
Mean \pm SD		130.9 \pm 30.2	109.5 \pm 10.5	t = 5.982	*0.001
Diastolic BP (mmHg)					
<90	47 (58.8)		80 (100)	X ² = 41.6	*0.001
≥ 90	33 (41.2)		0 (0.0)		
Mean \pm SD		82.9 \pm 19.2	68.9 \pm 7.4	t = 6.101	*0.001
Hypertension status of participants					
Hypertensive	33 (41.2)		0 (0.0)	41.6	*0.001
Non-Hypertensive.	47 (58.8)		80 (100)		

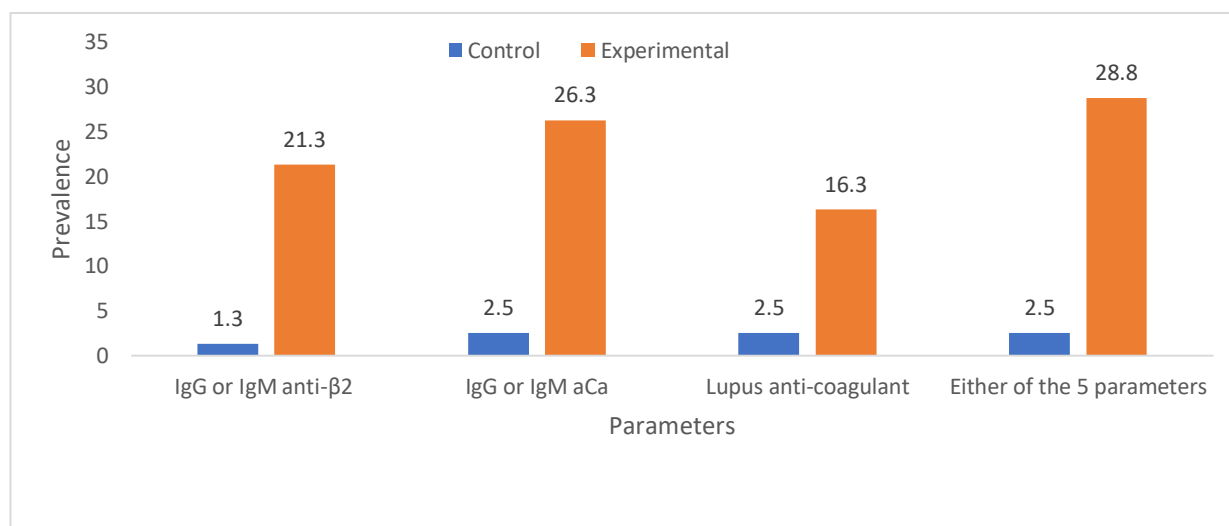


Figure 1: Prevalence of persistent positivity to all measured antiphospholipids

The prevalence of persistent positivity to all the measured antiphospholipids is set out in figure 1; Twenty-one (26.3%) the study group were persistently positive to at least one of anti-cardiolipins (IgM or IgG anti-cardiolipins) compared to 2.5% in the control group. Seventeen (21.3%) of the participants in the study group were persistently positive to at least one of beta 2 glycoprotein (IgG or IgM beta 2 glycoprotein) with only 1 (1.3%) among the controls, while 13 (16.3%) were persistently positive to lupus anti-coagulant compared to 2.5% in the controls. In general, the overall prevalence of the study group to anti-phospholipid antibodies was 28.8% and 2.5% in the healthy control group.

Table 4 gives the correlation between anti-phospholipid antibodies and miscarriage in study subjects. 60% of participants positive to IgG beta-2 glycoprotein had experienced at least 3 miscarriages. Of the total 12 participants who were positive to IgM beta 2 glycoprotein, 41.7% had experienced at least 3 miscarriages. Of the total of 14 participants positive to IgG anti-cardiolipins, 3 (21.4%) had experienced at least 3 miscarriages. 52.9% of participants positive to IgM anti-cardiolipins had experienced at least 3 miscarriages. A total of 13 participants were

found to be positive to Lupus anti-coagulant, of which 23.1% had experienced at least 3 miscarriages.

The status of participants to IgG anti-cardiolipins ($X^2 = 0.180$, p-value = 0.670, OR = 1.36, 95% CI for OR: 0.33 - 5.71), and Lupus anti-coagulant ($X^2 = 0.334$, p-value = 0.563, OR: 1.53, 95% CI for OR: 0.36 - 6.47) were not associated with occurrence of miscarriages (≥ 3) at 95% confidence level. The status of participants to each of IgG beta 2 glycoprotein ($X^2 = 14.289$, p-value < 0.001, OR: 11.25, 95% CI for OR: 2.6 - 48.66), IgM beta 2 glycoprotein ($X^2 = 5.711$, p-value = 0.017, OR: 4.68, 95% CI for OR: 1.22 - 17.97), and IgM anti-cardiolipins ($X^2 = 18.781$, p-value < 0.001, OR: 13.05, 95% CI for OR: 3.49 - 48.84) were associated with occurrence of miscarriages (≥ 3).

Of the total 10 participants positive to IgG beta 2 glycoprotein, 40% were hypertensive, 83.3% of participants positive to IgM beta 2 glycoprotein were hypertensive. 71.4% of participants positive to IgG anti-cardiolipins were hypertensive while 52.9% of participants positive to IgM anti-cardiolipins had hypertension, and 61.5% participants who were positive to lupus anti-coagulant

were hypertensive. The persistent positivity of participants to each of IgM beta2 glycoprotein ($X^2 = 8.37$, p -value = 0.003, OR: 9.78, 95% CI for Odds ratio: 1.98 –

48.41) and IgG anti-cardiolipins ($X^2 = 4.95$, p -value = 0.025, OR: 4.67, 95% CI for Odds ratio: 1.32 – 16.65) were associated with hypertension (table 5).

Table 4: correlation between Anti-phospholipids antibodies and miscarriage in study subjects

Biochemical parameters	Miscarriages n (%)		Test statistic	p-value	Odds ratio	95% CI for odds ratio
	Less than 3	At least 3				
IgG beta 2 glycoprotein						
Positive	4 (40)	6 (60)	$X^2 = 14.289$	* <0.001	11.25	2.60 – 48.66
Negative	60 (88.6)	8 (11.4)				
IgM beta 2 glycoprotein						
Positive	7 (58.3)	5 (41.7)	$X^2 = 5.711$	*0.017	4.68	1.22 – 17.97
Negative	59 (86.8)	9 (13.2)				
IgG anti-cardiolipins						
Positive	11 (78.6)	3 (21.4)	$X^2 = 0.181$	0.670	1.36	0.33 – 5.71
Negative	55 (83.3)	11 (16.7)				
IgM anti-cardiolipins						
Positive	8 (47.1)	9 (52.9)	$X^2 = 18.781$	* <0.001	13.05	3.49 – 48.84
Negative	58 (92.1)	5 (7.9)				
Lupus anti-coagulant						
Positive	10 (76.9)	3 (23.1)	$X^2 = 0.334$	0.563	1.53	0.36 – 6.47
Negative	56 (83.6)	11 (16.4)				

* p -value < 0.05 indicates significance

Table 5: Correlations between Anti-phospholipids and hypertension in the study group (*significant; $p < 0.05$)

Biochemical parameters	Hypertension n (%)		Test statistic	p-value	Odds ratio	95% CI for Odds ratio
	Hypertensive	Not hypertensive				
IgG beta 2 glycoprotein						
Positive	4 (40.0)	6 (60.0)	$X^2 = 0.007$	0.932	0.94	0.29 -3.10
Negative	29 (41.4)	41 (58.6)				
IgM beta 2 glycoprotein						
Positive	10 (83.3)	2 (16.7)	$X^2 = 8.37$	*0.003	9.78	1.98 – 48.41
Negative	23 (33.8)	45 (66.2)				
IgG anti-cardiolipins						
Positive	10 (71.4)	4 (28.6)	$X^2 = 4.95$	*0.025	4.67	1.32 – 16.65
Negative	23 (34.8)	43 (65.2)				
IgM anti-cardiolipins						
Positive	9 (52.9)	8 (47.1)	$X^2 = 1.218$	0.270	1.83	0.62 – 5.38
Negative	24 (38.1)	39 (61.9)				
Lupus anti-coagulant						
Positive	8 (61.5)	5 (38.5)	$X^2 = 2.636$	0.104	2.69	0.79 – 9.12
Negative	25 (37.3)	42 (62.7)				

DISCUSSION

Early pregnancy is faced with many symptoms associated with physiological, physical and psychological disturbances. This could be a result of hormonal changes which affect various organs of the body; the fetus might also be lost which could lead to frustration without any clue as to the cause of the problem.

Persistent positivity to auto-antibodies to phospholipids and phospholipids binding protein was significantly higher in the study than in the control group. This is not unexpected as the clinical factors such as hypertension and miscarriages which are the predisposing factors to the occurrence of an anti-phospholipid syndrome (APS) were evident only among participants in the study group. Previous studies have shown an association between APA and other medical conditions such as hypertension and pre-eclampsia.^{21,23} However, this was in contrast to other reports where no association was found with any clinical pathology.^{21,24}

In this study, the prevalence of APS among pregnant women with one or more complications such as hypertension, and recurrent pregnancy loss was 28.8% compared to 2.5% among healthy pregnant women in the control group.

This finding is higher compared with the study done in Benin City Nigeria among women with preeclampsia in which a prevalence of 10.0% was found in the study group and 0% among apparently healthy pregnant women controls.¹⁴ The prevalence in this study is also higher compared with the study done in Lagos by Akinbami *et al* who reported a prevalence of 2.3% using IgG ACA.²⁵ It is also higher compared to the study done by Awodu *et al* who reported a

prevalence of 15.4% using KCT coagulation assay for Lupus antibodies.¹

However, the prevalence of APLS found in this study is consistent with findings among women with unexplained recurrent abortion in Wad Medani Obstetrics and Gynaecological Teaching Hospital, Gezira where a prevalence of 26% was reported.¹⁸ The disparity in prevalence between this study and most studies done in the country could be attributed to the fact that this study utilized triple auto-antibodies to detect the occurrence of the anti-phospholipids syndrome as opposed to single auto-antibodies used in other studies.

Several retrospective and prospective studies have also shown that triple aPL positivity (i.e aCL, anti β 2-GP1 and LA positivity) correlates more strongly with both thrombosis and pregnancy morbidity than the presence of single or double positivity.^{26,27}

CONCLUSION

This study has shown that the prevalence of antiphospholipid syndrome among pregnant women with previous pregnancy complications such as recurrent fetal wastage, IUGR, premature birth and those with complications such as hypertension in the index pregnancy in LAUTECH Teaching Hospital Ogbomoso is relatively high. It is worthy of note that the majority of the participants would have been missed using either single or double antibodies. Therefore, this study has demonstrated that using LAC, IgG ACA, IgM ACA, IgG anti- β 2GP1, IgM anti- β 2GP1 will help in identifying many asymptomatic patients that will benefit from early prophylactic treatment and proper monitoring for good pregnancy outcome in the future.

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Conflicts of Interests

The authors declared no conflict of interest.

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