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The Significance Of IgM / IgG Beta-2-Glycoprotein And Lupus Anti-Coagulant In The Diagnosis Of Antiphospholipid Syndrome Among Pregnant Women With Complication In Lautech Teaching Hospital, Ogbomoso.

[1]Oloyede T W, [2]Salawu A A.[3]Owonikoko K M, [4]Alatishe TA, [2]Kareem R A, [5]Oke EO, [5]Akande JO, [2]Ogunro P S,

[1]Department of Chemical Pathology, Federal Medical Centre, Katsina. Katsina State, Nigeria
[2]Department of Chemical Pathology, LAUTECH Teaching Hospital, Ogbomoso, Oyo State,Nigeria
[3]Department of Obstetrics and Gyneacology, LAUTECH Teaching Hospital, Ogbomoso Oyo State, Nigeria
[4]Department of Psychiatry, LAUTECH Teaching Hospital, Ogbomoso Oyo State, Nigeria
[2]Department of Chemical Pathology, LAUTECH Teaching Hospital, Ogbomoso Oyo State, Nigeria
[5]Department of Chemical Pathology, Bowen University Teaching Hospital, Ogbomoso Oyo State,Nigeria
[5]Department of Chemical Pathology, Bowen University Teaching Hospital, Ogbomoso Oyo State,Nigeria
[2]Department of Chemical Pathology, LAUTECH Teaching Hospital, Ogbomoso Oyo State. Nigeria
Corresponding Author: Abdulkareem Afolabi Salawu

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ABSTRACT: Background: Pregnancy is associated with thrombosis risks and its morbidity is among the most common presentations of antiphospholipid syndrome (APS). This study was done to evaluate the significant of antibody to beta-2-glycoprotein and lupus anticoagulant in the diagnosis of APS

Method: One hundred and sixty consented participants were recruited consisting of eighty-study group whose pregnancies have been confirmed with history of complications and eighty healthy pregnant women as control. Blood specimens were collected on two occasions into 0.5% trisodium citrate anticoagulant and plain bottles for estimation of antibodies to lupus anticoagulant (LA) and human beta-2-glycoprotein 1(IgG and IgM) respectively using Enzyme Linked Immunosorbent Assay (ELISA) kits.

Result: Present of persistent positivity to human lupus anticoagulant and human beta-2-glycoprotein 1(IgG and IgM) after 12 weeks was 26.3% and 2.5% among the pregnant women with complications and healthy pregnant women respectively. There was also strong association between these antibodies and pregnant women with at least two miscarriages and among pregnant women with hypertension during pregnancy.

Conclusion: This study has shown that using either IgG and IgM anti beta-2-glycoprotein or LAC is a useful tool in the diagnosis of antiphospholipid syndrome among pregnant women with previous history of pregnancy complications in LAUTECH Teaching Hospital Ogbomoso. This is relatively high compared to reports from other similar studies in the country due to the use of multiple antibodies use in this study.

KEY WORDS: antiphospholipid syndrome, beta-2-glycoprotein, lupus anticoagulant, ELISA.

I. INTRODUCTION

Pregnancy which is also known as gravidity or gestation is the time during which one or more offspring's develop inside a woman.[1]Pregnancy is associated with thrombosis risks and its morbidity is among the most common presentations of APS.[2] Normal pregnancy is associated with changes in the haemostatic system that would seem to result into an hypercoagulable state for prevention of haemorrhage during delivery.[3] These changes include increase in level of factors 11, V11, 1X, X11 and von Willebrand factor, increase in fibrinogen levels to twice that of non-pregnant state, and free and total protein antigen levels decrease, as well as decrease in activity of these protein occurring very early in pregnancy.[4,5,6] However, protein C remains unchanged but there is increased inactivated protein C resistance with mutation of factor V Leiden. Other markers of hypercoagulable state include increase thrombin-antithrombin complexes, prothrombin fragment 1 and 2, peak thrombin generation and increased D-Dimer levels.[7] However, this changes in homeostasis is usually secondary to antiphospholipid syndrome which is

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mostly been overlooked especially in this part of the world. Early pregnancy is faced with a lot of symptoms which are associated with physiological, physical and psychological disturbances. This could be as a result of hormonal changes which affect various organs of the system in the body; the foetus might also be lost which could lead to frustration without any clue to the cause of the problem.

Beta-2 glycoprotein 1 (beta 2 GP1, also called apolipoprotein H) is a three hundred and twenty-six (326) amino acid polypeptides synthesized by hepatocytes, endothelial cells and trophoblast cells. β_2-glycoprotein I is an important autoantigen in patients with APS. It also plays a role in lipoprotein metabolism, such as anti-atherogenic property, triglyceride removal and enhancement of lipoprotein lipase. This study adopted the use of antibeta2 glycoprotein 1 IgG or IgM anti-β2GP1 and human lupus anticoagulant using ELISA method in the presence of clinical features suggestive of APS among patient attending LAUTEACH teaching hospital Ogbomoso.

The general objective of this study is to determine the significant of IgM/IgG beta-2-glycoprotein and lupus anti-coagulant in the diagnosis of antiphospholipid syndrome among pregnant women with complication in Lautech Teaching Hospital, Ogbomoso. Pregnancy complications such as foetal wastage, preeclampsia, IUGR, premature birth are heterogenous conditions associated with a lot of physical and emotional stress that have been challenging to the physicians and patients. In many of cases, despite extensive investigations, the aetiology still remains unknown.[17] However, antiphospholipid syndrome, an important aetiology remained one of the less researched areas in this part of the world and its implication in the aetiopathogenesis of complications of pregnancy in relation to the foetal wastage and maternal co-morbidity had been long overlooked. Most earlier studies utilized single antibodies in estimating the prevalence of this potentially preventable disease which resulted in under reporting of the actual prevalence in this part of the world compared to other researches that utilized triple antibodies in the developed world.[18, 19]

II. MATERIALS AND METHODS

This was longitudinal descriptive study carried out in LAUTECH Teaching Hospital Ogbomoso. One hundred and sixty consented participants were recruited consisting of eighty pregnant women attending Booking Clinic, Antenatal Clinic, Gynaecological Emergency Unit whose pregnancies have been confirmed by serum human chorionic gonadotropin (HCG) assay and by ultrasonography with past history of ≥2 consecutive spontaneous abortions, past history of previous unexplained intrauterine fetal death, history of previous preterm delivery and people with systolic blood pressure ≥140mmHg and diastolic blood pressure of ≥90 in the index pregnancy were included in the study after obtaining informed consent. The same number of controls subjects without history of pregnancy complication and not having any autoimmune or any medical disease, history of thromboembolic, and had at least one live birth were recruited in the study. Ethical clearances were obtained from the ethical review committee of Ladoke Akintola University of Technology Teaching Hospital, Oyo State.

SAMPLE COLLECTION, STORAGE AND LA BORATORY ANALYSIS: Ten (10) mls of blood was collected from the antecubital vein of each of the participant on two occasions (at least 12 weeks' interval), 4.5mls was dispensed into a sample bottle containing 0.5mls of 3.2% (0.109M) trisodium citrate anticoagulant. The citrated samples were centrifuged at 1500rpm for 15 minutes and the supernatant (platelet poor plasma) was separated into a plain tube and stored in -20°C freezer. The citrated sample was used for LA assay. Another 5.5mls of blood was dispensed into a plain container, allowed to clot and retracted. The clotted sample was centrifuged at 3000rpm for 10mins and the supernatant (serum) was separated into another plain container and stored in a -20^0C freezer until analyzed. Only those results with medium to high titre units were selected as positive.

Laboratory Analysis of Biochemical Parameters : The human beta-2-glycoprotein 1 IgG and IgM ELISA kits and the Human lupus anticoagulant ELISA Kit were used for the detection of IgG and IgM antibodies to beta-2-glycoprotein 1 and lupus anticoagulant in human serum.[15,16] Using indirect enzyme immunoassay from SPAN Biotech Limited with lot numbers and reference numbers E20170926003and β2GP1 389R, E20170926004 and β2-GP1 409R and E20170926005 HLA 503G respectively. The assays were done using Labtech LT-4000 microplate Reader at a wavelength of 450 nm.

Statistical Analysis: Data entry was analyzed using Statistical Package for Social Sciences (SPSS) version 21.0. Categorical variables were expressed in percentages and continuous variables

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were summarized using mean ± standard deviation. Relationship between categorical variables were analyzed using chi-square, Fisher's test and likelihood ratio test where appropriate. Difference in means between continuous variables were analyzed using t-test. Clinical complications such as miscarriages and hypertension were disaggregated into categories; Miscarriage (<3 / ≥3), Hypertension (Hypertensive / Not Hypertensive). Clinical parameters were used as independent variables, Status of participants to antiphospholipid was used as dependent variable and a binary logistic regression was conducted to examine the effect of clinical factors on the distribution of antibodies. Level of significance was set at 5%.

Institutional Ethical Approval was obtained for this study. Participants gave their written consent and their results were made available to their managing Obstetrician for their adequate management.

III. RESULTS

The total number of participants was 160, each group consisting of 80 subjects and all were suitable for analysis. The age range of the participants was 15-44 years with a mean age ±SD of 29.9 ±4.9 years, majority of the participants were age between 30-34 years. Fifty of the participants in the study group has had two or more miscarriages and thirty-three participants had suffered pregnancy induced hypertension (PIH) with eight with severe eclampsia.

Participants in both groups were tested for the presence of IgG/IgM beta-2-glycoprotein 1 and Lupus anticoagulant at first contact and twelve weeks after to check for persistent positivity to the above antibodies.

VARIABLES	Control group n = 80	Study group n = 80	Test statistic	p-value
Gestational Age				
Minimum	13	13		
Maximum	29	30		
Mean ± SD	20.25 ± 4.48	22.65 ± 4.67	t = -3.318	*0.001
Miscarriages				
0	0 (0.0)	30 (37.5)		
1 - 2	0 (0.0)	36 (45.0)		
≥3	0 (0.0)	14 (17.5)		
Foetal death				
Yes	0	2 (2.5)		
No	80 (100)	78 (97.5)		
Past history of fetal growth retardation				
Yes	0 (0)	1 (1.2)		
No	80 (100)	79 (98.8)		
Premature Birth				
≥1	0 (0)	7 (9.2)		
Previous Eclampsia or severe pre-eclampsia during pregnancy				
Yes	0 (0)	4 (5)		
No	80 (100)	76 (75)		
Number of children at full term				
≥1	37 (46.2)	40 (52.6)	X^2 = 0.10	0.752
Height (meters)				
Mean ± SD	**1.61 ± 0.6**	**1.60 ± 0.6**	**t = 1.220**	**0.224**

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Weight (Kg)				
Mean ± SD	65.63 ± 12.51	70.32 ± 11.5	t = -2.467	*0.015
Systolic BP (mmHg)				
<140	80 (100)	50 (62.5)	X^2 = 36.9	*0.001
≥ 140	0 (0.0)	30 (37.5)		
Mean ± SD	109.5 ± 10.5	130.9 ± 30.2	t = -5.982	*0.001
Diastolic BP (mmHg)				
<90	80 (100)	47 (58.8)	X^2 = 41.6	*0.001
≥ 90	0 (0.0)	33 (41.2)		
Mean ± SD	68.9 ± 7.4	82.9 ± 19.2	t = -6.101	*0.001
Hypertension status of participants				
Hypertensive	0 (0.0)	33 (41.2)	41.6	*0.001
Non-Hypertensive.	80 (100)	47 (58.8)		

*p-value < 0.05 indicate significance, x^2 = Chi-square statistic.

Table 1: Anthropometric measurements, clinical and obstetric parameters of participants disaggregated by groups

Pattern of biochemical parameters among participants at first contact

Participants in both groups were tested for the presence of the three auto-antibodies. The proportion of participants who tested positive for each biochemical parameter were recorded. Table 3 depicts the prevalence of each auto-antibody disaggregated by groups. The prevalence of participants' positivity to IgG beta 2 glycoprotein was significantly higher in the study group (n = 17, 21.3%) compared with the control group (n = 4, 5%), χ^2 value= 7.89, df = 1, p-value = 0.005. The proportion of participants who were positive to IgM beta 2 glycoprotein in the study group (n = 15, 18.8%) and control group (n = 6, 7.5%) did not differ significantly, χ^2 = 3.5, df = 1, p-value = 0.06. Positivity to Lupus anti-coagulants among participants in the study group differed significantly compared to the controls (n = 14, 17.5% vs n = 4, 5%), χ^2 = 5.07, df = 1, p-value = 0.0240.

Biochemical parameters	**Control**	**Study**	**χ^2 value**	**df**	**p-value**
	n (%)	**n (%)**			
IgG beta 2 glycoprotein	4 (5.0)	17 (21.3)	7.89	1	*0.005
IgM beta 2 glycoprotein	6 (7.5)	15 (18.8)	3.5	1	0.06
Lupus anti-coagulant	4 (5.0)	14 (17.5)	5.07	1	*0.024

*p-value < 0.05 indicate significance, x^2 = Chi-square statistic.

Table 2: Prevalence of positivity to anti-phospholipids anti-bodies among participants at first contact disaggregated by groups.

Pattern of Biochemical parameters among participants after twelve weeks

After twelve weeks interval, participants in the control and the study groups were re-assessed to estimate the prevalence of persistent positivity to each biochemical parameters. Significantly lower proportion (n=1, 1.3%) of participants in the control group were persistently positive to IgG beta 2 glycoprotein compared to the study group (n=10, 12.5%), χ^2 = 6.25, df = 1, p-value = 0.01**.** Persistent positivity to IgM beta 2 glycoprotein was significantly higher in study group (n= 12, 15%) compared to the controls (n =1, 1.3%), χ^2 = 8.4, df = 1, p-value = 0.004. The

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prevalence of persistent positivity to Lupus anti-coagulant was significantly higher in the study group (n = 13, 16.3%) compared with the controls (n =2, 2.5%), χ^2 = 7.4, df = 1, p-value = 0.007.

Biochemical parameters	Control n (%)	Study group n (%)	χ^2value	df	p-value
IgG beta 2 glycoprotein	1 (1.3)	10 (12.5)	6.25	1	*0.01
IgM beta 2 glycoprotein	1 (1.3)	12 (15)	8.4	1	*0.004
Lupus anti-coagulant	2 (2.5)	13 (16.3)	7.4	1	*0.007

*p-value < 0.05 indicate significance, x^2 = Chi-square statistic.

Table 3: Prevalence of persistent positivity to anti-phospholipids anti-bodies among participants disaggregated by groups after 12 weeks interval

Figure 1 below showed the prevalence of persistent positivity to the combinations of the biochemical parameters.

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 study group participants to anti-phospholipids antibodies was 26.25% and 2.5% in the healthy pregnant women. This implies that 26.25% participants were positive to at least one of the three biochemical parameters.

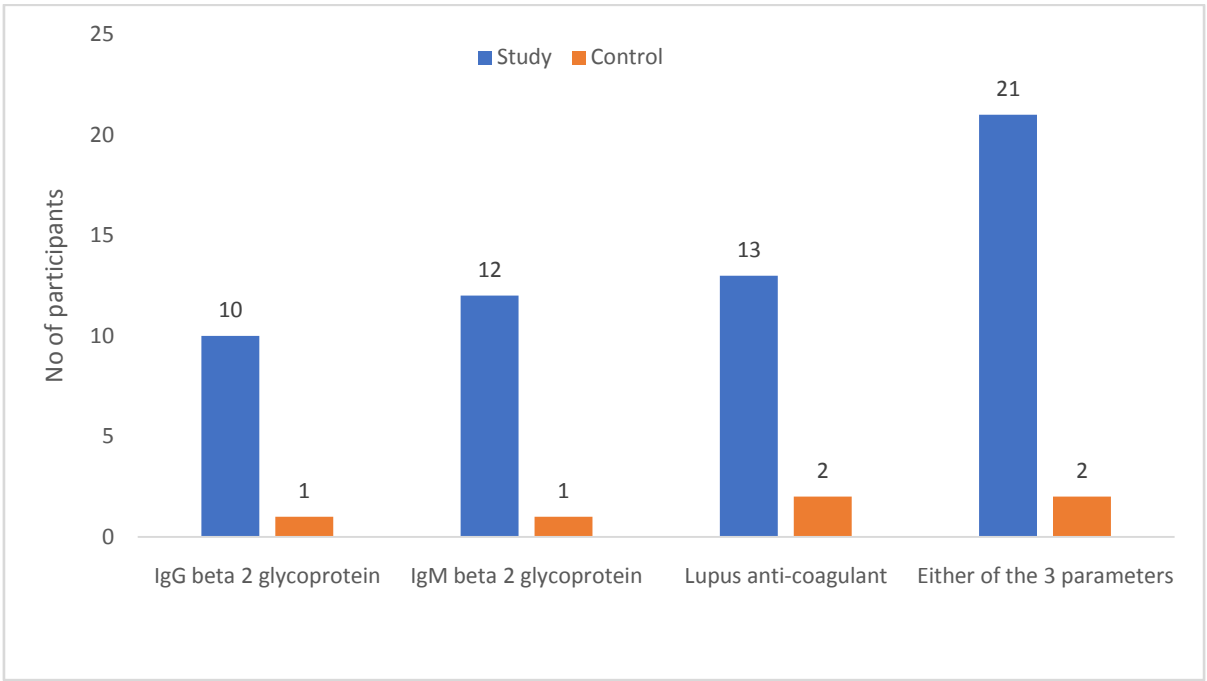

Figure 1: Prevalence of persistent positivity to IgG beta 2 glycoprotein, IgM beta 2 glycoprotein and Lupus anti-coagulant

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RELATIONSHIP BETWEEN PARTICIPANTS STATUS OF ANTI-PHOSPHOLIPIDS ANTIBODIES AND CLINICAL PARAMETERS

Table 4: Represents the relationship between persistent positivity to anti-phospholipids antibodies and miscarriages. Six (60%) of the participants who were 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, five (41.7%) had experienced at least 3 miscarriages. The total of 13 participants were found to be positive to Lupus anti-coagulant, of which 23.1% (n=3) had experienced at least 3 miscarriages. Inductively, there is an association between persistent positivity 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) against number of miscarriages, however there was no association with LA (x^2 = 0.334, p-value 0.563, OR = 1.53, 95% CI for OR: 0.36-6.47) and number of miscarriages

	Miscarriages n (%)					
Biochemical parameters	**< 3**	**≥ 3**	**Test statistic**	**p-value**	**Odds ratio**	**95% CI for odds ratio**
IgG beta 2 glycoprotein						
Positive	4 (40)	6 (60)	X^2 = 14.289	*<0.001	11.25	2.60 – 48.66
Negative	62 (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)				
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, df – degree of freedom, χ^2 – Chi square statistic.

Table 4: Cross tabulation between study group participants' status of anti-phospholipids antibodies against level of miscarriage.

Out of the total 10 participants who were positive to IgG antibeta-2-glycoprotein, 4 (40%) participants were hypertensive, ten of twelve (83.3%) participants who were positive to IgM antibeta-2-glycoprotein were hypertensive and 61.5% (8/13) participants who were positive to lupus anti-coagulant were hypertensive. The persistent positivity among 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).

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)				

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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)				

*p-value < 0.05 indicates significance, df – degree of freedom, χ^2 – Chi square statistic.

Table 6: Cross tabulation between study group participants' status of anti-phospholipids antibodies against participants hypertension status.

IV. DISCUSSION

Persistent positivity to auto-antibodies to phospholipids and phospholipids binding protein syndrome was significantly higher in the study group than in the control group. This is not unexpected as the clinical factors such as hypertension and miscarriages which are the predisposing factors to occurrence of anti-phospholipids syndrome were evident only in participants in the study group. In this study, the prevalence of APLS among pregnant women with one or more complications such as hypertension, recurrent pregnancy loss was 28.8% and the prevalence of 2.5% among healthy pregnant women using presence of the clinical symptoms and presence of either of the three antibodies. This finding is higher compared with the study done in Benin City among women with preeclampsia which found the prevalence of 10.0% and 0% among apparently healthy pregnant Nigerian women.[20] Awodu et al also found a lower prevalence in Benin City (15.4%) using KCT coagulation assay for LA.[21] However, the prevalence of APLS found in this study is consistent with finding done by Ahamed et al among women with unexplained recurrent abortion in Wad Medani Obstetrics and Gynaecological Teaching Hospital, Gezira who found the prevalence to be 26%.[22] 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 anti-phospholipids syndrome which is contrary to the use of single auto-antibodies used in other studies. Several retrospective and prospective studies have also shown that triple aPL positivity (i.e antiβ2-GP1 and LA positivity) correlates more strongly with both thrombosis and pregnancy morbidity than the presence of single or double positivity.[23,18]

In this study, variability occurred in the distribution of IgG and IgM anti beta 2 GLP1 found at first contact and its persistent positivity after twelve weeks. This might be due to initial early hormonal effect on the endometrium and hypercogulable state of pregnancy.[3]The prevalence of IgG and IgM antiβ2-GPL1 in the study group was 21.3% and 18.8% respectively at first contact and it was significantly higher than that of the control group; 5.0% and 7.5% respectively. However, 12.5% and 15% had persistent positivity after 12 weeks compared to 1.3% and 1.3% in the control group. The difference in prevalence following twelve weeks interval may be as a result of other co-morbidity associated with early pregnancy and suppression of immunity which usually occur during early pregnancy. It can also be as a result of modification of endothelial cells and interference with clotting system.[3]In this study the prevalence of human antiβ2-GPL1 (IgG/IgM) was 21.3% for the study group and 1.3% for the control group. Jaume et.al found a lower prevalence in a study conducted among women with spontaneous pregnancy loss at Vall d'Hebron University Hospital, Barcelona, Spain, who reported the prevalence of 9.3% and 0% for IgG antiβ2-GPL1 in the study group and control group respectively, the prevalence of 1.8% and 1.4% for antiβ2-GPL1 in the study group and control group respectively and a general prevalence (IgG or IgM) of 9.3% and 1.4% in the study group and control group respectively.[19] This disparity may be attributed to the sample size considered by Jaume et.al who considered 54 participants and 68 participants in the study and control group respectively.[19]

In this study, 14 (17.5%) participants were positive for Lupus anticoagulant in the study group while it existence was evident only in 5% of participants in the control group at first contact. There was a statistical significant difference in persistent positivity between the study group (16.3%) and the control group (2.5%) after twelve weeks interval. Compared with this study, the prevalence of LA was higher (24%) in a study conducted by Olaniyi et al in Ibadan, Nigeria among pregnant women with recurrent foetal loss and also finding in this study is also contrary to other studies by Adelowo and Akinbami who found the prevalence of LA to be 9.3% & 4.35% respectively.[24,25] Ibrahim et al also found a lower prevalence (4%) in Zaria among pregnant women with recurrent pregnancy losses.[26] This discrepancy might be due to the variability in methods

employed as this study made use of one of the sensitive methods in detecting Lupus anticoagulant.

In this study, majority of participants who were positive to IgG antiβ2-GPL1 had at least three miscarriages and also larger proportion had hypertension. Participant with three or more miscarriages are 11 times more likely to be positive to IgG antiβ2-GPL1 compared to fewer number of miscarriages and participants who have hypertension are equally likely to be positive compared to non-hypertensive participants.

Persistent positivity of participants to IgM antiβ2-GPL1 was significantly higher in participants with at least 3 pregnancy losses and hypertension. Participants with three or more pregnancy loss are four times more likely to be positive than participants with fewer number of miscarriages, and hypertensive participants are 9 times more likely to be positive compared to non-hypertensive counterparts. Our findings are consistent with the finding in a study by Marai et.al in which elevated anti-β2GPI IgG but not IgM was linked with increased recurrent spontaneous miscarriage.[27] This is contrary to the findings by Sater et.al, carried out among women with recurrent spontaneous miscarriage who reported higher recurrent spontaneous miscarriage not associated with positivity to IgG anti-β2GPI.[28]

V. CONCLUSION

Majorities of patient with APS have been missed due to use of single antibody check in many studies done in this part of the world and this study has demonstrated the significant of using more than one antibody in the diagnosis of patient with APS. Therefore, using either LAC, 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 future pregnancies.

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