EVALUATION OF HEPATIC, RENAL AND CEREBRAL FUNCTION TEST IN PREECLAMPSIA-ECLAMPSIA SYNDROME AND ITS CORRELATION TO MATERNAL AND FETAL OUTCOME

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ARTICLE INFO

Received : 30 April, 2021

Accepted : 03 March, 2022

Published : 22 June, 2022

ORA 289

DOI: https://doi.org/10.3126/bjhs.v7i1.45790

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Citation

Evaluation of Hepatic, Renal and Cerebral Function Test in Preeclampsia-eclampsia Syndrome and its Correlation to Maternal and Fetal Outcome. Sangita Patra, Suchibrata Das, Sujata Dalai, Pallab Kumar Mistri. BJHS 2022;7(1)17. 1678-1683.

ABSTRACT

Introduction

Hypertensive disorders complicates 5-10% of pregnancies all over the world and its incidence in India was found to be 10.08% as per data of National Eclampsia Registry (NEP).

Objectives

The objectives of this study were to determine the incidence of abnormal liver, renal and cerebral function test among patients with preeclampsia and eclampsia and their correlation to maternal and fetal outcome.

Methodology

The study was a prospective cohort study comparing the maternal and fetal outcomes of preeclampsia and eclampsia patients with abnormal parameters (cases; n=50) and pre-eclampsia and eclampsia patients with normal parameters (controls; n=50). Both case and control were examined clinically apart from biophysical and biochemical investigation.

Result

Deranged LFT was present in approximately 56% -70% of cases. Serum albumin was decreased in 80% of cases. Prothrombin time (PT) was raised in 48% of cases. Abnormal GFR, urea, creatinine and uric acid level were present in 44%, 10%, 10% and 64% of cases. Among all the pregnancy outcomes in preeclampsia and eclampsia cases with abnormal LFT, preterm labour, PPH, IUFD, meconium stained liquor and neonatal death had significant “p” value <.05. There were 16% preterm labours, 60% IUGR, 36% ARF, 18% Neonatal death, in cases with abnormal RFT. It was found from the study that CVA, Cerebral hemorrhage, fetal distress, and still birth were present in 16%, 24%, 36% and 8% of cases with abnormal cerebral function.

Conclusion

Deranged liver function test was associated with increased incidence of postpartum hemorrhage (P value=0.0001) and postpartum eclampsia (P value <0.0001).
Deranged Renal Function Test is associated with increased incidence of IUGR (P value=0.0002)

KEYWORDS

eclampsia, elevated liver enzymes, maternal morbidity and mortality, preeclampsia, perinatal morbidity and mortality.

INTRODUCTION

Hypertensive disorders complicates 5-10% of pregnancies all over the world and its incidence in India was found to be 10.08% as per data of National Eclampsia Registry (NEP). Prevalence of eclampsia is 1.9% among registry patients. Considering a global scenario, according to World Health Organization (WHO) multi country survey, incidence of hypertensive disorders in pregnancy is 2.73%, incidence of preeclampsia is 2.16% and eclampsia is 0.28%.[1] They form one of the deadly triad along with hemorrhage and infection contributing to maternal and fetal morbidity and mortality.[2] The World Health Organization systematically reviews maternal mortality worldwide and in developed countries 16% of maternal death were reported to be due to hypertensive disorders.[3] The complications of preeclampsia includes eclampsia, cerebral hemorrhage, cardiovascular complications, hepatic failure, acute renal failure (ARF) , pulmonary edema, Acute Respiratory Distress Syndrome (ARDS), Disseminated Intravascular Coagulation (DIC), Hemolysis, Elevated Liver Enzymes, Low Platelet Count (HELLP) Syndrome, retinal detachment, cortical blindness, hypoxic cerebral damage and even maternal chronic hypertension and death.[3] ACOG 2013 Bulletin has classified hypertensive disorders in pregnancy into four categories- chronic hypertension of any etiology, Gestational hypertension, Preeclampsia-eclampsia syndrome and preeclampsia superimposed on chronic hypertension.[4] In United Kingdom, among 38% eclamptic cases, seizure occurred without any prior documentation of either hypertension or proteinuria in the hospital setting. De novo seizure in the absence of preeclampsia suggest that pregnancy alone may be a state of increased seizure susceptibility due to decreased expression of gamma amino butyric acid receptors ($GABA_AR_s$) and and/or neuro-inflammation that acts to lower seizure threshold.[5] In the pathogenesis of preeclampsia, placenta is the central organ, since the removal of placenta abolishes the disease. In preeclampsia the invasion of the cytotropho blast into the spiral arteries is incomplete, i.e. only in the superficial layer of the decidua.[6] The typical histopathological changes characteristics of preeclampsia is glomerular endotheliosis i.e. fibrin deposition, endothelial swelling and loss of capillary spaces. It resolves at variable rates postpartum. Lately, podocytic alteration, podocyturia, enhanced apoptosis, downregulation of nephron and other key proteins of slit diaphragm may explain proteinuria in preeclampsia.[6] Disturbance in the vascular development of placenta resulting in a placental hypoperfusion and ischemia. The damaged placenta secretes a wide range of antiangiogenic factors into the maternal circulation causing systemic endothelial cell dysfunction and microangiopathy. The endothelial damage in liver can produce periportal hemorrhagic necrosis with the release of hepatocellular enzymes into the circulations. Alanine Aminotransferase (ALT) is considered more liver specific than Aspartate Amino Transferase AST.[7] On the basis of observed total oxidant status (TOS) and total antioxidant status (TAS) it has been inferred that increased oxidative stress and antioxidative defense mechanism may contribute to the diseases process in preeclampsia. Increased formation of reactive oxygen species (ROS) may contribute to renal dysfunction apart from renal dysfunction. Uric acid, creatinine and urea may possess water soluble/hydrophilic antioxidant property, which inhibit or delay cellular damage through the free radical scavenging property and it also prevents strong antioxidant activities towards ROS in aqueous phase. Elevated blood uric acid together with urea and creatinine level may predict and correlate with the severity of preeclampsia.[8] Women with preeclampsia have a 3-4 fold increased risk of developing chronic hypertension and a 2 fold increased risk of developing ischemic heart diseases, stroke and venous thromboembolism later in life.[10] Our aims and objectives were to determine the incidence of abnormal liver, renal and cerebral function test in preeclampsia and eclampsia cases and to study the effect of abnormal liver function, renal function and cerebral function on maternal and fetal outcome in preeclampsia and eclampsia cases.

METHODOLOGY

The Prospective Cohort study was conducted at the Department of Obstetrics and Gynecology, Medical College Hospital, Kolkata-73, from 01.02.19 to 31.01.2020. This is a prospective cohort study. All preeclampsia and eclampsia mothers with normal (control) and abnormal (case) liver function, renal function and cerebral function were included in our study. Pregnancy with chronic hypertension and /with superimposed preeclampsia–eclampsia, pregnancy with epilepsy, pregnancy with cerebrovascular accident, chronic hypertension, multiple gestation, molar pregnancy, intrahepatic cholestasis, viral hepatitis, portal hypertension with esophageal varices, Wilsons diseases, autoimmune hepatitis, hepatic adenomas, hepatocellular carcinoma, nonalcoholic fatty liver diseases and any systemic illness were excluded from our study. The Institute of Ethics Committee of Medical College and Hospital Kolkata approved our study. Informed consent of the patients were taken before including them into the study. The criteria for the diagnosis of preeclampsia and eclampsia were in accordance with the guidelines of the American College of Obstetricians and Gynecologists, January 2019. There were 50 patients of preeclampsia and eclampsia with abnormal liver function, renal function and cerebral function (Cases) and 50 patients of preeclampsia and eclampsia with normal liver function, renal function and cerebral function (Controls). We calculated the sample size by using formula for cohort study i.e. $(p0\,q0 + p1\,q1)(z1 - a/2 + z1 -)^2 / (p1 - p0)^2$. Assuming from previous study[2], the prevalence rate of PIH patients with abnormal LFT 66% and that of PIH patients with normal LFT 34% , the calculations as follows: p0 = proportion of PIH patients with normal LFT 0.34, p1= proportion of PIH patients with abnormal LFT 0.66, q0=1-p0=1-0.34=0.66 and q1=1-p1=1-0.66=0.34, z1-alpha/2=1.96, z1-beta=0.84. Applying the above mentioned formula we had $n1=n2 = (.34*.66+.66*.34)(1.96+0.84)^2 / (0.66-0.34)^2 = 34.26$ approximately 35. The minimum estimate of sample size 35 each for diseased with exposed and non-exposed. This was the estimate of sample size when there was crude association

between exposure and disease without any confounder or variables. In this study there was at least three broad special group of variables like LFT, RFT and Cerebral function tests, the sample size would increase by at least 10% multiplied by three (10% increment of sample size for each variable). Hence 30% of 35 = 10.5. Adding 10.5+35= 45.5 and nearest tenth approximately 50 for each group exposed and non-exposed. Therefore we had taken 50 PIH patients with normal LFT and 50 PIH patients with abnormal LFT. The response rate was 85.47%. (100 patients responded out of 117 total study subjects). Patients were examined from 20 weeks' period of gestation up to 7th day of delivery. Both cohorts were examined clinically as well as subjected for all the same relevant investigations. Apart from routine investigations, determination of total protein in 24 hours urine, complete haemogram including platelet count, for the first time, please use full form with abbreviation followed by abbreviations only in successive uses.....Liver Function Test (LFT), Renal Functional Test (RFT), coagulation profile (Prothrombin time{Prothrombin Time/International Normalized Ratio (PT/INR), activated Plasma Thromboplastin Time (aPTT)}, activated plasma thromboplastin time and INR) and ultrasonography (USG) along with Doppler velocimetry as well as Investigations for CNS involvement like CT scan, EEG, .. Lumbar Puncture were done if indicated, (coma, convulsion and / cerebral hemorrhage). All these investigations were done for both cohorts. Patients, who did not attend antenatal clinic previously but admitted at hospital just at the time of labour were examined clinically. All blood and urine investigations (as baseline) were done at that time. Biophysical investigations like CT Scan, EEG, and LP were done at that time if necessary and if possible. Serum for HBsAg and IgM HEV were done for all the study subjects.

We put the data about the study patients over preplanned proforma. Then data were entered in MS Excel according to parameters. They were analyzed by calculating frequency and percentages. The tables and graph charts were prepared based over frequency and percentage calculations. “Contingency table” were obtained and “Fisher's Exact Test” is done to obtain', p value and relative risk with 95% confidence interval.

RESULTS

TABLE 1: Incidence of Abnormal LFT, RFT & Cerebral Function Test Parameters Among Preeclampsia-Eclampsia Syndrome (Cases), N=50

Derranged parameters LFT Parameters	Patients with pre-eclampsia, (n=20)	Patients with eclampsia (n=30)	“p” value	Relative risk	95% Confidence Interval	Total number of patients with deranged parameters; n (%)
Total bilirubin (I)	6	2	0.0469	2.250	1.252- 4.042	8 (16%)
AST (I)	16	19	0.3451	1.714	0.6874-4.275	35(70%)
ALT(I)	15	13	0.0419	2.357	1.013-5.484	28 (56%)
Serum Albumin (D)	20	20	0.0034	Infinity	Infinity	40 (80%)
P- time (I)	6	18	0.0475	0.4643	0.2130- 1.012	24 (48%)
GFR (D)	10	12	0.5669	1.273	0.6475-2.502	22 (44%)
Urea(I)	3	2	0.3772	1.588	0.7078-3.564	5(10%)
Creatinine(I)	3	2	0.3772	1.588	0.7078-3.564	5(10%)
Uric acid(I)	16	16	0.0742	2.25	0.8865-5.710	32 (64%)
GCS (4/5)	0	27	<0.001	0.000	infinity	27 (54%)
Plantar extensor	0	12	0.0014	0.000	infinity	12 (24%)
Cerebral edema	4	8	0.7400	0.7917	infinity	12 (24%)
Retinal hemorrhage	2	3	1.000	1.000	0.3224-3.101	5 (10%)

LFT: Liver function test; I: increased, D: Decreased, PT: Prothrombin Time: Prothrombin, RFT: Renal Function Tests, GCS: Glasgow Coma Scale

It had been found that 16% of cases having increased total bilirubin level. Out of 50 cases, there were 30 patients with eclampsia and 20 patients with pre-eclampsia. Among them, 16% had increased total bilirubin level. Liver enzymes were also raised i.e. increased level of AST and ALT were observed in 70% and 56% of cases respectively. Better not to comment on ALP as it is nonspecific in pregnancy. Liver enzymes were also raised i.e. increased level of AST , ALT and Alkaline Phosphatase were observed in 70%, 56% and 60% of cases respectively. Serum albumin was decreased in 80% of cases. . 48% of the cases presented with raised Prothrombin Time (PT). There was significant (“p” value) difference in LFT parameters derangement like total bilirubin, ALT , serum albumin and P- time (PT) between preeclampsia and eclampsia cases. Abnormal Glomerular Filtration Rate (GFR), urea, creatinine and uric acid level were present in 44%, 10%,10% and 64% of cases of preeclampsia and eclampsia. Abnormal GCS (4/5) was found in 54% of cases. Plantar extensor, cerebral edema and retinal hemorrhage were present in 24%, 24% and 10% of cases. There was significant (“p” value) difference in cerebral

function test parameters derangement like abnormal Glasgow coma scale and plantar extensor reflex between preeclampsia and eclampsia cases. Better to use the table description after the table

TABLE 2: Effect of Abnormal LFT on maternal and fetal outcome among cases (n=50) vs controls (n=50).

Maternal and fetal outcome	Cases (n=50)	Controls (n=50)	'P' value	Relative Risk	95% of confidence interval
Preterm labour	23 (46%)	10(20%)	0.0102	1.730	1.197-2.500
Abruptio placentae	13 (26%)	6 (12%)	0.1247	1.498	1.017-2.206
PPH	36 (72%)	16(65%)	0.0001	2.374	1.474-3.824
Postpartum Eclampsia	21 (42%)	0	<0.0001	2.724	2.039-3.639
IUGR	17(34%)	20 (40%)	0.6790	0.8771	0.5755- 1.337
IUFD	0	10 (20%)	0.0012	0.000	Inf- Inf
Birth Asphyxia	14 (28%)	18 (36%)	0.5205	0.8264	0.5257-1.299
Meconium stained liquor	8 (16%)	18(36%)	0.0390	0.5421	0.2945-0.9978
Neonatal Death	9 (18%)	22 (44%)	0.0089	0.4886	0.2725-0.8762

PPH: Postpartum hemorrhage; IUGR: Intrauterine growth restriction; IUFD: Intra uterine fetal death

There were 46% preterm labour, 26% abruption placentae, 72% PPH,42% postpartum eclampsia, 34% IUGR, 28% birth asphyxia, 16% meconium stained liquor and 18% neonatal death in preeclampsia and eclampsia cases. The most common complication was PPH (RR 2.374; 95%CI 1.4744444444-3.824; p value= 0.0001) The least common complication in this study was meconium stained liquor (RR 0.5421; 95%CI 0.2945-0.9978( ). Among all the pregnancy outcome preterm labour, PPH, IUFD, meconium stained liquor and neonatal death had significant "p" value <.05 in preeclampsia- eclampsias cases in this study.

TABLE 3: Effect of Abnormal RFT on maternal and fetal outcome among cases (n=50) vs controls (n=50).

Maternal and fetal outcome	Cases (n=50)	Controls (n=50)	'P' value	Relative Risk	95 % of confidence interval
Preterm labour	8 (16%)	2(4%)	0.0916	1.714	1.172-2.508
IUGR	30(60%)	11(22%)	0.0002	2.159	1.444-3.226
ARF	18 (36%)	7 (14%)	0.0198	1.688	1.179-2.416
Neonatal death	9 (18%)	5 (10%)	0.3881	1.348	0.8607-2.113

There were 16% preterm labour, 60% IUGR , 36% ARF, 18% Neonatal death, in preeclampsia eclampsia cases. The most common complication was IUGR (RR 2.159; 95%CI 1.444-3.226 ; p value 0.0002). The least common complication was preterm labour and neonatal death with a non significant "p" value 0.0916 and 0.3881 respectively

TABLE 3: Effect of Abnormal RFT on maternal and fetal outcome among cases (n=50) vs controls (n=50).

Maternal and fetal outcome	Cases (n=50)	Controls (n=50)	P value	Relativ e risk	95% confidence interval
CVA (Cerebrovascular accident)	8 (16%)	1 (2%)	0.0309	1.926	1.398-2.653
Cerebral hemorrhage	12 (24%)	3 (6%)	0.0226	1.789	1.266-2.530
Fetal distress	18 (36%)	5 (10%)	0.0037	1.883	1.338-2.650
Still birth	4 (8%)	2 (4%)	0.6777	1.362	0.7458-2.488 Please write in short about the findings of table number 4

It was found from the study CVA, Cerebral hemorrhage, Fetal distress, and still birth were present in 16%,24%,36% and 8% of preeclampsia and eclampsia cases respectively. The most common complication was fetal distress with a significant p value 0. 0037.The other complications like CVA, Cerebral hemorrhage had significant p value like 0.0309 and 0.0226 respectively. (Table 3)

DISCUSSION

According to the study by Sasmita D et al.[1] fetal outcome in pregnancies affected with pregnancy induced hypertension (PIH) was observed. In this study prematurity and NICU admission rate were 29.2% and 18,.6% respectively which is quite low. The reason behind it was late onset preeclampsia was prevalent in the study. The reason behind it was late onset preeclampsia which was prevalent in the study Perinatal outcome is worst in early gestational age.[1] In the study done by Mahajan P et al,[2] there was significant elevation in the level of SGOT,SGPT and alkaline phosphatase at the time of derangement exactly corresponded with our study . The most common fetal complications in the study by Mahajan P et al like prematurity, [2]IUGR etc. were same as in our study. Our study showed similar type of outcome as the retrospective study done by Pillai S , where the commonest maternal complication was atonic PPH (23.63%) but abruption (7.27%0, DIC (2.72%), pulmonary edema and renal dysfunction (7.27%) were also present.[3] The fetal complications in this study were prematurity (65%), IUGR (21.81%), meconium aspiration (4.54%), IUFD (6.36%), still birth (2.72%) and neonatal death (9.09%).[3] Placental abruptio and postpartum hemorrhage were the most common maternal complication in eclampsia and preeclampsia in this study. Other complications were DIC, acute renal failure and pulmonary edema. This result was comparable to the results of studies conducted in India. These results were comparable to the results of studies conducted in India The most common neonatal complication seen in preeclampsia in this study was low birth weight (LBW).[5] The objective of the study done by Ghumman *Surveen*, Goel *Neerja et al* to evaluate the feto-maternal outcome of women with renal disease and the effect of pregnancy on renal disease.[13] Hypertension and intrauterine growth retardation (IUGR) occurred in 8 out of the remaining 13 cases (61.5%), anemia in 7 (53.8%), urinary tract infection in 3 (23%), premature rupture of membranes in 2 (15.3%), prematurity in 7 (53.8%), fetal distress in 4 (30.8%), still birth in 1 (7.6%), and neonatal death in 2 (15.3%). Out of the remaining 13 cases, hypertension and intrauterine growth restriction (IUGR) occurred in 8 (61.5%), anemia in 7 (53.8%), urinary tract infection in 3 (23%), premature rupture of membranes in 2 (15.3%), prematurity in 7 (53.8%), fetal distress in 4 (30.8%), still birth in 1 (7.6%), and neonatal death in 2 (15.3%). Renal function worsened in 2 cases (15.3%). Fetomaternal complications were more in severe renal disease. Our study also revealed same type of outcome like preterm labour (16%), IUGR (60%), ARF (36%) and neonatal death (18%) in preeclampsia and eclampsia mother with abnormal renal function. Marilyn J. Cipolla Marilyn JC[14] had established in his study that cerebral autoregulation mechanism is totally lost in preeclampsia and eclampsia leading to cerebral edema formation responsible for different neurological sequel.[14] Paul Nkemtendong Tolefac et al Paul NTet al. presented a case report of spontaneous hemorrhagic stroke complicating severe preeclampsia).[15] Our study showed different pregnancy outcome in preeclampsia and eclampsia with abnormal cerebral function tests, like CVA (16%), cerebral hemorrhage (24%), fetal distress (36%) and still birth (8%).

CONCLUSION

Preeclampsia and eclampsia are the significant causes of maternal and fetal morbidity and mortality in our country. Deranged liver, renal and cerebral function tests parameters are associated with poor maternal and fetal outcome in preeclampsia and eclampsia. It is very essential to recognize early warning symptoms and signs to avert the life threatening complications in the cases where prevention is not totally possible.

RECOMMENDATIONS

Provision of quality antenatal health care services, investigations, timely delivery, intensive monitoring in the intrapartum and postpartum period, essential education to the women and accessible health care services to the socioeconomically deprived and rural population are required.

LIMITATIONS OF THE STUDY

Single study centre, referral bias, reason for NICU admission would not be sought for as neonates in NICU would not be followed up till discharge.

ACKNOWLEDGEMENTS

We sincerely acknowledge the support received from the Principal, faculty and administration of MCH, Kolkata for carrying out the research work.

CONFLICT OF INTEREST

None

FINANCIAL DISCLOSURE

None

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