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Original Research Article

A comparative study of antiphospholipid antibodies in preeclampsia and normotensive pregnant women

Chandrapal Mayur[1], Sangeeta Popli[1], Aditi Singh[2], Rajiv K. Ranjan[3]*, Rahul Kumar[2]

[1]Department of Obstetrics and Gynecology, Hindu Rao Hospital and North DMC Medical College, Delhi, India
[2]Department of Biochemistry, North DMC Medical College and HRH, Delhi, India
[3]Department of Biochemistry, Hindu Rao Hospital and North DMC Medical College, Delhi, India

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***Correspondence:**
Dr. Rajiv K. Ranjan,
E-mail: Rajeevawadh@gmail.com

ABSTRACT

Background: Hypertensive disorders of pregnancy cause major portion of maternal morbidity, mortality and poor feto maternal outcome. Abnormal trophoblastic invasion changes are seen in placental development in preeclamptic mother. Preeclampsia harms mother and baby, causing complications like intrauterine fetal death (IUFD), fetal growth restriction (FGR), and preterm delivery. Antiphospholipid antibodies (APLA) trigger coagulation, complement activation, and impaired syncytiotrophoblast differentiation, contributing to preeclampsia development. The study compared Antiphospholipid antibodies (anti-β2GPI, anticardiolipin, lupus anticoagulant) in preeclampsia and normotensive pregnancies. Detecting APLA may help predict preeclampsia and guide timely, specific management for at-risk women.
Method: The present study was conducted in Hindu Rao Hospital, New Delhi from January 2021 to May 2022. It was an observational case-control study which involved 100 normotensive pregnant women and 100 preeclamptic women who met the inclusion criteria. Blood pressure was measured in sitting position, and women were classified as preeclamptic or normotensive. Antiphospholipid antibodies were tested by enzyme linked immunosorbent assay (ELISA) and analyzed in the Biochemistry department. The following tests, anticardiolipin antibodies (aCL)-IgM and IgG, anti-beta-2 glycoprotein-IgM and IgG B and dilute Russell's viper venom time (DRVVT) screened lupus anticoagulant were done; presence of any antibody was positive, outcomes compared.
Results: In this study, out of 100 preeclamptic patients, 20 were positive for APLA antibodies (9 were positive among non-severe preeclampsia and 11were positive among severe preeclampsia) and out of 100 normotensive pregnant women, 3 were positive for APLA antibodies. Receiver operating characteristic (ROC) analysis showed lupus anticoagulant had 93% sensitivity and 97% specificity. APLA positivity was linked to preeclampsia, FGR, preterm delivery, lower segment caesarean section (LSCS), and neonatal complications.
Conclusions: The study found APLA prevalence of 20% in preeclamptic (9% non-severe, 11% severe) and 3% in normotensive women. Anticardiolipin and lupus anticoagulant differed significantly ($p<0.05$), but anti-β2GPI showed no significant difference ($p>0.05$).

Keywords: Cephalohematoma, Instrument assisted vaginal deliveries

INTRODUCTION

Hypertensive disorders of pregnancy are a leading cause of maternal and perinatal mortality and morbidity globally. In India the prevalence of preeclampsia, gestational hypertension, chronic hypertension, and eclampsia are 5.6%, 1.5%, 0.15%, and 0.60% respectively. Gestational hypertension is defined as a systolic blood pressure of 140 mmHg or more or a diastolic blood pressure of 90 mmHg or more, or both, on two occasions at least 4 hours apart after 20 weeks of gestation in a previously normotensive woman. Preeclampsia is a syndrome that chiefly includes

the development of new onset hypertension with proteinuria that resolves by the end of 6th week postpartum.[1] Proteinuria is defined as protein (mg)/creatinine (mg) ratio of >0.3 in two random urine samples or protein >300 mg/dl in 24-hour urine collection.[1] It has been estimated that preeclampsia complicates 2–8% of pregnancies worldwide.[1]

In the comparative study of antiphospholipid antibody (APLA) levels in preeclamptic and normotensive pregnant women, pre-eclampsia developing before 34 weeks is classified as early-onset, whereas cases occurring at or after 34 weeks are termed late-onset pre-eclampsia. The condition can lead to severe maternal complications, including cerebral encephalopathy, intracranial hemorrhage, pulmonary edema, hepatic failure or rupture, acute renal failure, and placental abruption with disseminated intravascular coagulation (DIC), underscoring its clinical significance in maternal-fetal health. Eclampsia is defined by new onset tonic-clonic, focal, or multifocal seizures in the absence of other causative conditions such as epilepsy, cerebral arterial ischemia and infarction, intracranial haemorrhage, or drug use.

Chronic hypertension

Chronic underlying hypertension is diagnosed in women with documented blood pressures >140/90 mm Hg before pregnancy or before 20 weeks of gestation, or both.[1]

Preeclampsia superimposed on chronic hypertension

Preeclampsia superimposed on chronic hypertension is the new occurrence of preeclampsia in pregnant patient with chronic hypertension of any etiology. It is the new onset proteinuria or other end organ dysfunction in addition to pre-existing hypertension. Among these, the preeclampsia syndrome either alone or superimposed on chronic hypertension is the most dangerous.[1] APLA are a group of circulating autoantibodies directed against the phospholipids, which are the main lipid constituents of cell membranes and organelles.

Antiphospholipid antibodies include, lupus anticoagulant anticardiolipin antibody anti-beta2 glycoprotein-I antibody (they may be IgG, IgM, and IgA classes, alone or in combination). The stimulus for autoantibody production is unclear but environmental triggers such as bacteria, viruses, vaccines, drugs, and other factors are potentially capable of inducing a variety of antiphospholipid antibodies in genetically susceptible individuals.[2]

This may lead to antiphospholipid syndrome. The autoantibodies formed lead to activation of the cascade of events like activation of various procoagulants, inactivation of natural anticoagulants, complement activation and inhibition of syncytiotrophoblast differentiation which may cause preeclampsia.

Research objectives

The study objectives were to determine the prevalence of antiphospholipid antibodies (anti-β2GPI, anticardiolipin, lupus anticoagulant) in preeclamptic and normotensive pregnant women, to compare the levels of individual APLA between preeclamptic and normotensive pregnancies, to assess the association of APLA positivity with maternal and fetal outcomes in preeclampsia, to evaluate the potential of APLA as a predictive marker for preeclampsia risk.

Problem statement

Preeclampsia lacks reliable early markers, leading to maternal and fetal complications, necessitating evaluation of APLA as a predictive tool.

METHODS

This observational case control study was conducted on 200 pregnant women who came to the Department of Obstetrics and Gynaecology at Hindu Rao Hospital, Delhi.[3] Study was conducted from January 2021 to May 2022. Informed consent was obtained from each patient. This study was approved from institute ethics committee (IEC/NDMC/2020/32). Patients with pre-existing conditions such as essential hypertension, chronic illnesses, multifetal pregnancies, recurrent spontaneous miscarriages, history of deep vein thrombosis, autoimmune diseases, coagulation factor deficiencies, use of anticoagulant or steroid therapy, or previous thromboembolic disorders were excluded.[4] This study included pregnant women aged 18–35 years with a single fetus. Cases comprised women diagnosed with preeclampsia (systolic BP >140 mmHg or diastolic BP >90 mmHg on two occasions at least four hours apart after 20 weeks of gestation in previously normotensive women, along with proteinuria), and controls were normotensive pregnant women. This observational case-control study was conducted at Hindu Rao Hospital, Delhi, from January 2021 to May 2022.[5] Patients were selected based on strict inclusion/exclusion criteria, with ethical approval obtained, and results analysed statistically.

Blood pressure (systolic and diastolic) was measured in sitting position in right brachial artery with auscultatory method with the help of sphygmomanometer and stethoscope.[6] Based on their blood pressure (systolic >140 mmHg and diastolic >90 mmHg) and proteinuria patients were divided into case (preeclamptic women) and control (normal pregnant women). Their blood samples were sent to biochemistry and pathology laboratory. The antiphospholipid antibody samples were tested by enzyme-linked immunosorbent assay (ELISA). Antiphospholipid antibodies were measured using antiphospholipid antibodies were measured using a fully automated Bio-Rad ELISA reader reader and all samples are clearly department of biochemistry. The following test anticardiolipin antibodies (aCL)-IgM and IgG, anti beta2

glycoprotein-IgM and IgG and lupus anticoagulant was screened using the dilute Russell viper venom test (DRVVT).[7] One or more of the above antibodies were considered as positive.

This study was conducted following strict ethical standards to protect participants' rights and well-being. Participants were provided with clear information regarding the study's purpose, procedures, and voluntary participation. Informed consent was obtained, and confidentiality and anonymity of participant data were strictly maintained. Data was securely stored and used solely for research purposes, ensuring compliance with relevant ethical guidelines in industrial psychology research.

RESULTS

A total of 200 pregnant women who met the inclusion criteria were included in the study. Table 1 shows distribution of APLA antibodies with the cases and controls. There was statistically significant association between blood pressure and anti beta2 glycoprotein-1 IgG, anti-cardiolipin IgM, anti-cardiolipin IgG and lupus anticoagulant (LAT1/LAT2). Overall mean value for anti beta2 glycoprotein-1 IgG was 2.23±4.52.

Table 1: Comparison of antibody titre with cases and controls (n=200).

Variables	Normotensive, n=100 (%)	Non severe preeclampsia, n=54 (%)	Severe pre-eclampsia, n=46 (%)	Total, n=200 (%)	P value[1]
Anti-beta 2 glycoprotein 1 IgM	1.7±1.9	3.4±8.2	2.9±6.3	2.4±5.4	0.13
Positive	0 (0)	2 (3.7)	2 (4.3)	4 (2.0)	0.061
Negative	100 (100)	52(96)	52 (96)	196 (98)	
Anti-beta 2 glycoprotein 1 IgG	2.23±2.97	2.39±7.19	2.02±3.18	2.23±4.52	>0.9
Positive	1 (1.0)	1 (1.9)	1 (2.2)	3 (1.5)	0.8
Negative	99 (99)	53 (98)	45 (98)	197 (98)	
Anti-cardiolipin antibody IgM	1.8±2.2	3.8±8.3	5.8±10.8	3.3±7.1	0.005
Weakly positive	3 (3.0)	5 (9.3)	6 (13)	14 (7)	0.032
Strongly positive	0 (0)	1 (1.9)	1 (2.2)	2 (1.0)	
Negative	97 (97)	48 (89)	39 (85)	184 (92)	
Anti-cardiolipin antibody IgG	1.67±1.61	2.81±4.06	2.89±4.78	2.26±3.35	0.045
Weakly positive	0 (0)	4 (7.4)	3 (6.5)	7 (3.5)	0.009
Strongly positive	0 (0)	0 (0%)	0 (0%)	0 (0)	
Negative	100 (100)	50 (93)	43 (93)	193 (96)	
Lupus anticoagulant (LAT1 / LAT2)	0.85±0.18	0.87±0.35	0.93±0.43	0.88±0.30	0.3
Positive	3 (3.0)	5 (9.3)	7 (15)	15 (7.5)	0.027
Negative	97 (97)	49 (91)	39 (85)	185 (92)	

[1]One-way ANOVA; Fisher's exact test

While it was 2.23±2.97, 2.39±7.19 and 2.02±3.18 for normotensive, non-severe pre-eclampsia and Severe Pre-eclampsia respectively. Anti cardiolipin IgM was negative in 97%, 89% and 85% for normotensive, non-severe pre-eclampsia and severe pre-eclampsia respectively. Anti cardiolipin IgG was negative in 100%, 93% and 93% for normotensive, non-severe pre-eclampsia and severe pre-eclampsia respectively. Further lupus anticoagulant (LAT1/LAT2) was positive for 3%, 9.3% and 15% of normotensive, non-severe pre-eclampsia and severe pre-eclampsia respectively. Table 2 ROC curves above diagonal line are deemed as reasonable ability to predict pre-eclampsia. Aside from anti beta 2 glycoprotein 1–IgG (AUC-62.2% (54.4-70%)) other parameters were non-significant as AUC was crossing over the 50% demarcating line. Lupus anticoagulant had maximum sensitivity (93% (68-100%)) and least sensitivity was found to be for anti-cardiolipin antibody IgG (47% (37-56%)). Overall specificity is 97%, while sensitivity is only 20%.

Table 2: Receiver operating characteristic curve of APLA antibody titre for predicting pre-eclampsia.

Variables	Anti-beta2 glycoprotein 1 IgM (%)	Anti-beta2 glycoprotein 1 IgG (%)	Anticardiolip-in antibody IgM (%)	Anticardiolip-in antibody IgG (%)	Lupus anticoagulant (LAT1/LAT2) (%)
AUC (95% CI)	52.9	62.2	55.8	56.0	52.5
Cut-off	0.91	0.90	1.62	0.88	0.57
Accuracy (95% CI)	56	62	55.5	57	59.5
Sensitivity (95% CI)	68	75	67	47	93

Continued.

Variables	Anti-beta2 glycoprotein 1 IgM (%)	Anti-beta2 glycoprotein 1 IgG (%)	Anticardiolip -in antibody IgM (%)	Anticardiolip -in antibody IgG (%)	Lupus anticoagulant (LAT1/LAT2) (%)
Specificity (95% CI)	44	49	44	67	27
PPV (95% CI)	67.86	74.8	66.85	47	92.35
NPV (95% CI)	44.1	49.13	44.11	66.87	27.17
Precision (95% CI)	67.84	74.81	66.85	47.1	92.35

Figure 1 shows echocardiographic changes in pregnant women. LV mass and RWT increase from normotensive to superimposed preeclampsia. Diastolic function (E/e', TR velocity, LAVi) worsens, indicating progressive concentric hypertrophy with severity.[15]

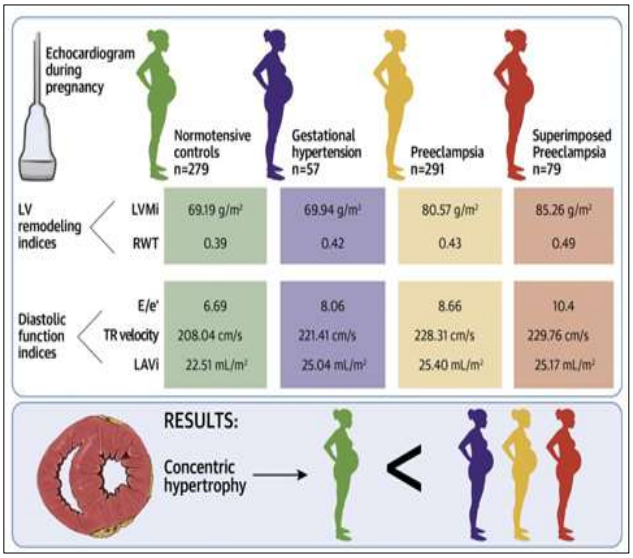

Figure 1: Central illustration.

DISCUSSION

The present study was an observational case-control study conducted in Hindu Rao Hospital, New Delhi, to determine the presence of APLA in preeclampsia and in normotensive pregnant women.[8] This study included 200 pregnant women between the age group of 18-35 years with singleton pregnancy above 20 weeks of gestation who consented and participated in the study. Amongst 200 pregnant women 100 with preeclampsia were included in the case group and 100 normotensive pregnant women were included in control group.

Our study was an effort to study the comparison of APLA in preeclampsia and normotensive pregnant women to determine if the presence of APLA could be used for predicting the likelihood of developing preeclampsia. Our study found the prevalence of APLA in preeclampsia (cases) to be 20% (non-severe preeclampsia were 9% and severe preeclampsia were11%) while in normotensive pregnant women (control) to be 3%.[9]

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 inter-laboratory assays, sensitivity and specificity of the kit used and the threshold use to define APLA positivity.

Antiphospholipid antibodies in cases and control

Most of the APLA positive patients, 20 out of 23, were from cases (9 and 11 from non-severe pre-eclamptic and severe pre-eclamptic patients respectively) while APLA negative were almost equally distributed within cases (45%) and control (55%).[10] There was statistical significance of APLA positivity and preeclampsia (p value <0.001).

Anti beta-2 glycoprotein I and preeclampsia

This study reported anti-beta-2 glycoprotein I IgM antibody in mild and severe preeclampsia were 3.7% and 4.3% respectively. Anti-beta-2 glycoprotein I IgG antibody in normotensive pregnant women, non-severe and severe preeclampsia were 1%, 1.9% and 2.2% respectively. In this study there were no significance of anti-beta-2 glycoprotein I antibodies and preeclampsia. Our study results were correlating well with Lee et al who concluded that there was no association of anti-beta-2 glycoprotein I (IgM and IgG) in preeclampsia and normotensive pregnant women (p value >0.05).[3] This study had comparable findings with Kaur et al who reported that there was no significance between anti-beta-2 glycoprotein I (IgM and IgG) in preeclampsia and normotensive pregnant women (p value >0.05).[2] Kaur et al reported that there was no association between APLA and hypertensive cases in pregnancy.[11]

Anticardiolipin antibodies and preeclampsia

In this study we found that the association of anticardiolipin antibodies and preeclampsia. IgM anti cardiolipin antibodies were positive in normotensive (3%), non-severe preeclampsia (9.3%) and in severe preeclampsia (1.9%). IgG anti cardiolipin antibodies were positive in normotensive 0%, non-severe preeclampsia 7.4% and in severe preeclampsia 6.5% and 0%. Our study was comparable with Khanum et al who reported 20% and 7% of preeclamptic women and normotensive pregnant women had positive anticardiolipin antibody respectively and concluded association of anticardiolipin antibodies with preeclampsia.[5] Branch et al also reported a significant association between anticardiolipin antibodies and preeclampsia.[6]

Lupus anticoagulant antibodies and preeclampsia

In this study we found that the prevalence of lupus anticoagulant antibodies was higher in non-severe preeclampsia and severe preeclampsia and showed association of lupus anticoagulant antibodies and development of preeclampsia. This study was similar with study by Awodu et al who reported a rate of 15.4% using coagulation assay for LA and reported association between cases and controls, there is association of Lupus anticoagulant antibodies (mild preeclampsia 9.3% and severe preeclampsia 15%) found in this study.[7] Awodu included 26 preeclamptic women.[12] But this study had 100 preeclamptic women. This study included all sensitive and specific assay methods for anti-beta 2 glycoprotein I and anticardiolipin by ELISA and DRVVT screening and confirmatory test for Lupus anticoagulant antibodies.[16] Our study had similar findings with previous study by Salam et al who reported prevalence of LA was 22.1% in women with preeclampsia or eclampsia and 3.4% in control.[8] And reported an association between LA and preeclampsia. This study had prevalence of 9.3% in mild preeclampsia, 15% in severe preeclampsia and 3% in normotensive pregnant women.

Association of antiphospholipid antibodies in preeclampsia and normotensive pregnant women

There was statistical association between blood pressure and anti-beta-2 glycoprotein-1 IgG, anti-cardiolipin IgM, anti-cardiolipin IgG and lupus anticoagulant (LAT1/LAT2).[13] Overall mean value for anti-beta-2 glycoprotein-1 IgG was 2.23±4.52, while it was 2.23±2.97, 2.39±7.19 and 2.02±3.18 for normotensive, non-severe pre-eclampsia and severe pre-eclampsia respectively. Anti cardiolipin IgM was negative in 97%, 89% and 85% for normotensive, non-severe pre-eclampsia and severe pre-eclampsia respectively. Anti cardiolipin IgG was negative in 100%, 93% and 93% for normotensive, mild pre-eclampsia and Severe Pre-eclampsia respectively.[14] Further lupus anticoagulant (LAT1/LAT2) was positive for 3%, 9.3% and 15% of normotensive, non-severe pre-eclampsia and severe pre-eclampsia respectively.

Limitations

The study was limited by a small sample size and single-center design. Short follow-up and lack of longitudinal data may affect generalizability. Resource constraints restricted testing of all APLA subtypes and related risk factors.

CONCLUSION

Preeclampsia adversely affects the pregnancy outcomes – both maternal as well as fetal. Hence, this condition needs early detection, prompt initiation of treatment and follow up. This study found the prevalence of APLA (anti-beta 2 glycoprotein I, anticardiolipin and lupus anticoagulant antibodies) was 20% in preeclampsia women (non-severe preeclampsia 9% and severe preeclampsia 11%) and 3% in normotensive pregnant women at Hindu Rao Hospital. This prevalence rate of APLA in preeclampsia is higher than normotensive pregnant women which was statistically significant. Moreover, there was a statistically significant difference between the levels anticardiolipin Abs in the preeclamptic patients and normotensive patients. Hence, for prediction of development of preeclampsia, the routine screening for Antiphospholipid antibody is not recommended but it may be considered only in high-risk pregnancies.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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