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Original article

Lupus Anticoagulant in PIH and Pregnancy Outcome

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ABSTRACT

Background: Hypertensive disorders continue to occur globally, complicating 5-20% of pregnancies. Antiphospholipid antibodies are one of the risk factors in the development of pregnancy induced hypertension. Aim of this study is to determine prevalence of lupus anticoagulant (LAC) in PIH and its effect on foetal outcome. **Materials and Method:** This prospective study was conducted at Department of General Medicine and Obstetrics of a tertiary care centre over one year. The study comprised of 100 third trimester pregnant women, aged 18-34 years with blood pressure more than 140/90 mm Hg on two occasions at least 6 hours apart. 50 normal pregnant women in third trimester comprised control group. **Results:** In the present study, the prevalence of LAC in the hypertensive women in their third trimester was found to be 14%. LAC positivity was found in greater percentage among severe hypertensive patients than in moderate hypertensive group (16.6% Vs 4.8%). **Conclusion:** In the present study, it was found that LAC is associated with severe PIH, thrombocytopenia, IUGR, increased operative interference and increased neonatal mortality. Thus it is concluded that LAC should be screened in all patient who have PIH and bad obstetric history.

KEYWORDS: Lupus, PIH, Pregnancy.

INTRODUCTION

Hypertensive disorders continue to occur globally, complicating 5-20% of pregnancies. They are a common cause of intervention/operative mortality and cause around 15-20% maternal mortality and 20-25% perinatal mortality because they predispose to intrauterine growth retardation and iatrogenic preterm delivery performed for foetal and maternal indications [1]. Antiphospholipid syndrome or antiphospholipid antibody syndrome (APS or APLS), or often also Hughes syndrome, is an autoimmune, hypercoagulable state caused by antiphospholipid antibodies. APS provokes blood clots (thrombosis) in both arteries and veins as well as pregnancy-related complications such as miscarriage, stillbirth, preterm delivery, and severe preeclampsia.

The diagnostic criteria require one clinical event, i.e. thrombosis or pregnancy complication, and two antibody blood tests spaced at least three months apart that confirm the presence of either lupus anticoagulant (LAC), or anti-β2-glycoprotein-I (since β2-glycoprotein-I antibodies are a subset of anti-cardiolipin antibodies (ACA), an anti-cardiolipin assay can be performed as a less specific proxy)[2]. Antiphospholipid antibodies (APA) are one of the risk factors in the development of pregnancy induced hypertension (PIH). APAs are a family of autoantibodies that bind to negatively charged phospholipids and/or phospholipid binding proteins. These are clinically important because of their strong association with thrombosis, recurrent miscarriage and thrombocytopenia[3]. The two most studied APA are LAC and ACA. Aim and objective of this study was to determine the prevalence of LAC in PIH and its relationship to foetal outcome.

MATERIALS AND METHODS

The present study was carried out in the Department of Medicine in association with department of Obstetric of a tertiary care centre. Level of LAC assessed in study group as well as control group. All subjects were futhur followed up till delivery to notice any complications like thrombocytopenia, operative delivery, still birth, Intrauterine growth reatardation (IUGR) and neonatal mortality. The study group comprised of 100 third trimester pregnant women, aged 18-34 years with blood pressure more than 140/90 mm Hg on two occasions at least 6 hours apart. Females with twin pregnancies, chronic illnesses such as diabetes, endocrine disorders, renal failure or connective

tissue disorder were excluded from the study. Cases were classified as mild, moderate and severe according to the degree of hypertension (mild: diastolic BP 90-100 mm Hg; moderate: diastolic BP 101-110 mmHg; severe diastolic BP more than 110 mmHg).

50 normal pregnant women in third trimester comprised control group. All routine investigations including complete hemogram, kidney function test, liver function test, blood sugar level and blood grouping done in all patients. Blood for LAC was obtained by clean venepuncture with minimal stasis using a single plastic syringe and was collected into 105 mM trisodium citrate tubes. Platelet poor plasma was obtained by double centrifugation at 3000 rpm for 20 minutes at room temperature. All samples for LAC assay from patients and controls were processed within 2 hours of venepuncture. LAC activity was measured by the activated partial thromboplastin time (aPTT) according to the method of Proctor and Rapaport with relevant modifications. For each batch of test samples, plasma collected from normal healthy women (pooled) was included to arrive at normal reference control clotting time.

The test was carried out in 3 stages. Brain cephalin was used as a phospholipid reagent. For determination of aPTT, cephalin was diluted 1 in 10 dilutions in 0.9% saline. 100µl of patients' plasma and 100µl of diluted cephalin were mixed and incubated exactly for 2 minutes at 37^0C. After incubation 100µl of 25 mM calcium chloride was added and the clotting time was measured using automated stopwatch. Clotting times were measured in duplicates and are expressed in seconds.

The general guidelines for the diagnosis of LAC suggested by the Kingston antiphospholipid antibody study group was followed[4] .A patient's plasma was considered LAC positive when the following criteria was fulfilled: 1) Prolongation of coagulation time in stage I; 2) Consistent prolongation after mixing patient's plasma with equal volumes of normal control plasma in stage II and 3) Inhibition of anticoagulant affect, thereby reversal to normal aPTT, when direct cephalin reagent (excess phospholipid) was added.

RESULTS

In the present study, the prevalence of LAC in the hypertensive women in their third trimester was found to be 14%. No subjects in control group tested positive for LAC.(Table.1) 43.5% among subjects had severe hypertension where as 24.4% had moderate hypertension. LAC positivity was found in greater percentage among severe hypertensive patients than in moderate hypertensive group (16.6% Vs 4.8%).(Table.2)

Thrombocytopenia (29.8% Vs 7.8%), operative delivery (33.3% Vs 19.8%), still birth rate (12.8% Vs 2.9%), rate of IUGR (70.9% Vs 6.7%), neonatal mortality (18% Vs 3.3%) were more in the LAC +ve patients than those who were hypertensive but were LAC –ve. Mean gestational age at delivery in LAC +ve patients was also less than those who were not LAC +ve.(Table.3)

Table 1. Characteristics of Cases and Control

	Cases (Pregnant females with PIH)	Control (Normal Pregnant females)	p value
Number	100	50	
Participant's Age in years (Mean± SD)	24.5 ±8.1	23.8 ±8.8	0.5
LAC +ve (%)	14 %	-	<0.0001
Mean Gestational Age at the time of delivery (weeks) (Mean ±SD)	30.3 ± 4.5	35.6 ±3.7	0.005

Table 2. Severity of Hypertension and LAC Positivity

	Mild Hypertension	Moderate Hypertension	Severe Hypertension	p value
Number	30	28	42	
Participant's Age in years (Mean ±SD)	23.8 ±6.1	24.4 ±7.9	24.9 ±9.3	
LAC +ve (%)	4.8%	8.8%	16.6%	0.005

Table 3. Complications among Pregnant Females with PIH

	LAC +ve Hypertensive	LAC –ve Hypertensive	p value
Number	14	86	
Thrombocytopenia	29.8%	7.8%	0.001
Operative Delivery	33.3%	19.8%	0.002
Still Birth Rate	12.8%	2.9%	0.005
Rate of IUGR	70.9%	6.7%	<0.0001
Neonatal Mortality	18%	3.3%	0.001
Mean Gestational Age at the time of delivery in weeks (mean ±SD)	28.8 ±3.2	31.4 ±3.8	0.001

DISCUSSION

Antiphospholipid syndrome can be primary or secondary. Primary antiphospholipid syndrome occurs in the absence of any other related disease. Secondary antiphospholipid syndrome occurs with other autoimmune diseases, such as systemic lupus erythematosus. In rare cases, APS leads to rapid organ failure due to generalised thrombosis; this is termed "catastrophic antiphospholipid syndrome" and is associated with a high risk of death[5].

Various mechanisms have been postulated by which LAC induces PIH and its associated complications. The net effect is endothelial cell injury at the placental site causing thrombosis and the resulting placental ischemia triggers the hypoxia which can lead to early onset preeclampsia, IUGR, preterm delivery or intrauterine death. Various investigators have studied association of LAC and PIH.

Our study showed that greater percentage of LAC positivity among severe hypertensive patients. Complications like thrombocytopenia, operative delivery, still birth rate, rate of IUGR and neonatal mortality were more in the LAC +ve patients. Various studies also shown high incidence of LAC in PIH and associated complications. Huong et al. had reviewed data of 75 consecutive pregnancies in 47 women. The outcome of the other 75 pregnancies was one embryonic loss, 8 fetal deaths, 16 prematurates, and 38 full term births. After exclusion of one fetal death associated with congenital anomaly, live birth rate was 72.9%[6]. Carmona et al. studied seventy-seven pregnancies in 56 women with LAC positive.

There were seven first-trimester miscarriages (9%) and five intrauterine fetal demises (6.5%). Thus, the probability of having a live baby under treatment was 82% (95% CI 71.3-89.6%), a figure significantly greater (P <0.001) than that observed before therapy (25.7%; 95% CI 18.7-33.7%) [7]. Lynch et al had done a prospective cohort study in women with normal pregnancies. Eligible patients included 451 low-risk, nulliparous pregnant women who came to the obstetrics clinic before 25 weeks gestation; 408 were enrolled and 389 had blood drawn at the first prenatal visit and completed clinical follow-up.

Ninety-five patients (24.4%) had elevated LAC levels by one or more measures at the first prenatal visit: 15.8% of the LAC positive and 6.5% of the LAC-negative patients experienced fetal loss (relative risk, 2.44; 95% CI, 1.29 to 4.62) [8]. Pattison et al. had done a study to determine prevalence, clinical association and predictive power of antiphospholipid antibodies in nine hundred and thirty-three consecutively booked pregnant women. Nine women (1.0%) had anticardiolipin antibodies, 11 (1.2%) had lupus anticoagulant and two had both antibodies. The fetal mortality rate for women with antibodies was 167/1000. Pre-eclampsia occurred significantly more often in women with auto-antibodies [9] Miković Z, et al.[10] also noticed findings similar to our study.

CONCLUSION

In the present study, it was found that LAC is associated with severe PIH, thrombocytopenia, IUGR, increased operative interference and increased neonatal mortality. Thus it is concluded that LAC should be screened in all patient who have PIH and bad obstetric history.

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