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Preeclampsia related investigative parameters and its association with maternal outcome.

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Abstract

Background: Preeclampsia is the most challenging clinical entity affecting both mother and the foetus. It is one of the leading causes for maternal as well as perinatal morbidity/mortality. Preeclampsia appears to be mild in about 75% of the cases and severe in 25% of them. The present study is an attempt to analyse maternal and perinatal outcome in a severe preeclampsia and to find the usefulness of the clinical and investigative work up as predictors of outcome.
Materials and methods: In this observational study 140 women with a severe preeclampsia who were evaluated and managed at a tertiary care hospital were recruited. Clinical, haematological and other biochemical investigative parameters were noted and subsequently correlated with various adverse maternal outcomes.
Results: Mean arterial pressure>127 mmHg (p=0.042), uric acid>7 mg/dl (p=0.001), platelet count<1, 00,000 cells/cc (p=0.003), serum creatinine>1.2 mg/dl (p=0.025) were significantly associated with poor maternal outcome in women with severe preeclampsia.
Conclusions: Maternal and perinatal morbidity is still high among women with severe preeclampsia. Timely caesarean delivery seems to improve perinatal outcomes in settings with facilities for new-born care.

Keywords: Preeclampsia, Investigative parameters, Adverse outcomes.

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Introduction

Preeclampsia is the most challenging clinical entity affecting both mother and the foetus. It is a predisposing factor for maternal as well as perinatal morbidity/mortality. Incidence of preeclampsia in developing nations has been reported to be around 4-18% [1]. The hypertension disorders are the second most common obstetric cause for stillbirths and early neonatal deaths [1-3]. Approximately 1, 00,000 women die worldwide per annum because of eclampsia [4]. In worldwide, preeclampsia and eclampsia contribute towards death of women for every 3 minutes [5].

In most of the cases, about 75% preeclampsia appears to be mild and severe in remaining 25% of them [6]. Severe pre-eclampsia is defined as diastolic Blood Pressure (BP) of at least 110 mm Hg or systolic BP of at least 160 mm Hg, and/or symptoms, and/or biochemical and/or haematological impairment [7]. In its extreme, the preeclampsia may lead to hepatic and renal dysfunction, Central Nervous System (CNS) abnormalities and Disseminated Intravascular Coagulopathy (DIC). Besides, placental insufficiency may cause foetal growth restriction and related perinatal complications. Premature birth either spontaneous or induced for indications is an important cause for perinatal morbidity/mortality.

Systematic reviews showed that haemorrhage and hypertensive disorders together contribute towards an increase in number of maternal deaths in developing countries. The observed a maternal mortality is around 5% among women with the preeclampsia/eclampsia [8]. As per WHO bulletin on perinatal deaths in developing countries, 23.6% of 171 perinatal deaths from 7993 pregnancies were due to preeclampsia. Among women with an eclampsia it was observed that an adverse perinatal outcome is influenced by factors such as antepartum eclampsia, gestational age less than 32 weeks, convulsions more than 5, blood pressure more than 160/100 mmHg, urine albumin levels over 1+, vaginal preterm births, low birth weight babies and a lower 5th minute Apgar score. Systolic blood pressure had a significant influence on perinatal death [9].

Thangaratinam et al. found that, the maternal and foetal complications could not be predicted by uric acid in women with preeclampsia [10]. Brown found that absence of protein in urine might be used to predict outcomes accurately in 1348 women diagnosed with preeclampsia [11].

Contradicting reports are found in the literature regarding the role of investigative workups and predictive role of these parameters as an indicator of severe disease that terminate pregnancy. Thus the present study is an attempt to analyse maternal and perinatal outcome in severe preeclampsia and to find the usefulness of the clinical and investigative work up as predictors of outcome.

Material and Methods

In this observational study 140 women with a severe preeclampsia who were evaluated and managed at a Beijing Chaoyang Hospital, Capital Medical University, Beijing were recruited. Women who had blood pressure ≥ 160/110 mmHg with proteinuria of any degree and blood pressure ≥ 140/90 mmHg with proteinuria ≥ 2+ were included in this study. An informed consent form was obtained from the subject's prior participation in this study. The study protocol was approved by institutional ethics committee.

Women with a severe preeclampsia were evaluated and managed as per the hospital protocol. Blood pressure of study subjects was measured by using mercury sphygmomanometer with appropriate cuff size tied at heart level. The women were monitored clinically as well as by investigative work up.

Proteinuria was estimated daily by dip stick method. Serum analysis of uric acid, creatinine, and renal and liver function tests was done by using automated analyser Hitachi p800. Platelet count and protein estimates in 24 hour urine were done at admission and as indicated by the clinical disease behaviour.

Peripheral smears was done to look for spherocytosis, schizocytosis, reticulocytosis, anisocytosis, triangular cells, helmet cells and burr cells for screening for HELLP syndrome. Fundus oculi was examined using ophthalmoscope for hypertension induced changes and the findings were graded as per Keith, Wagner and Barker classification [12]. Sonographic estimation of foetal growth, weight and amount of liquor was carried out. Foetal condition was monitored by foetal heart rate auscultation and foetal heart rate tracings, doppler analysis and modified biophysical profile.

Women were put on antihypertensive drugs-Alpha methyl dopa (maximum dose up to 2 g/day)/labetalol (800 mg/day)/ amlodipine and/or nifedipine (up to 30 mg); dose adjustments or treating with additional drugs was done as per individual requirement. Two doses of intramuscular dexamethasone 12 mg, 12 hours apart was given for preterm salvageable pregnancies.

Women on expectant management were asked to report if they had headache or epigastric pain or vomiting or visual disturbances, those with eclampsia received magnesium sulphate (Pritchard regime) with standard monitoring for magnesium toxicity.

Pregnancy was terminated for eclampsia, uncontrolled hypertension in spite of being on maximum dose of antihypertensive, persisting/progressively deteriorating clinical symptoms or the biochemical markers, occurrence of complications such as placental abruption, eclampsia, renal failure and indication of non-reassuring foetal status.

The decision regarding the route of delivery was based on estimated foetal weight, salvage ability, gestational age, amniotic fluid index, foetal status and cervical score. The neonates were managed by the specialist neonatology team who blind to other parameters.

All the subjects were monitored and the investigative parameters were compared with various maternal outcome. The maternal outcomes were further divided into normal outcome, eclampsia and other complications (Abruption, HELLP, renal failure, pulmonary oedema, cardiomyopathy, and cerebral haemorrhage).

Perinatal outcome measures that were studied include live births, Foetal Growth Restriction (IGUR), still births, neonatal complications (sepsis, intraventricular hemorrhage, hyperbilirubinemia, necrotizing enterocolitis) and neonatal death.

Statistical analysis

Continuous variables were presented as Mean ± SD or Median and interquartile range. The categorical variables were presented as percentages/proportions. Chi square test was done to find the association between investigative parameters and adverse outcomes. A p value<0.05 was considered to be statistically significant.

Data was analysed by using Statistical Package for Social Sciences (SPSS, version 16, Chicago, IL).

Results

The median age of women with severe preeclampsia was 26 (18, 38) years. 11 were above 35 years and 6 had teenage pregnancies. Two third of the group 86 (61.4%) was primigravidae. Previous history of preeclampsia, bad obstetric history and chronic hypertension was seen in 25 women.

Associated medical disorder systemic lupus erythematosis and pheochromocytoma was seen in 4 women. It was observed that mean gestational age at diagnosis of severe preeclampsia was 30 ± 13 weeks and gestational age at delivery was 33 ± 12 weeks. Due to maternal or foetal indications emergency caesarean delivery was done in 105 (75%) and 35 (25%) had vaginal delivery. Among vaginal deliveries 4 lad spontaneous onset of labor and 25 had induced preterm delivery.

Table 1 show the clinical and biochemical characteristics of the study population. Abnormal value above cut-off to define severe preeclampsia was found commonly for proteinuria (90%). Other investigations had values in the severe preeclampsia range only in 12-34% of the group.

Table 2 show the maternal complications observed in the study population. Among 29 women with eclampsia, 25 women have antepartum eclampsia at the time of arrival and 2 each had antepartum and postpartum eclampsia after admission.

Association between investigative parameters and its maternal outcome is shown in Table 3. The mean arterial pressure>127 mmHg (p=0.042), uric acid>7 mg/dl (p=0.001), platelet count<1, 00,000 cells/cc (p=0.003) and serum creatinine>1.2 mg/dl (p=0.025) were significantly associated with poor maternal outcome in women with severe preeclampsia (Table 3). The others parameters were not significant (Table 3).

Among 140 women, 114 had perinatal complications. Still birth was seen in 33, neonatal morbidity was observed in 81 (neonatal deaths 8). Of the 114 with perinatal complications 106 were preterm and 8 were term babies. In the preterm group 81 (69%) babies survived out of 88 live new-borns, the rate survival was 92%.

Among term babies 4 (50%) were still births (1 due to abruption, 2 were due to severe IUGR and oligoamnios and 1 due to severe oligoamnios), there was one neonatal death due to severe respiratory distress syndrome.

Table 1. *Clinical and biochemical characteristics of the study population (N=140).*

Variables	Cut-off values	Number (%)
Systolic blood pressure (mmHg)	≤ 140	35 (25%)
	140-160	63 (45%)
	>160	42 (30%)
Diastolic blood pressure (mmHg)	90-110	118 (84%)
	>100	22 (16%)
Mean arterial Pressure (mmHg)	<127	96 (69%)
	>127	44 (31%)
Urine Protein	1+	14 (10%)
	≥ 2+	126 (90%)
24 h Urine protein (g) (n=42)	<3	33 (24%)
	3-5	9 (5)
Serum Creatinine (mg/dl)	≤ 1.2	123 (88%)
	>1.2	17 (12%)
Serum Uric Acid (mg/dl)	≤ 7	106 (76%)
	>7	34 (24%)
Aspartate Transaminase (IU)	≤ 70	129 (92%)
	>70	11 (8%)
Alanine Transaminase (IU)	≤ 70	123 (87%)
	>70	17 (13%)
Lactate Dehydrogenase (IU)	≤ 600	96 (69%)
	>600	44 (31%)
Platelets (lakhs/ml)	≤ 1	25 (18%)
	>1	115 (82%)

Table 2. *Maternal complications observed in the study population (N=140).*

Complications	Number (%)
Eclampsia	29 (21%)
Abruption	5 (4%)
HELLP	6 (4%)
Renal failure	9 (6%)
Pulmonary oedema	4 (3%)
Cardiomyopathy	1 (0.7%)
Cerebral haemorrhage	1 (0.7%)
Discharge against medical advice	2 (1.4%)
Maternal mortality	Nil

Table 3. *Association between clinical and biochemical parameters with maternal outcome in women with severe preeclampsia (N=140).*

Variables		Outcomes		p value
		Normal	Complications	
Mean arterial pressure (mmHg)	<127 (n=96)	70 (73%)	26 (27%)	0.042
	>127 (n=44)	22 (50%)	22 (50%)	
Urine protein	1+ (n=14)	12 (86%)	2 (14%)	0.224
	≥ 2+ (n=126)	78 (62%)	48 (38%)	
24 h Urine protein (g) (n=24)	<0.3 (n= 6)	6 (100%)	0	0.817
	0.3-3 (n=33)	27 (82%)	6 (18%)	
	3-5 (n=9)	7 (78%)	2 (22%)	
Haemoglobin (gm%)	<11 (n=48)	33 (69%)	15 (31%)	0.777
	11-13 (n=58)	35 (60%)	23 (40%)	
	>13 (n=34)	28 (83%)	6 (17%)	
Total count (cells/cc)	<11000 (n=38)	28 (74%)	10 (26%)	0.523
	>11000 (n=102)	65 (64%)	37 (36%)	
Serum creatinine (mg/dl)	<1.2 (n=120)	88 (73%)	35 (27%)	0.025
	>1.2 (n=20)	5 (25%)	15 (75%)	
Serum uric acid (mg/dl)	<7 (n=103)	79 (76%)	24 (25%)	0.001
	>7 (n=37)	11 (30%)	26 (70%)	
Platelet count (lakh/ml)	<1 (n=28)	10 (36%)	18 (64%)	0.003
	>1 (n=112)	80 (71%)	32 (29%)	

Discussion

The maternal and perinatal morbidity and mortality due to preeclampsia has come down dramatically in developed countries. This has been achieved by improvements in

antenatal care and early hospitalization and proper maternal and foetal surveillance. However, preeclampsia-eclampsia still stands as one of the major complications in pregnancy. The present study was done to find out the association between investigative parameters with maternal outcome in women with a severe preeclampsia. To look for the usefulness of the clinical and investigative work up as predictors of outcome.

In this study, the mean arterial pressure>127 mmHg (p=0.042), uric acid>7 mg/dl (p=0.001), platelet count<1, 00,000 cells/cc (p=0.003), serum creatinine>1.2 mg/dl (p=0.025) were significantly associated with poor maternal outcome in women with a severe preeclampsia.

It has been observed that preeclampsia is more common in young or elderly primigravidas and it is reported that maternal age>35 years is significantly associated with preeclampsia [13]. This is due to progressive vascular damage that occurs with aging [13]. However in our study the mean age of women with preeclampsia is 26 year probably because in this region the age of primigravidas is mostly between 20-30 years.

In this study, the most common maternal complication was eclampsia, flowed by renal failure, HELLP syndrome placental abruption and pulmonary oedema. Preeclampsia associated rare complications such as cerebral haemorrhage and cardiomyopathy were observed. This was in comparison with findings from various other studies [14-17].

In our study, Mean Arterial Pressure (MAP) was considered as one of the measures to find out the association with the maternal outcome. We noted that women has eclampsia or other preeclampsia related complications even at blood pressures- systolic or diastolic or both- not at a level beyond the cut off of 160/110 mmHg for severe preeclampsia. When we considered MAP more 127 mm Hg, 31.8% had eclampsia, 18.2% had other maternal complications, 52.3% had normal outcome and one woman had cerebral haemorrhage. Studies by Menzies and Zhang have reported that there is no relation between blood pressure and adverse maternal outcome [18,19]. However Martin, found correlation between systolic blood pressure more than 160 mmHg and stroke [20]. Systolic blood pressure also had a significant (p<0.05) influence on perinatal deaths in the study by Dhananjay among women with eclampsia [9].

Proteinuria was always thought to be a good indicator of the severity of preeclampsia. In this present study random urine protein more than 2+ was seen in 129 patients; 22.2% had eclampsia and 15.8% had other complications. Twenty four hour urinary protein testing could be done only for 42 women. In other cases decision to terminate pregnancy had to be taken immediately, hence there was no time for 24 hour analysis. Seventy seven percent of women whose 24 hour urine protein was 3 to 5 grams had normal outcome. Chan et al. and Thangaratnam et al. have demonstrated that no level of proteinuria could be used to predict outcomes and is a poor indicator of either maternal or foetal outcome [21,22].

In the study which included 1348 women diagnosed with pre-eclampsia using the International Society for the Study of Hypertension in Pregnancy classification system, the presence proteinuric pre-eclampsia was an independent predictor for preterm birth and perinatal mortality compared with women with non-proteinuric pre-eclampsia [23]. Also data from the Pre-eclampsia Integrated Estimate of Risk (PIERS) study, a prospective study of 2023 women with preeclampsia, showed that none of dipstick, spot protein-creatinine ratio, or the 24 h urine test predicted maternal or foetal outcomes accurately (AUC ROC<0.7 in all cases) [24].

There is elevation of haemoglobin and haematocrit caused by decrease in plasma volume. It is known that haemoconcentration is a hallmark of eclampsia, because of hemoconcentration there is decreased regional perfusion and leads to altered cerebral auto regulatory function which can in turn lead to PRES [25]. In present study one woman had haemoglobin more than 13 g% and 21.4% had between 11 to 13 g% had eclampsia. HELLP syndrome was seen in women with haemoglobin 11 to 13 g% in 4 and more than 13 g% in two women. One study showed that increased haemoglobin/ haematocrit reflects the severity of preeclampsia. So haemoglobin/hematocrit is not good predictors of eclampsia [26].

Preeclampsia is a proinflammatory state caused by placental hypoperfusion. In this study 105 women had total count more than 11000/cc, 4 patients with HELLP had total count more than 11000/cc. A study by Terrone was done in a series of 177 patients of severe preeclampsia alone [27]. The WBC counts were significantly higher in patients with HELLP syndrome (12,500/cc ± 442) than in patients with severe preeclampsia (10,300/cc ± 228). Platelet count varied inversely with WBC counts and the finding of an association between increasing leukocytosis and worsening thrombocytopenia early in the course of HELLP syndrome supports the hypothesis that it may represent an inflammatory state. But it is not a good predictor for maternal outcome in severe preeclampsia.

It is also seen that women with serum uric acid more than 7 mg/dl, 47.1% had eclampsia and 29.4% had other maternal complications. This was comparable with the other studies Thangaratinam et al. where they found threshold value of serum uric acid of 475.8 mmol/L had increased likelihood of adverse maternal outcome [10]. In contrary a study by Thangaratinam et al. in a combined cohort of 634 women, using a threshold level of 350 l umol/L observed that serum uric acid was a poor predictor of eclampsia and poor predictor of maternal and fetal complications [10]. In this present study women who had uric acid less than 7 mg/dl 12.2% had eclampsia and 10.3% had other severe preeclampsia related complications.

In the present study it was found that women who had serum creatinine more than 1.2 mg/dl were found to have other maternal complications like abruption, renal failure etc. Women who had serum creatinine less than 1.2 mg/dl were found to have 18.6% eclampsia and 9.7% other maternal complications. Other studies have also found that serum creatinine>1.2 mg/dl is associated with adverse maternal outcome [28,29].

Platelet count less than 1, 00,000 cells/cc was associated with maternal complications other than eclampsia. This was comparable with the studies where they have found that platelet count less than 100×10^9 was found to be associated with the increased incidence of adverse maternal and perinatal outcomes [30,31].

In this study, the mean arterial pressure>127 mmHg, uric acid>7 mg/dl, platelet count<1, 00,000 cells/cc and serum creatinine>1.2 mg/dl were significantly associated with maternal complications and eclampsia. As the observation are not consistent across the studies, it probably worthwhile to develop and check the usefulness of a scoring system to predict outcome.

Limitations

The study is limited by it sample size which is too small to look for association with individual maternal complication and perinatal complication. Hence we had to group them as maternal and perinatal outcome. In this study we did not attempt to find the association between of individual clinical and investigative parameter with the perinatal outcome, because firstly as shown in the study perinatal outcome is mainly influenced by gestational age and birth weight. Second, there are other factors such as insults at birth, mode of delivery etc. which will influence the outcomes; hence the number will be too small for multivariate analysis.

Conclusions

Maternal and perinatal morbidity is still high among women with severe preeclampsia. Mean arterial pressure>126 mmHg, serum uric acid>7 mg/dl, platelet count<1, 00,000 cells/cc, serum creatinine>1.2 mg/dl were found be associated significantly with poor maternal outcome in women with severe preeclampsia. Prematurity and foetal growth restrictions are the main factors causing perinatal morbidity/ mortality. Timely caesarean delivery seems to improve perinatal outcome in settings with facilities for new-born care.

Conflict of Interest

None

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