ORIGINAL RESEARCH

Elevated prothrombin time and activated partial thromboplastin time with raised hepatic enzymes as predictor of progression to eclampsia

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Abstract

Introduction: Pre-eclampsia is a complex multisystem disease, diagnosed by sudden-onset hypertension (>20 weeks of gestation) and at least one other associated complication, including proteinuria, maternal organ dysfunction or uteroplacental dysfunction and this may progress to eclampsia also has neurological features. A recent survey bought to light that in India the 76.34% and 17% patients of pre-eclampsia are in 21-30 years and adolescent age group, respectively, with 81% of patients being primigravida. Liver diseasesmust be considered in pregnancy as due to physiological changes many alterations in hepatic excretory and synthetic functions are noted and these may be pathological also attributable to preeclampsia.

Aims and objectives: To study whether severity of preeclamapsia is a factor for prediction to eclampsia.Liver transaminases alone or in conjunction with prothrombin time/international normalised ratio (PT/INR) and activated partial thromboplastin time (aPTT) may be used predictor of progression of pre-eclampsia to eclampsia.

Material and Methods: 100 primigravida females who presented to this hospital antenatally and were diagnosed with preeclampsia after following criteria of the study.

Observations: 11 females progressed to eclampsia and out of these 8 had mild and only three had severe preecalmpsia. Two females with isolated elevation of liver transaminases and six with elevated liver transaminases and coagulation parameters progressed to eclampsia.

Conclusion: Progression of preeclampsia to eclampsia is independent of severity of preeclampsia pointing to multifactorial causes. Elevation of Prothrombin time/INR and activated partial thromboplastin time (both or singularly) may be used as predictive indicator of progression to eclampsia in preeclamptic patients with elevated liver transaminases.

Keywords: Preeclampsia, Eclampsia, Liver transaminases, prothrombin time/ international normalised ratio (PT/INR) and activated partial thromboplastin time (aPTT)

Introduction

Pre-eclampsia is a complex multisystem disease, diagnosed by sudden-onset hypertension (>20 weeks of gestation) and at least one other associated complication, including proteinuria, maternal organ dysfunction or uteroplacental dysfunction (1)and this may progress to eclampsia which in addition to above also has neurological features most common beingnew-onset, generalized, tonic-clonic seizures or coma in a patient with preeclampsia and can occurantepartum, 20 weeks after gestation, intrapartum, and postpartum. (2) The Blood pressure must be measured by well calibrated sphygmomanometer, preferably glass tube – mercury and two readings must be taken with atleast four hour time interval but within 6 hours and the readings must be systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg. The risk factors

for development of eclampsia/preeclampsia include maternal age ≥30 years,low educational attainment,high body mass index (BMI), nulliparity, absence of antenatal care,gestational diabetes, cardiac or renal disease, pyelonephritis or urinary tract infection, severe anemia and elevated liver enzymes (3)A recent survey bought to light that in India the 76.34% and 17% patients of pre-eclampsia are in 21-30 years and adolescent age group, respectively, with 81% of patients being primigravida.(4)

Liver diseasesmust be considered in pregnancy as due to physiological changes many alterations in hepatic excretory and synthetic functions are noted. With progresssion of pregnancy, decreasing levels of albumin are seen as hemodilution increases. However, deterioration of synthetic liver functions may cause prolonged PT/INR and aPTT along with decreased factor V activity causing an increased thrombotic risk instead of bleeding tendency which is one of the factors in etiopathogenesis of eclampsia. (5)

Aim and Objectives

To study the effect of deteriorating liver function as monitored by serum glutamic – pyruvic transaminase (SGPT), serum glutamic oxaloacetic transaminase(SGOT), alkaline phosphatase (ALP) on progression of pre-eclampsia to eclampsia and subsequently using these parameters in conjunction with prothrombin time/ international normalised ratio (PT/INR) and activated partial thromboplastin time (aPTT) to assess if this combination can be a predictor ofprogression of pre-eclampsia to eclampsia.

Material and methods

The study was conducted prospectively after taking institutional ethics committee clearance and consent of every participant for a period of two year duration from July 21 to July 23 where 100 primigravida attending this hospital were included as per the criteria defined

1. **Inclusion criteria:** Age within 20-30 years,Body Mass Index between (21.0+/- 1.2) with no prior history of hypertension, abortion or intrauterine foetal death and minimum three ante natal visits, who developed pre-eclampsia.
2. **Exclusion criteria:** Females with low platelet counts &/ hemolysis, known neurological disorder, hypertensive disorder or on anti-hypertensive drugs, diabetes mellitus, renal disease, thyroid disorder or liver disorder including hepatitis patients were excluded.

Blood pressure was measured on all ante-natal visits using Mercury-glass sphygmomanometer with readings being taken with atleast four hour time intervals but within 6 hours.

These pregnant females were followed up with respect to Blood pressure, proteinurea, liver enzymes (S.bilirubin, SGOT, SGPT, ALP), PT/INR and aPTT.Classification ofPreeclampsia into controlled/Non severe (less than 160 mmHg systolic and110 mm Hg diastolic)andand uncontrolled/Severe (more than 160 mm Hg systolic and110 mm Hg diastolic), as per blood pressure and proteinurea greater than equal to 300mg/24 hours or persistent 1 + -positive urine dipstick test. (6) Another Pre-eclampsia defining criteriaapart from elevation of blood pressure and proteinureawas doubling of liver transaminases (Normal range: SGOT 8-40 IU/L and SGPT-5-35 IU/L),(6) values greater than 80 IU/L were considered significant.

Normal prothrombin time was upto 14 ceconds with INR 1.0, values greater than 20 seconds / INR 1.4 were considered raised activated Partial Thromboplastin Time aPTTupto 38 seconds was considered normal and values greater than 50 seconds were considered raised was elevation of liver enzymeswas done and further into those with isolated mild elevation of hepatic enzymes (<= 2 times) and pre-eclampsia with elevation of hepatic enzymes (> two times) along with increased PT/INR and aPTT.

Blood samples for liver enzyme estimation and coagulation studies (PT/INR &aPTT) were taken in plain gel and Citrate vaccutainers respectively by phlebotomyusing universal precautions. Estimstion of liver enzymes was done on fully automatic biochemistry analyser (ERBA EM-200) and PT / INR were evaluated on semi-automatic coagulation analyser (Stago-start max). Urinary protein estimation was done using dipstick method, preferably on early morning, midstream clean catch sample.

Using these data the females were classified into those with controlled/Non severe (medicine/ exercise /life style modification) and uncontrolled/Severe pre-eclampsia using blood pressure of greater than 160/110 mmHg, as cut off value. Another clssification of these pre-eclampsia patients was done, based on those with isolated elevation of hepatic enzymes and pre-eclampsia with elevation of hepatic enzymes along with elevation of PT and aPTT.

These pregnant females were followed till the completion of therepregnacy and any development of neurological clinical features and or tonic –clonic seizures were documented as Eclampsia.

All data analysis was done using spss software ver. 22

Observations

Pre-eclampsia was present in all pregnant females under study and the majority of them developed sudden onset hypertension greater than 140/90 mmHg between 28-32 weeks of gestation (70%), 20% after 32 weeks and 10 percent between 20-25 weeks.

Non severe preeclampsia as documented by blood pressure measurement was evident in 90 cases and 10 cases had severe preeclampsia, but only eleven cases progressed to eclampsia. Of these 8 cases were of non-severe pre-eclampsia and three were of severe eclampsia. A chi-square test with Yates correction gave a p value of .136 which was not significant, when correlation of severity of pre-eclampsia was

taken as a predictor of progression to eclampsia. (Table 1)

Table 1:

	Preeclampsia(Non Severe)	**Preeclampsia(Severe)**	**Marginal Row Total**
Eclampsia (Present)	8(9.9)[0.36]	3(1.1)[3.28]	11
Eclampsia (Not Present)	82(80.1)[0.05]	7(8.9)[0.41]	89
Marginal Column Total	90	10	100 (Grand Total)

The chi-square statistic is 4.0972. The *p*-value is .042956. Significant at $p<.05$.The chi-square statistic with Yates correction is 2.2245. The *p*-value is .135837. Not significant at $p<.05$

In patients of pre-eclampsia, isolated elevation of hepatic enzymes (SGOT, SGPT) of more than double was seen in 65 cases whereas elevation of hepatic enzymes with increased PT/aPTT or both was seen in 25 cases. In 10 cases there was no increase in hepatic enzymes or PT and or aPTT.Progression to eclampsia was seen in 2 cases with isolated elevation of hepatic enzymes and in 6 cases of elevation of hepatic enzymes with increased PT/aPTT or both. A chi-square test with Yates correction gave a p value of .007 which was significant when isolated elevation of hepatic enzymes and elevation of hepatic enzymes with increased PT/aPTT or both, were used to predict progression to eclampsia. Table 2

Table 2:

	Elevated livertransaminases	**Elevated livertransaminases + (PT &aPTT)**	**Marginal Row Total**
Eclampsia (Present)	2(5.78)[2.47]	6(2.22)[6.42]	8
Eclampsia (Not Present)	63(59.22)[0.24]	19(22.78)[0.63]	82
Marginal Column Total	65	25	90 (Grand Total)

The chi-square statistic is 9.7598. The *p*-value is .001784. Significant at $p<.05$The chi-square statistic with Yates correction is 7.3473**.** The *p*-value is .006716. Significant at $p<.05$

Discussion

The diagnosis of preeclampsia is based upon sudden onset hypertension with blood pressure greater than 140/90 mm Hg and proteinureageater than equal to 300mg/24 hours or a consistently positive 1 + Urine dipstick test or with evidence of maternal organor uteroplacental dysfunction. (1) One of the criteria for diagnosis of Pre-eclampsia, is raised Serum transaminases (greater than two times the normal value) along with new onset hypertension, in pregnant female. (6) The same criteria were used for patient selection in our study with age and BMI matched patients, after excluding other possible causes of hypertension in pregnancy. All the patients had proteinurea but only 90 patients had elevation of liver enzymes. This was in stark contrast to study of Hammoud and Ibdah who found elevation of hepatic enzymes in only 10 percent of patients and that too of severe eclampsia, but their study was with reference to progresion to HELLP syndrome in pre eclampsia and the cut off in their study for elevated hepatic transaminases was 500 IU /L. (7) But a study by Hazari, Hatolkar&Munde with reference to abnormal hepatic enzymesin preeclampsia patients found increased levels of SGOT and SGPT in45% and 87.5 % of women, respectively a finding similar to our study which may be attributed to the patient profile in Indian context.

In their study titled Preeclampsia–Eclampsia, Gupte&Waghanalysed the data in FOGSI-ICOG National Eclampsia Registry and found that maximum number of patients were in 21-30 year age group and 17% were adolescents and 81% of patients were primigravida. This data prompted us to conduct our study in 20-30 years age group. Progression to eclampsia was seen in 11 patients which was much higher than reported average of 1-5%, **(**4,8); the reason being denominator in our study was patients of Pre-eclampsia, as compared to other regstries were the denominator was number of registered deliveries.

A chi square test anlysis to determine the correlation between severities of pre eclampsia as defined by blood pressure gretaertha 160/110 mmHg with progression to eclampsia found p value > 0.05 and was not significant. This led us to conclude that severity of precelampsia has no correlation with progression to eclampsia and like pre eclampsia has multifactor etiopathogenesis. (4,9)

Within the liver, hepatocytes are involved in the synthesis of most blood coagulation factors, such as fibrinogen, prothrombin, factor V, VII, IX, X, XI, XII, as well as protein C and S, and antithrombin, whereas liver sinusoidal endothelial cells produce factor VIII and von Willebrand factor (10) Liver dysfunction portends poor prognosis and is noted in upto 50% of patients with pre-eclampsia (11, 12) So we hypothesized that synthetic liver function may also be affected and measurement of PT/INR and APTT can be used as a predictive indicator of progression to eclampsia in patients of Pre-eclampsia, in conjunction with elevated liver enzymes. A similar etiopathogenesis for progression to eclampsia was proposed by Maxime*etal* where they concludedthat deterioration of synthetic liver functions may cause prolonged PT/INR and aPTT along with decreased factor V activity causing an increased thrombotic risk

instead of bleeding tendency which is one of the factors in etiopathogenesis of eclampsia. (5) A chi-square test for predicting progression to eclampsia with respect toisolated elevation of hepatic enzymes and elevation of hepatic enzymes with increased PT/aPTT or both was significant leading us to conclude that these two parameters used in conjunction can be used a s predictor of eclampsia, in patients of preeclampsia.A chi-square test with Yates correction gave a p value of .007 which was significant when isolated elevation of hepatic enzymes and elevation of hepatic enzymes with increased PT/aPTT or both, were used to predict progression to eclampsia. Table 2

Conclusion

Preeclampsia is a much more common in females of younger age group 20-30 years and primigravida, especially in rural centers where there is early age of marriage and first pregnancy. Progression of preeclampsia to eclampsia is independent of severity of preeclampsia pointing to multifactorial causes. Elevation ofProthrombin time/ INR and activated partial thromboplastin time(both or singularly) may be used as predictive indicator of progression to eclampsia in preeclamptic patients with elevated liver transaminases.

Note: The above study was presented as poster in CME cum Hands on Workshop on Diagnostic Immunohistochemistry and Flowcytometry : Clinical Utility and Challenges- Need of the hour - Mid Year Teaching Program of Indian Association of Pathologists and Microbiologists (IAPM, UP Chapter) held on 06- August-2023 at Rohilkhand Medical College and Hospital Bareilly UP India and was awarded the second prize in its category.

Conflict of Interest: None

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