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Original Research Article

Antiphospholipid Antibodies in Women with Preeclampsia Seen at the University of Benin Teaching Hospital, Benin City, Nigeria

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ABSTRACT

INTRODUCTION: APLA have been associated with a number of obstetric complications however their role in the pathogenesis of preeclampsia has remained an issue of controversy. There is a dearth of information on APLA in preeclamptic women in our environment.
OBJECTIVES: The aim of this study is to determine the prevalence of antiphospholipid antibodies in preeclampsia among women presenting to UBTH Benin City and to determine pregnancy outcome in APLA positive women with preeclampsia.
METHODS: This is a case control study. Consecutive pregnant women diagnosed of preeclampsia and age-parity matched normal on-going pregnant women were recruited as participants for the study. Antiphospholipid antibodies were assayed using dilute Russel viper's venom (DRVV) Lupus Anticoagulant (LA screen and confirm kits) and total anticardiolipin antibody (ACA) enzyme linked immunosorbent assay (ELISA) kits.
RESULTS: The prevalence of APLA in preeclampsia was 10% while none (0%) of the controls was positive. This was not statistically significant p value = 0.056 however the odd of detecting APLA in preeclampsia is infinite. There were no significant differences in the obstetric history, pregnancy complications, maternal and birth outcomes between APLA positive and APLA negative women with preeclampsia. However APLA positive preeclamptic women are at increased risk of abruptio placenta and low birth weight with odd ratios of 5.83 and 1.71 respectively.
CONCLUSION: The prevalence of APLA though increased in women with preeclampsia there is no association between APLA and preeclampsia in the study participants. Therefore a routine assay of APLA in women at risk of preeclampsia may not be justified however women with preeclampsia with other clinical features of antiphospholipid syndrome should be investigated for APLA.
Keywords: Incidence, Antiphospholipid antibodies, Preeclampsia.

INTRODUCTION

Antiphospholipid antibodies (APLA) constitute a heterogeneous group of circulating antibodies against anionic phospholipids with the most important ones being anticardiolipin antibodies (ACA),

anti-β_2-glycoprotein I (β_2 GP I) and lupus anticoagulants (LA).[1] In relation to pregnancy, they are association with recurrent fetal loss and complications such as preeclampsia retarded fetal growth or placental insufficiency. [2- 4]

Preeclampsia is defined as the onset of proteinuric hypertension after 20 weeks of pregnancy; a systemic disease of the later stages of pregnancy that affects about 5 - 10% of all pregnancies [5, 6] and is the most common, yet least understood disorder of pregnancy . It is a rapidly progressive condition characterized by high blood pressure, platelet aggregation, swelling of the lower extremities and protein in urine. [7] It is one of the most dangerous complications of pregnancy, and it remains an important cause of feto-maternal morbidity and mortality, particularly in developing countries where it accounts for a significant cause of maternal deaths.[8] Despite the high prevalence and severity of preeclaampsia, its patho-physiology is still poorly understood and its aetiology has not yet been fullyelucidated.

Several publications have associated antiphospholipid antibodies with miscarry-ages, retarded intrauterine growth[1, 2] and others with preeclampsia [9,10] although this latter correlation remains controversial.[11, 12]

There are few local studies on antiphospholipid antibodies; its prevalence in pregnancy and their contribution to pregnancy related complications in our environment are yet to be fully evaluated. Hence this study is aimed to determine the prevalence of LA and antiphospholipid antibodies in women with preeclampsia in our environment.

Objectives

The objectives of this study are to determine the prevalence of antiphospholipid antibodies in women with preeclampsia, to determine the association between APLA and preeclampsia, to determine pregnancy outcome in APLA positive women with preeclampsia and to determine if any, the relationship between platelet counts and APLA.

MATERIALS AND METHODS

Study Design: This is a hospital based prospective study.

Study Area: The study conducted at the University of Benin Teaching Hospital (UBTH). The centre is a tertiary health facility located in Benin City, Edo state, Nigeria. The hospital serve as a research centre, a training institute for undergraduate and postgraduate medical (including residency) training as well as a major referral centre serving Edo and neighbouring Delta, Kogi and Ondo states.

Study Population: There are two groups of participants in this study.

Group 1 (Case group): Comprises pregnant women with preeclampsia recruited from the antenatal clinic and labour ward. They were followed up till delivery to determine pregnancy outcome. Pregnancy outcomes measured include mode of delivery, any other maternal complications, and baby's birth outcome (viability and birth weight).

Group 2 (Control group): Normal pregnant women without preeclampsia recruited from the antenatal clinic. These are age and parity matched with the test group.

Sample Size: A total of 100 women were studied. These included 50 women with preeclampsia (case group) and 50 age - parity matched normal on going pregnant women (control group).

Ethical Approval: The study was approved by the research and ethics committee of UBTH.

Inclusion criteria:

- Pregnant women with preeclampsia defined by:
    - Diastolic pressure >90mmHg and or systolic blood pressure > 140mmHg on two

occasions at least 6 hours apart occuring after 20 weeks gestation;
    - Presence of proteinuria
- Verbal or written consent to participate.

Exclusion criteria:

- Pregnant women with recurrent spontaneous miscarriages, history of deep vein thrombosis and autoimmune disease.
- Individuals on anticoagulant therapy and those with coagulation factor deficiencies in their pre-pregnancy states were excluded as these conditions may give a false positive LA assay result.
- Individuals with infectious diseases (HIV inclusive) and malignancies were excluded. These conditions are associated with antiphospholipid antibody production thus could become a confounder.
- Those on steroid therapy were excluded. Steroids normalize LA activity giving a false negative result.

PROCEDURE:

Sample collection and storage: About 12mls of blood was collected from the antecubital vein of each of the study subject. 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 at -80°C in the blood bank freezer. The citrated sample was used for LA assay.

Another 5mls of blood was dispensed into a plain container, allowed to clot and retract. The clotted sample was centrifuged at 1500rpm for 10mins and the supernayant (serum) was separated into another plain container and stored in a -80 ^{0}C freezer until analysed.

The remaining 2.5mls of blood was dispensed into an ethylenediaminetetrachloroacetic acid (EDTA) container. The sample was analysed for full blood count immediately.

LABORATORY ASSAYS

Lupus Anticoagulant Assay: Dilute Russel Viper venom test (DRVVT) was used to screen for LA. Mixing test was done on samples with prolonged screening results and DRVVT confirm test was used for confirmation. LA screen kits (LOT 6Y12B00) and LA confirm kits (LOT 6X12B00) by TECHNOCLONE DIAGNOSTICS GmbH, Vienna were used for the analysis. An LA screen/LA confirm ratio >1.2 and a percentage correction ratio greater than 10% were used to define LA positivity.

Anticardiolipin Assay: ACA titer was measured using an enzyme immunoassay test kit by Bioquant Diagnostics, San Diego, USA.

Full Blood Count: Blood count was estimated using Haematology automated analyzer MODEL SYSMEX KN21, Japan.

Data Analysis: Data was analyzed using the SPSS software 16. LA and ACA results of test and control and other non parametric variables were compared using Chi-square test or Fishers Exact test as appropriate. The risk of preeclampsia associated with APLA was tested by calculating odd ratio (OR) in preeclamptic women. The relationship between blood counts and APLA was estimated using Spearman's correlation test. $P < 0.05$ was considered significant.

RESULTS

A total of 100 women were studied comprising 50 pregnant women with preeclampsia and age-parity matched 50 normal ongoing pregnant women as control. The mean ages of the study participants were 31.6 ± 4.7yrs and 30.9 ± 5.4 yrs respectively. Thirty of the preeclamptic

women were booked in UBTH and twenty were unbooked. Eleven of the preeclamptic women had mild preeclampsia while thirty nine had severe preeclampsia. Details of the subjects' demographics are as shown in Table 1.

Table 1: Demographic parameters and prevalence of antiphospholipid antibodies.

PARAMETER	PREECLAMPSIA Mean SD N = 50	CONTROL Mean SD N = 50	P value	Odd ratio
Age	31.6 4.7	30.9 5.4	0.479	
Gravidity	4 2	3 2	0.706	
Parity	1 1	1 1	0.377	
Gestational age at Sampling	33 9	31 4	0.022	
BOOKING STATUS				
Booked	20 (40)	50 (100)		
Unbooked	30 (60)	0 (0)		
PREVALENCE	Freq. (%)	Freq. (%)		
Lupus Anticoagulant	2 (4)	0 (0)	0.495	infinity
Anticardiolipin	4 (8)	0 (0)	0.117	infinity
APLA	5 (10)	0 (0)	0.056	infinity

Table 2: Comparison of variables between APLA positive and APLA negative women with preeclampsia

PARAMETER	N = 50 Mean SD	APLA POSITIVE (N = 5) Mean SD	APLA NEGATIVE (N = 45) Mean SD	*P value*	*Odd Ratio*
Age	31.6 4.7	31.8 4.0	31.6 4.8	0.914	
Gravidity	4.0 2.0	5.2 0.4	3.4 1.9	0.036	
Parity	1.0 1.0	2 1	1 1	0.077	
Gestational age at Sampling	33.0 9.0	35.2 5.8	33.7 5.1	0.553	
BOOKING STATUS	FREQ (%)	FREQ (%)	FREQ (%)		
Booked	20 (40)	1 (20)	19 (42.2)	0.636	0.34
Unbooked	30 (60)	4 (80)	26 (57.8)	0.636	2.92
SEVERITY					
Mild	11 (22)	1 (20)	10 (22.2)	1.000	1.13
Severe	39 (78)	4 (80)	35 (77.8)	1.000	1.14
OBSTETRIC HISTORY					
History of Spontaneous Miscarriages	4 (8)	0 (0)	4 (8.9)	1.000	0.00
Previous history of Preeclampsia	7 (14)	0 (0)	7 (15.6)	1.000	0.00
History of IUFD	2 (4)	0 (0)	2 (4.4)	1.000	0.00
History of Preterm delivery	1 (2)	0 (0)	1 (2.2)	1.000	0.00
GESTATIONAL AGE AT DELIVERY					
Preterm (<37 weeks)	21 (42)	2 (40)	19 (42.2)	1.000	0.91
Term (≥ 37 weeks)	29 (58)	3 (60)	26 (57.8)	1.000	1.10
MODE OF DELIVERY					
Spontaneous Vaginal Delivery (SVD)	24 (48)	2 (40)	22 (48.9)	1.000	0.77
Emergency Cesarean Section	23 (46)	3 (60)	20 (44.4)	0.651	1.88
Elective Cesarean Section	2 (4)	0 (0)	2 (4.4)	1.000	0.00
Not Delivered (died before delivery)	1 (2)	0 (0)	1 (2.2)	1.000	0.00
COMPLICATION					
DIC	2 (4)	0 (0)	2 (4.4)	1.000	0.00
Abruptio Placenta	3 (6)	1 (20)	2 (4.4)	0.276	5.38
Maternal Death	2 (4)	0 (0)	2 (4.4)	1.000	0.00
FETAL OUTCOME					
Alive	40 (80)	4 (80)	36 (80)	1.000	1.00
Stillbirth/IUFD	10 (20)	1 (20)	9 (20)	1.000	1.00
BIRTH WEIGHT (Mean SD)	2.50 0.6	2.32 0.8	2.50 0.8	0.627	
<2.5 (Kg)	24 (48)	3 (60)	21 (46.7)	0.661	1.71
>2.5 (Kg)	26 (52)	2 (40)	24 (53.3)	0.661	0.58

The prevalence of APLA in preeclampsia was 10% while none (0%) of the controls was positive. This was not statistically significant p value = 0.056 however the odd of detecting APLA in preeclampsia is infinite. There were no significant differences in the obstetric history, pregnancy complications, maternal and birth

outcomes between APLA positive and APLA negative women with preeclampsia as shown in table 2. However APLA positive preeclamptic women are at increased risk of abruptio placenta and low birth weight with odd ratios of 5.83 and 1.71 respectively.

There was no significant difference in haematological parameters between APLA positive and APLA negative women (as shown in table 3). However there was a negative correlation between anticardiolipin antibody and platelet counts but this was not statistically significant.

Table 3: Haematological parameters in APLA positive and APLA negative women with preeclamsia.

HAEMATOLOGICAL PARAMETERS	N = 50 Mean SD	APLA POSITIVE (N = 5) Mean SD	APLA NEGATIVE (N = 45) Mean SD	P value
WBC ()	11.75 4.2	8.8 3.0	12.1 4.2	0.095
Granulocytes ()	8.4 3.6	5.6 2.7	8.7 3.6	0.061
Lymphocytes ()	2.5 0.7	2.6 0.7	2.5 0.7	0.151
Monocytes()	0.8 0.3	0.6 0.3	0.8 0.3	0.064
Haemoglobin (g/dl)	10.6 1.5	10.7 0.6	10.7 1.6	0.966
Haematocrit (%)	32 3.9	33.4 4.1	31.9 3.9	0.407
Platelets ()	228.0 48.0	231.0 73.0	227.0 46.0	0.893

DISCUSSION

The role of APLA in the aetiopathogenesis of obstetric complications such as recurrent spontaneous miscarriages has been well established. Women with antiphospholipid syndrome (APS) are known to have increased risk of developing preeclampsia however the role of APLA in preeclampsia in general is still unclear.

This study found the prevalence of APLA in preeclampsia to be 10% while those of the control population comprising normal pregnant women to be 0%. The prevalence though increased with an infinite odd ratio, is however not statistically significant.

The prevalence rate found in this study is slightly below the rates reported in other studies. [10, 13, 14] Prevalence rates may differ from one study to another depending on the selection criteria of the study population, sample size studied, the number and type of antiphospholipid antibody assayed, variations in interlaboratory assays, sensitivity and specificity of the kit used and the threshold use to define APLA positivity. It is possible that there may be some variations in the prevalence rates from one race to another.

The prevalence rates reported in the literatures (11-29%) were based on studies conducted in non African populations. [10, 13, 14] There are limited studies on APLA in women with preeclampsia of African descent. Furthermore autoimmune diseases are more prevalent in Caucasians than in African populations. This may explain the relatively higher rates reported in the non African studies. The above prevalence range was based on study that tested for anticardiolipin specifically; this study assayed both ACA and LA yet found a relatively lower rate. It is likely that there may be some racial differences in the prevalence of APLA. Nodler et al [22] reported a relatively lower prevalence rate of APLA in black women with preeclampsia compared to whites.

Awodu et al [16] reported a rate of 15.4% using KCT coagulation assay for LA; this is higher than the rate found in this study. The study by Awodu included 26 women with preeclampsia whose obstetric history and therefore their risk status were not stated. Furthermore the exclusion criteria were not stated. Is it possible that possible confounding variable were not considered in the Awodu study? This study has a larger

sample size (50), excluded possible confounding variables such as recurrent spontaneous miscarriage, HIV infections, and autoimmune diseases and also a very sensitive and specific assay methods DRVVT screening test, mixing test, DRVVT confirmatory test for the detection of LA and β_2 GP I dependent ACA ELISA assay were utilized in this study.

The lack of a significant association between APLA and preeclampsia found in this study is in agreement with several other studies reported in the literature. [17-19] Dreyfus et al [17] and Lee et al [19] in recent studies found no significant association between APLA and preeclampsia.

Some investigators have reported an association between anticardiolipin antibodies and preeclampsia. [20- 22] Van Pampus et al [14] studied 345 patients with a history of severe preeclampsia, compared with 67 women who remained normotensive during pregnancy. In their study, elevated levels of anticardiolipin antibodies were more common in women with a history of severe preeclampsia compared with controls (20.9% versus 7.5%, $P < .05$). One possible explanation for the discrepancy in the result of this study and those studies that found significant association is the definition of a "positive test" for anticardiolipin antibodies. Van Pampus et al [13] included a large number of women with low positive titers (borderline) of anticardiolipin antibodies in the group that was considered to have a positive test. However, low positive anticardiolipin antibodies are of questionable clinical significance. [15] If the study is reanalyzed by considering only patients with moderate-to-high levels of anticardiolipin antibodies to "test positive," the association between these antibodies and preeclampsia may be absent.

Branch et al [21] reported a significant association however; the positive result may be attributed to a selection bias. The study included women with severe preeclampsia. In contrast our study included women both with severe and mild preeclampsia. Though 4 (80%) of the APLA positive women with preeclampsia had severe disease, there was still no significant difference in the severity of preeclampsia in the APLA positive and APLA negative women with preeclampsia ($P > 0.05$).

Preeclampsia generally is associated with serious maternal and fetal complications such as DIC, abruptio placenta, maternal deaths and adverse fetal outcome. [8] APLA positivity may not be accountable for the adverse events. This study found no significant difference in the prevalence of adverse obstetric history, pregnancy related complications and outcome between APLA positive and APLA negative women with preeclampsia. Two maternal deaths were recorded and none of the women were positive for APLA. Thus APLA cannot explain the poor obstetric outcome in women with preeclampsia. The prevalence of abruptio placenta and preterm delivery of 20% and 40% respectively in APLA positive preeclamptic women in this study agrees with the rates reported by Saha et al. [4] These frequencies though were not statistically significant but the risk of abruptio placenta in the APLA positive women in this study was very high with an odd ratio of 5.38.

The average birth weight of newborns delivered by APLA positive mothers (2.32Kg) was lower than those with negative APLA (2.5Kg) and this was not statistically significant. This conflicts with the findings of Sletnes et al [2] who reported a significant difference in birth weight of neonates delivered by both groups of mothers. However there was an increased risk of low birth weight in APLA positive preeclamptic women with an odd ratio of 1.71 found in this study. One of the 5 newborn from APLA positive women with

preeclampsia was a stillbirth; the number of stillbirths/IUFD found in this study was not significantly different between APLA positive and APLA negative women with preeclampsia. Similarly, a large study of patients with fetal death, widely accepted to be associated with antiphospholipid syndrome, found no association with antiphospholipid antibodies. [23]

The majority (60%) of the women in this study (with preeclampsia) did not receive antenatal care in this facility (unbooked); they were referred when the pregnancy became complicated and some of them never received any care. Poor socioeconomic status may be contributory to failure to attend quality clinics where pregnancy can be supervised and this may contribute to the low birth weight recorded in a high proportion of the babies in this study.

Preeclampsia may be associated with low platelet count especially when complicated by DIC and HELLP syndrome. [24, 25] Two of the study subjects had DIC and had low platelet counts but this was not sufficient to alter the average platelet count of the studied population. There was no significant difference in the haematological parameters of APLA positive and APLA negative preeclamptic women. This study did not find any significant correlation between APLA and platelet counts.

The question is what is the implication of the lack of a significant association between APLA and preeclampsia found in this study? APLA may not be responsible completely for the pathology and adverse events seen in preeclamptic women. There is the possibility that they share a common pathogenetic pathway. Still there is a possibility of other APLA not assayed in this study contributing to the pathology seen in preeclampsia.

This study has shown that prospective testing for APLA in women at risk for preeclampsia may not be justified. However APLA testing should be considered in women with early onset severe preeclampsia, especially when additional clinical features of APS are present.

CONCLUSION

This study using DRVVT lupus anticoagulant and anticardiolipin assays has found the prevalence of APLA in preeclampsia women seen at the University of Benin Teaching Hospital (UBTH) to be 10%. This prevalence rate of APLA in preeclampsia though increased compared to the control group was not statistically significant however the odd of detecting APLA in preeclamptic women in this study is infinite.

The risk of abruptio placenta and low birth weight is relatively increased in APLA positive preeclamptic women. APLA may not account completely for the pathology and adverse outcomes associated with preeclampsia.

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