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*RESEARCH ARTICLE*

# DETERMINANTS OF MORTALITY AND COMPLICATIONS IN HYPERTENSIVE DISORDERS OF PREGNANCY : A SINGLE CENTER EXPERIENCE

**Mishra A.[1], Malik S.[1], Pangtey P.[1], Gautam A.[1] and Verma P.K[2]**

1. Department of Obstetrics & Gynecology.
2. Department of Anaesthesia, Vardhman Mahavir Medical College & Safdarjung Hospital, New Delhi, India.

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## *Abstract*

Our retrospective cohort study set out to identify the determinants of adverse maternal and perinatal outcome in patients admitted to intensive care (ICU) with severe features of Hypertensive Disorders of Pregnancy(HDP).Case files of patients with severe pre-eclampsia and eclampsia (including HELLP syndrome) were analyzed.The prevalence of HDP was 6.01% and eclampsia 0.99%. Parity did not affect the severity of disease nor survival. The incidence of chronic hypertension was 15.38% and 12.5% in survivors and non-survivors respectively. There was a high number of patients who did not receive any antenatal care prior to admission in both the groups [69% and 87%]. Severe anemia was significantly higherin non-survivors (42%) than in survivors (13%). Symptoms such as blurred vision, respiratory distress, oliguria, altered sensorium and absent fetal movements were prognostic markers. Multiple seizures and a time lapse between the onset of symptoms and administration of magnesium sulfate produced an increased mortality. The stillbirth rate, as expected, was high is those who demised (62.5%).We conclude that complications due to hypertension in pregnancy should be considered as a failure to provide quality antenatal care and represent a missed opportunity to detect and treat raised blood pressure.



## Introduction:-

HDP complicated approximately 10-17% of all pregnancies in low- to middle-income countries (LMICs). [1,2,3] In high resource countries, the prevalence is low, 7% in United States and only 1-2% of all pregnancies in some of the European countries.[4,5,6] In LMICs, the prevalence of preeclampsia and eclampsia has increasedfrom 9.4 to 12.4 per 1,000 deliveries owing to a rising prevalence of obesity, delayed age of childbearing and increasing use of assisted reproductive technologies.[7] Possible mechanisms for HDP are vasospasm, endothelial activation, abnormal placentation and maternal inflammatory response.[8] Globally this results in 50,000-100,000 maternal deaths and 50,000 perinatal deaths annually,[9,10,11]usually due to eclampsia, acute renal failure, disseminated intravascular coagulopathy, acute respiratory distress syndrome, cerebrovascular accident, pulmonary dysfunction or oedema[12] , majorityoccuring in low resource settings. Many researchers have created statistical models to predict survival including parity, maternal age, period of gestation, co-morbid conditions, systolic blood pressure, deep tendon reflexes, and urine protein to creatinine ratio, platelet count, serum alanine amino transaminase, blood urea, serum creatinine, oxygen saturation, prior preeclampsia, body mass index, diastolic blood pressure, placental growth factor

**Corresponding Author:- Priyanka Pangtey, MS**
Address:- Ward 3, VMMC and Safdarjung Hospital.

and treatment with antihypertensives or magnesium sulphate.[13,14]Our purpose for undertaking this study was to identify the determinants of adverse maternal and perinatal outcome in HDP with severe features in Intensive Care Unit (ICU) admitted patients.

## Methods:-

Ours was a retrospective cohort of critically ill patients of severe preeclampsia and eclampsia (including HELLP syndrome) admitted to intensive care of our tertiary care centerbetween January and December 2019.After clearance from the institutional ethics committee the study was carried on. Those with very short admission stay (<4 hours)due to early mortality in casualty or labour room were not included. Inclusion criteria (ACOG practice bulletin 202) required: -

[1] Systolic BP>160 mmHg and diastolic > 110 mmHg, or an increment of 30 mm systolic or 15 mm diastolic from previous blood pressure readings
[2] Proteinuria (albuminuria > 300 mg in 24h or proteinuria > 2 g /24h)
[3] Elevation of serum creatinine >106.1 umol/L
[4] Platelet count < $100X10^9$ cells/L
[5] Elevated liver enzymes [AST and ALT]
[6] Persistent headache, visual disturbances
[7] Persistent epigastric pain

As per ACOG practice bulletin 202, eclampsia is the convulsive manifestation of the hypertensive disorders of pregnancy. It 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 hemorrhage, or drug use. Eclampsia oftenis preceded by premonitory signs of cerebral irritation such as severe and persistent occipital or frontal headaches, blurred vision, photophobia, and altered mental status, but can occur in the absence of warning signs or symptoms.

The cohort was divided into two groups, survivors and non-survivors. We evaluated and compared clinico-epidemiological parameters, laboratory investigations, treatment received, obstetric intervention, maternal and perinatal outcome of all the cases. On the basis of these, we determinedcomplications and mortality, as well as the overall mortality and morbidity.

Categorical variables were presented in number and percentage and continuous variables as mean ± standard deviation. Quantitative variables were compared using the independent t test between the two groups. Qualitative variables were compared using $\chi^2$/Fisher's Exact test. A p value of <0.05 was considered statistically significant. The data was analyzed using Statistical Package for Social Sciences (SPSS) version 21.0.

## Results:-

There were 28,563 deliveries, 1718 cases of HDP and 283 of eclampsia giving a prevalence of 6.0 % and 0.99% respectively.

For the year 2019, our total maternal mortality was 181, of whom 54 (29.8%) died of HDP. 24 patients of HDP died in ICU, 17 died in labour room – eclampsia unit (imminent delivery or non availability of beds in ICU at that given time) and 13 died within an hour in Gynecology casualty during initial stabilization.

During our study period, there were 1480 admissions to ICU with 516 deaths. Obstetric admissions were 299 (20.2%) of all ICU admissions. We had 63 patients of HDP admitted and 24 died in ICU, contributing to 4.6% of mortality in ICU. Overall mortality rate of our ICU was 34.8% while case fatality of HDP was 38.09% which is higher than rest of the patients admitted in ICU.

Out of these 63 patients of HDP - 52 patients [29 survivors and 21 non-survivors] were referred to us by other hospitals. Out of total patients, 16 were suffering from severe pre-eclampsia and 47 had eclampsia. 37 were antepartum eclampsia and 10 were post-partum eclampsia. Survivor group had 22 patients of eclampsia and non-survivors had 25 patients of eclampsia.

Non-survivors were admitted at a significantly lesser gestational age. All the survivors and non-survivors were anemic [Haemoglobin<11 gm%]. However severe anemia [ Haemoglobin<7 gm %] was significantly higher in non-survivors (Table 5). Presence of diabetes, twins or pre-existing chronic diseases did not affect survival in present study. Only four patients in survivor group and none of non-survivor had treatment for hypertension in antenatal period [p = 0.288]. (Table1)

It was found that blurred vision, respiratory distress, oliguria, altered sensorium and loss of fetal movement was significantly greater in non-survivors. There was no difference in mean systolic blood pressure and mean diastolic blood pressure before commencement of therapy in both these groups and it was in range of severe disease. Most significant determinant of mortality was multiple seizures. (Table 2)

Significantly higher proportion of survivors received anti-hypertensives and anticonvulsant [Magnesium Sulphate - MgSO4] in the peripheral centre before reaching our hospital. A worth noting observation was that a subset of these patients received only intramuscular 10 gm Magnesium Sulphate and no loading intravenous dose of 4 gm. These patients were significantly more in non-survivors than survivors as they continued to have seizures in the transit. Although the number was small [n=5] to make a definitive comment but it certainly reflects lack of uniform protocol in peripheral centers. (Table 3)

Another important finding was delay in receiving first dose of Magnesium Sulphate more than 6 hours after onset of severe symptoms which was significantly more in non-survivors as compared to survivors.

During their stay in our hospital all these patients were treated according to hospital protocol with anti-hypertensives, Magnesium Sulfate and other drugs according to the case. However, use ofNitro-glycerine drip [ 4 Vs 11 p value =0.002] and Inotropes [13 Vs 19 p value 0.001] was significantly higher in non-survivors. Inotrope administration was mostly in preterminal stage of multiorgan failure.

As for the complications - eclampsia, HELLP, deranged coagulation, pulmonary oedema, acute renal failure, intracranial haemorrhage, septicaemia, post-partum haemorrhage and dilated cardiomyopathy were significantly higher in non-survivors. (Table 4,5)

In present study mode of delivery did not seem to affect survival. In survivor group, 26 patients had vaginal delivery and 13 patients had caesarean section. In non-survivor group, 17 patients had vaginal delivery and 7 had caesarean section. Fetal growth restriction in survivor and non- survivor group was 31% and 38% respectively. Stillbirth was significantly more in non- survivor group – 63% whereas in survivor group it was 26% (p value =0.008). Early neonatal death in survivor and non-survivor group was 10% and 17% respectively.

## Discussion:-

In present study prevalence of HDP was 6.01% and eclampsia 0.99 %. Other studies from different parts of India reported the incidence of hypertensive disorders of pregnancy to be 7.8 - 9.1% , preeclampsia - 5.4% and eclampsia - 0.6%. [15, 16,17]

Worldwide preeclampsia and eclampsia are supposed to be affecting more primigravida as compared to multigravida however mortality is more in multigravida especially grand multipara.[18] In present study, parity did not affect the severity of disease and survival. Our observation is seconded by another study from central India.[16]

Incidence of chronic hypertension in present study was higher than other studies which was 15.38% and 12.5% in survivors and non-survivors respectively. In other studies, it was 0.17% and 1.9% in total patients of hypertensive disorders in pregnancy.[16, 18] We interpret this difference as the prevalence of chronic hypertension in HDP may be less but chronic hypertension superimposed preeclampsia causes poorer prognosis leading to critical illness.

Significant points of our study were high number of patients who did not receive any antenatal care in both the groups [69% and 87% respectively]. The difference between the two groups was not significant but it is remarkable that all these patients were near-miss which is an indirect evidence that lack of antenatal care is one of the most important and preventable determinant of severe disease. Studies from Africa concluded that lack of prenatal care, delay in referral and lack of clarity in protocol of management in the hospitals were three main avoidable factors.[19,20]

Patients who developed severe disease at a lesser gestation had poorer prognosis. This observation is explained by predominant vascular pathology resulting in smaller placental volume, severe Fetal Growth Restriction (FGR) and more severe disease in these patients.[21]

In present study hypertensive disorders along with severe anaemia [Haemoglobin <7 gm %] had significantly higher mortality. Other researchers have also concluded that "coexistence of systolic and diastolic hypertension, HELLP syndrome and anaemia" is a deadly triad determining mortality. [22,23] It is explained by lack of antenatal care and nutritional deficiency of folic acid, calcium, micronutrients like zinc, magnesium, and antioxidants which are aetiologies of both the diseases.

Our study revealed that symptoms like - blurred vision, respiratory distress, oliguria, altered sensorium and loss of foetal movement were significantly greater in non-survivors. Thusthese features may be taken for prognostication and their presence demands promptinterevention.

There was no significant difference in mean systolic and diastolic blood pressure before commencement of therapy in both these groups and it was in the range of severe disease. We, however, did not encounter normotensive eclampsia much.

One of the most significant determinants of mortality was multiple seizures and time lapse between onset of symptoms and administration of Magnesium sulphate. Multiple seizures as important determinant of mortality which is recognized and supported by other studies too.[22] Most of these patients belonged to rural background and low socio-economic status. There was delay in seeking help and transportation. As per records some of these patients went to 2-3 centres before reaching our hospital. It reflects inadequacy of referral linkage. Transition from one facility to another wasted time and further deteriorated the condition of the patients who needed termination of pregnancy at the earliest.

Significantly higher proportion of survivors received antihypertensives and anticonvulsants in the peripheral centre that too within 6 hours of onset of symptoms before reaching our hospital. Early and appropriate treatment is vital for survival of these patients. Sak et al in his study of 167 eclamptic women also compared survivors to non-survivors and reported significantly increased risk of mortality in patients with multiple seizures, increased AST and ALT, high postpartum diastolic blood pressure, low haematocrit and haemoglobin levels.[22] A common observation of most of the researchers including Sak et al, Vigil-De Gracia et al and Martin et al is relationship of mortality with co-existence of eclampsia with HELLP syndrome. [22,23,24] . One meta-analysis including 32 studies of HDP interpreted gestational age, chest pain, dyspnoea, AST, platelet count and serum creatinine levels as predictors of maternal outcome in best performing multivariate model.[25] They also concluded that proteinuria is a poor predictor of outcome.[8]

There was no difference in mode of delivery in both the groups. In perinatal outcome, stillbirth was significantly more in non-survivor group. In another study from South India, the rate of Intrauterine Death (IUD), FGR and early neonatal death was found to be 12.67%, 22.06 % and 10.7 % respectively. This was lesser than both the groups of our study - 25.64 & 62.5% IUD, 30.77 & 37.5% FGR and 10.26% &16.67% neonatal death.[15] Poor perinatal outcome in non-survivor was attributed to prematurity, severe FGR and birth asphyxia due to multiple seizures. Other studies shared same view and reported 2-3 times higher perinatal mortality in severe hypertensive disorders.[26,27]

**Strength** –
Most of the studies in the literature were done in cohort of hypertensive disorders of pregnancy varying from mild - severe disease and focus mainly only the magnitude of mortality rather than the determinants. Even the studies done in this regard were multicentric studies where patients were treated in different hospitals with different protocols. Most researchers accept missing data as a constraint.[16] Our study analysed determinants of mortality survivors versus non-survivors only in critical patients admitted to intensive care unit who were treated as per the uniform hospital protocol, thus both groups were comparable.

**Limitation** –
This study is a retrospective study. In spite of good record keeping in ICU, history regarding quality of antenatal care and reasons for not seeking antenatal care could not be retrieved. Another limitation is that our hospital is a

tertiary care centre receiving such critical patients from neighboring threestates, that our data may not match with the population based studies done in India. This study was done on ICU admitted patients of Hypertensive disorders who were critically ill so case fatality rate is expected to be higher. We recommend a larger prospective population-based study in this respect.

## Conclusion:-

A large enquiry of maternal deaths in early part of last decade revealed 79% deaths from hypertensive disorders occur due to improper management and they are potentially preventable.[28] Clinical researches have also shown that about 60% of hypertension-related maternal mortality and morbidity is potentially preventable. Complications due to hypertension in pregnancy should be considered as failure to provide quality antenatal care and missed opportunity to detect and treat severe maternal hypertension. Wide access to medical services and quality antenatal care at primary level, better referral linkage, trained medical team and prompt management of the complications would be translate into better maternal and perinatal outcome. Most important step will be behaviour changing communication with general public emphasizing need of antenatal care and information regarding complications of hypertensive disorders of pregnancy.

**Table 1:-** Distribution of Clinico-epidemiological characteristics.

| | **Survivors[n=39]** | **Non Survivor[n=24]** | **P value** |
|---|---|---|---|
| **Age** | 24.6 ± 6.7 years | 26.9 ± 5.6 years | 0.165 |
| | | | |
| **Primiparity** | 16(41.03%) | 10(41.67%) | 0.831 |
| **Mean gestational age** | 35 ± 3.9 weeks | 30 ± 4.87 weeks | <.0001 |
| **No antenatal care** | 27(69%) | 21(87.5 %) | 0.132 |
| **Chronic Hypertension** | 6(15.38%) | 3(12.5%) | 1 |
| **Hypertension in previous pregnancy** | 8(20.51 %) | 6(25%) | 0.847 |
| **Diabetes/ GDM** | 3(7.6%) | 3(12.5%) | 0.666 |
| **Pre-existing Heart disease** | 2(5.12%) | 3(12.5%) | 0.36 |
| **Severe Anaemia** | 5(12.8 %) | 10(41.66%) | 0.021 |
| **Pre-existing respiratory Problem** | 3(7.6%) | 3(12.5%) | 0.666 |
| **Twins** | 2(5.12%) | 3(12.5%) | 0.36 |

***(Total ICU-HDP patients– 63)**

**Table 2:-** Comparison of Presentation.

| **Characteristics** | **Survivors[n=39]** | **Non Survivor[n=24]** | **P value** |
|---|---|---|---|
| | | | |
| **Received Antihypertensives in antenatal care** | 4(10.26%) | 0(0%) | 0.288 |
| **Headache** | 36(92.31%) | 24(100%) | 0.281 |
| **Oedema** | 39(100%) | 24(100%) | - |
| **Vomiting** | 26(66.67%) | 18(75%) | 0.676 |
| **Epigastric pain** | 24(61.54%) | 20(83.33%) | 0.092 |
| **Blurred Vision** | 17(43.59%) | 20(83.33%) | 0.003 |
| **Dyspnoea/Tachypnoea** | 16(41.03%) | 19(79..17%) | 0.007 |
| **Oliguria** | 2(5.13%) | 6(25%) | 0.045 |
| **Altered Sensorium** | 11(28.21%) | 22(91.67%) | <.0001 |
| **Loss of foetal movements** | 15(38.46%) | 17(70.83%) | 0.025 |
| **Mean Systolic BP on admission** | 160 ± 15.67mmHg | 166 ± 14.67mmHg | 0.136 |
| **Mean Diastolic BP on admission** | 116 ± 10.5 mmHg | 120 ± 11.45 mmHg | 0.161 |
| **Multiple Seizures** | 5(12.82%) | 19(79.17%) | <.0001 |

**Table 3:-** Comparison of treatment received prior to admission in our hospital.

| Treatment | Survivors[n=39] | Non Survivor[n=24] | P value |
|---|---|---|---|
| **Referred cases** | 29(74.36%) | 21(87.50%) | 0.337 |
| **Received antihypertensive in peripheral hospital** | 20(51.28%) | 5(20.83%) | 0.033 |
| **Received loading dose of MgSO4 in periphery** | 20(51.28%) | 5(20.83%) | 0.033 |
| **Received inadequate loading dose (Intramuscular only)** | 1(2.56%) | 5(20.83%) | 0.026 |
| **Received loading dose more than 6 hours of seizure** | 10(25.64%) | 17(70.83%) | 0.001 |

**Table 4:-** Comparison of complications.

| Complications | Survivors[n=39] | Non Survivor[n=24] | P value |
|---|---|---|---|
| **Eclampsia** | 25(64.10%) | 22(91.67%) | 0.018 |
| **Abruptio Placentae** | 12(30.77%) | 13(54.17%) | 0.114 |
| **Deranged Coagulation** | 0(0%) | 14(58.33%) | <.0001 |
| **Pulmonary Oedema** | 16(41.03%) | 19(79.17%) | 0.007 |
| **ARF** | 2(5.13%) | 6 (25%) | 0.045 |
| **PRES*** | 11(28.21%) | 13(54.17%) | 0.073 |
| **Intracranial Haemorrhage** | 0(0%) | 8(33.33%) | 0.0002 |
| **HELLP** | 4(10.26%) | 11(45.83%) | 0.002 |
| **Septicaemia** | 0(0%) | 7(29.17%) | 0.0006 |
| **PPH** | 4(10.26 %) | 12(50%) | 0.0008 |
| **Dilated Cardiomyopathy** | 89(20.51%) | 13(54.17%) | 0.013 |

PRES – Posterior Reversible Encephalopathy Syndrome

**Table 5:-** Investigations.

| Investigation | Survivor Mean value | Non- survivor Mean value | p value | Normal value range |
|---|---|---|---|---|
| Hemoglobin | 8 | 6.4 | .0039 | 11-14 g/dL |
| Platelet count | 164 | 155 | .279 | 150-450 X $10^9$/L |
| LDH | 247 | 449 | .000581 | 140-280 U/L |
| PT | 13 | 20 | .0015 | 12-14 s |
| PTT | 39 | 48 | < .00001 | 35-45 s |
| INR | 0.55 | 2.75 | < .00001 | <1 |
| Creatinine | 60.13 | 99.91 | .003155 | 35.4 – 70.7 umol/L |
| AST | 34 | 77 | .000479 | <40 IU/L |
| ALT | 32 | 78 | .000332 | <40 IU/L |

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**Contribution to authorship:**
AM: conception, planning, execution, analysis, manuscript preparation, reference search
SM: conception, planning, analysis
PP : analysis, manuscript preparation, reference search
AG: conception, planning, execution, analysis, manuscript preparation, reference search
PKV: conception, planning, analysis

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