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Assessment of maternal and perinatal outcomes in pre-eclampsia females admitted to government medical college bettiah, West Champaran, Bihar

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Abstract
In India, the incidence of eclampsia range from 1 in 500 to 1 in 30 (0.5%-1.8%). The occurrence, however, depends on the availability, accessibility and quality of antenatal care. Consequently, rates are higher where healthcare provision is constrained for a variety of reasons. Maternal mortality in eclampsia is intolerably high in India, and ranges from 2%-30%, much more in the established rural hospital than in urban equivalent. In India, the perinatal mortality of neonates of eclamptic mothers is also very high to the extent of about 30– 50%, in spite of all efforts of Government to bring down maternal and perinatal mortality. Hence based on above findings the present study was planned for Assessment of Maternal and Perinatal Outcomes in Pre-Eclampsia Females Admitted to
The present study was planned in Department of Obstetrics & Gynaecology, Government Medical College Bettiah, West Champaran, Bihar, India. In the present study 50 cases of the females were enrolled in the present study. The 25 females of pre-eclampsia were evaluated in Group I and remaining 25 females with normal pregnancy were evaluated in Group II. Maternal data were documented with respect to age, parity, socioeconomic status, whether urban or rural, status of antenatal care, gestational age at delivery and mode of delivery. Relevant maternal investigations were also obtained. Fetal outcome data were documented with respect to birth weight, still birth rate, asphyxia and its degree, gestational age, neonatal complications, neonatal death rate and overall perinatal loss. A pre-designed structured Performa was used to interview eligible women and clinical examination findings & investigations performed were noted.
The data generated from the present study concludes that Eclampsia is associated with significant maternal and perinatal morbidity and mortality. The higher death is due to high percentage of the patient being unbooked; majority receive no therapeutic intervention until admission. Good antenatal care, nutrition, health education, early diagnosis, good control of BP, early referral to higher centre, multidisciplinary approach will reduce morbidity as well as mortality in mother and baby.

Keywords: Preeclampsia, Maternal outcomes, etc

Introduction
Preeclampsia is one of the hypertensive (high blood pressure) disorders of pregnancy. It is a major cause of maternal and perinatal mortality (number of stillbirths and deaths of newborn in the first week of life) and morbidity. Hypertensive disorders of pregnancy occur in about 10% of all pregnant women around the world. Preeclampsia affects 3–5% of pregnancies. Along with preeclampsia, other diseases which are included in the group of hypertensive disorders of pregnancy are eclampsia, gestational hypertension and chronic hypertension. In Asia and Africa, nearly one tenth of all maternal deaths are associated with hypertensive disorders of pregnancy. In India, the incidence of preeclampsia is reported to be 8-10% among the pregnant women. According to a study, the prevalence of hypertensive disorders of pregnancy was 7.8% with preeclampsia in 5.4% of the study population in India.
Preeclampsia is a pregnancy specific hypertensive disease with multisystem involvement. It is a disorder of widespread vascular endothelial malfunction and vasospasm that occurs after 20 weeks of gestation and can present as late as 4-6 weeks postpartum (after child birth). According to the new guidelines given by American Congress of Obstetricians and Gynaecologists (ACOG) in 2013, the diagnosis of preeclampsia does not require the detection of high levels of protein in the urine (proteinuria) along with hypertension. Evidence shows that changes in kidney and liver can occur without signs of proteinuria, and the amount of protein in the urine does not predict how severely the disease will progress.
Preeclampsia is now to be diagnosed by persistent high blood pressure that develops during pregnancy or during the postpartum period and is associated with a lot of protein in the urine or the new development of decreased blood platelets, changes in the kidney or liver function, fluid in the lungs, or signs of brain disorder such as seizures and/or visual disturbances. HEELP syndrome and eclampsia are the serious complications of the preeclampsia. The majority of deaths related to preeclampsia can be prevented by providing timely and effective care to pregnant women presenting with such complications.
Pre-eclampsia (PE) is a disorder of pregnancy characterized by the onset of high blood pressure more than 140/90 mm and often a significant amount of protein in the urine. When it arises, the condition begins after 20 weeks of pregnancy. In severe disease there may be red blood cell breakdown, a

low blood platelet count, impaired liver function, kidney dysfunction, swelling, shortness of breath due to fluid in the lungs, or visual disturbances. Pre-eclampsia increases the risk of poor outcomes for both the mother and the baby. If left untreated, it may result in seizures at which point it is known as eclampsia [1].

Risk factors for pre-eclampsia include obesity, prior hypertension, older age, and diabetes mellitus. It is also more frequent in a woman's first pregnancy and if she is carrying twins. The underlying mechanism involves abnormal formation of blood vessels in the placenta amongst other factors. Most cases are diagnosed before delivery. Rarely, pre-eclampsia may begin in the period after delivery. While historically both high blood pressure and protein in the urine were required to make the diagnosis, some definitions also include those with hypertension and any associated organ dysfunction. Blood pressure is defined as high when it is greater than 140 mmHg systolic or 90 mmHg diastolic at two separate times, more than four hours apart in a woman after twenty weeks of pregnancy. Pre-eclampsia is routinely screened for during prenatal care [2].

Recommendations for prevention include: aspirin in those at high risk, calcium supplementation in areas with low intake, and treatment of prior hypertension with medications. In those with pre-eclampsia delivery of the baby and placenta is an effective treatment. When delivery becomes recommended depends on how severe the pre-eclampsia and how far along in pregnancy a woman is. Blood pressure medication, such as labetalol and methyldopa, may be used to improve the mother's condition before delivery. Magnesium sulfate may be used to prevent eclampsia in those with severe disease. Bedrest and salt intake have not been found to be useful for either treatment or prevention [3].

Pre-eclampsia affects 2–8% of pregnancies worldwide. Hypertensive disorders of pregnancy (which include pre-eclampsia) are one of the most common causes of death due to pregnancy. They resulted in 46,900 deaths in 2015 Pre-eclampsia usually occurs after 32 weeks; however, if it occurs earlier it is associated with worse outcomes. Women who have had pre-eclampsia are at increased risk of heart disease and stroke later in life. The word "eclampsia" is from the Greek term for lightning. The first known description of the condition was by Hippocrates in the 5th century BC [4].

Swelling (especially in the hands and face) was originally considered an important sign for a diagnosis of pre-eclampsia. However, because swelling is a common occurrence in pregnancy, its utility as a distinguishing factor in pre-eclampsia is not high. Pitting edema (unusual swelling, particularly of the hands, feet, or face, notable by leaving an indentation when pressed on) can be significant, and should be reported to a health care provider.

In general, none of the signs of pre-eclampsia are specific, and even convulsions in pregnancy are more likely to have causes other than eclampsia in modern practice. Further, a symptom such as epigastric pain may be misinterpreted as heartburn. Diagnosis, therefore, depends on finding a coincidence of several pre-ecclamptic features, the final proof being their regression after delivery.

Physiologically, research has linked pre-eclampsia to the following physiologic changes: alterations in the interaction between the maternal immune response and the placenta, placental injury, endothelial cell injury, altered vascular reactivity, oxidative stress, imbalance among vasoactive substances, decreased intravascular volume, and disseminated intravascular coagulation [5].

While the exact cause of pre-eclampsia remains unclear, there is strong evidence that a major cause predisposing a susceptible woman to pre-eclampsia is an abnormally implanted placenta. This abnormally implanted placenta may result in poor uterine and placental perfusion, yielding a state of hypoxia and increased oxidative stress and the release of anti-angiogenic proteins along with inflammatory mediators into the maternal plasma. A major consequence of this sequence of events is generalized endothelial dysfunction. The abnormal implantation may stem from the maternal immune system's response to the placenta, specifically a lack of established immunological tolerance in pregnancy. Endothelial dysfunction results in hypertension and many of the other symptoms and complications associated with pre-eclampsia. Those with pre-eclampsia may have a lower risk of breast cancer [6].

Abnormal chromosome 19 microRNA cluster (C19MC) impairs extravillus trophoblast cell invasion to the spiral arteries, causing high resistance, low blood flow, and low nutrient supply to the fetus [7].

Although much research into mechanism of pre-eclampsia has taken place, its exact pathogenesis remains uncertain. Pre-eclampsia is thought to result from an abnormal placenta, the removal of which ends the disease in most cases. During normal pregnancy, the placenta vascularizes to allow for the exchange of water, gases, and solutes, including nutrients and wastes, between maternal and fetal circulations. Abnormal development of the placenta leads to poor placental perfusion. The placenta of women with pre-eclampsia is abnormal and characterized by poor trophoblastic invasion. It is thought that this results in oxidative stress, hypoxia, and the release of factors that promote endothelial dysfunction, inflammation, and other possible reactions [5].

The clinical manifestations of pre-eclampsia are associated with general endothelial dysfunction, including vasoconstriction and end-organ ischemia. Implicit in this generalized endothelial dysfunction may be an imbalance of angiogenic and anti-angiogenic factors. Both circulating and placental levels of soluble fms-like tyrosine kinase-1 (sFlt-1) are higher in women with pre-eclampsia than in women with normal pregnancy. sFlt-1 is an anti-angiogenic protein that antagonizes vascular endothelial growth factor (VEGF) and placental growth factor (PIGF), both of which are proangiogenic factors. Soluble endoglin (sEng) has also been shown to be elevated in women with pre-eclampsia and has anti-angiogenic properties, much like sFlt-1 does [5].

Both sFlt-1 and sEng are upregulated in all pregnant women to some extent, supporting the idea that hypertensive disease in pregnancy is a normal pregnancy adaptation gone twisted. As natural killer cells are intimately involved in placentation and placentation involves a degree of maternal immune tolerance for a foreign placenta, it is not surprising that the maternal immune system might respond more negatively to the arrival of some placentae under certain circumstances, such as a placenta which is more invasive than normal. Initial maternal rejection of the placental cytotrophoblasts may be the cause of the inadequately remodeled spiral arteries in those cases of pre-eclampsia associated with shallow implantation, leading to downstream hypoxia and the appearance of maternal symptoms in response to upregulated sFlt-1 and sEng.

Oxidative stress may also play an important part in the pathogenesis of pre-eclampsia. The main source of reactive oxygen species (ROS) is the enzyme xanthine oxidase (XO) and this enzyme mainly occurs in the liver. One hypothesis is that the increased purine catabolism from placental hypoxia results in increased ROS production in the maternal liver and release into the maternal circulation that causes endothelial cell damage [8].

Abnormalities in the maternal immune system and insufficiency of gestational immune tolerance seem to play major roles in pre-eclampsia. One of the main differences found in pre-eclampsia is a shift toward Th1 responses and the production of IFN-γ. The origin of IFN-γ is not clearly identified and could be the natural killer cells of the uterus, the placental dendritic cells modulating responses of T helper cells, alterations in synthesis of or response to regulatory molecules, or changes in the function of regulatory T cells in pregnancy. Aberrant immune responses promoting pre-eclampsia may also be due to an altered fetal allorecognition or to inflammatory triggers [9]. It has been documented that fetal cells such as fetal erythroblasts as well as cell-free fetal DNA are increased in the maternal circulation in women who develop pre-eclampsia. These findings have given rise to the hypothesis that pre-eclampsia is a disease process by which a placental lesion such as hypoxia allows increased fetal material into the maternal circulation, that in turn leads to an immune response and endothelial damage, and that ultimately results in pre-eclampsia and eclampsia.

One hypothesis for vulnerability to pre-eclampsia is the maternal-fetal conflict between the maternal organism and fetus. After the first trimester trophoblasts enter the spiral arteries of the mother to alter the spiral arteries and thereby gain more access to maternal nutrients [28]. Occasionally there is impaired trophoblast invasion that results in inadequate alterations to the uterine spiral arteries. It is hypothesized that the developing embryo releases biochemical signals that result in the woman developing hypertension and pre-eclampsia so that the fetus can benefit from a greater amount of maternal circulation of nutrients due to increased blood flow to the impaired placenta. This results in a conflict between maternal and fetal fitness and survival because the fetus is invested in only its survival and fitness while the mother is invested in this and subsequent pregnancies [10].

Another evolutionary hypothesis for vulnerability to pre-eclampsia is the idea of ensuring pair-bonding between the mother and father and paternal investment in the fetus. Researchers posit that pre-eclampsia is an adaptation for the mother to terminate investment in a fetus that might have an unavailable father, as determined by repeated semen exposure of the father to the mother. Various studies have shown that women who frequently had exposure to partners' semen before conception had a reduced risk of pre-eclampsia. Also, subsequent pregnancies by the same father had a reduced risk of pre-eclampsia while subsequent pregnancies by a different father had a higher risk of developing pre-eclampsia.

In normal early embryonic development, the outer epithelial layer contains cytotrophoblast cells, a stem cell type found in the trophoblast that later differentiates into the fetal placenta. These cells differentiate into many placental cells types, including extravillous trophoblast cells. Extravillous trophoblast cells are an invasive cell type which remodel the maternal spiral arteries by replacing the maternal epithelium and smooth muscle lining the spiral arteries causing artery dilation. This prevents maternal vasoconstriction in the spiral arteries and allows for continued blood and nutrient supply to the growing fetus with low resistance and high blood flow.

In pre-eclampsia, abnormal expression of chromosome 19 microRNA cluster (C19MC) in placental cell lines reduces extravillus trophoblast migration. Specific microRNAs in this cluster which might cause abnormal spiral artery invasion include miR-520h, miR-520b, and 520c-3p. This impairs extravillus trophoblast cells invasion to the maternal spiral arteries, causing high resistance and low blood flow and low nutrient supply to the fetus. There is tentative evidence that vitamin supplementation can decrease the risk [11].

There have been many assessments of tests aimed at predicting pre-eclampsia, though no single biomarker is likely to be sufficiently predictive of the disorder. Predictive tests that have been assessed include those related to placental perfusion, vascular resistance, kidney dysfunction, endothelial dysfunction, and oxidative stress. Examples of notable tests include:

Doppler ultrasonography of the uterine arteries to investigate for signs of inadequate placental perfusion. This test has a high negative predictive value among those individuals with a history of prior pre-eclampsia [5].

Elevations in serum uric acid (hyperuricemia) is used by some to "define" pre-eclampsia, though it has been found to be a poor predictor of the disorder [5]. Elevated levels in the blood (hyperuricemia) are likely due to reduced uric acid clearance secondary to impaired kidney function.

Angiogenic proteins such as vascular endothelial growth factor (VEGF) and placental growth factor (PIGF) and anti-angiogenic proteins such as soluble fms-like tyrosine kinase-1 (sFlt-1) have shown promise for potential clinical use in diagnosing pre-eclampsia, though evidence is sufficient to recommend a clinical use for these markers. Recent studies have shown that looking for podocytes (specialized cells of the kidney) in the urine has the potential to aid in the prediction of pre-eclampsia. Studies have demonstrated that finding podocytes in the urine may serve as an early marker of and diagnostic test for pre-eclampsia [12].

In India, the incidence of eclampsia range from 1 in 500 to 1 in 30 (0.5%-1.8%). The occurrence, however, depends on the availability, accessibility and quality of antenatal care. Consequently, rates are higher where healthcare provision is constrained for a variety of reasons [13]. Maternal mortality in eclampsia is intolerably high in India, and ranges from 2%-30%, much more in the established rural hospital than in urban equivalent. In India, the perinatal mortality of neonates of eclamptic mothers is also very high to the extent of about 30– 50% [14], in spite of all efforts of Government to bring down maternal and perinatal mortality. Hence based on above findings the present study was planned for Assessment of Maternal and Perinatal Outcomes in Pre-Eclampsia Females Admitted to Government Medical College Bettiah, West Champaran, Bihar.

Methodology

The present study was planned in Department of Obstetrics & Gynaecology, Government Medical College Bettiah, West Champaran, Bihar, India. In the present study 50 cases

of the females were enrolled in the present study. The 25 females of pre-eclampsia were evaluated in Group I and remaining 25 females with normal pregnancy were evaluated in Group II. Maternal data were documented with respect to age, parity, socioeconomic status, whether urban or rural, status of antenatal care, gestational age at delivery and mode of delivery. Relevant maternal investigations were also obtained. Fetal outcome data were documented with respect to birth weight, still birth rate, asphyxia and its degree, gestational age, neonatal complications, neonatal death rate and overall perinatal loss. A pre-designed structured Performa was used to interview eligible women and clinical examination findings & investigations performed were noted.

All the patients were informed consents. The aim and the objective of the present study were conveyed to them. Approval of the institutional ethical committee was taken prior to conduct of this study.

Inclusion Criteria

All pregnant women are at or beyond 28 weeks of gestation, with singleton pregnancy and in the age group between 20-40 years are included.

Exclusion Criteria

Women with chronic hypertension, renal disease, cardio vascular disease, thyroid disease, liver disease, diabetes mellitus, twin pregnancy and molar pregnancy are excluded. Blood samples were collected with the consent of the patient and centrifuged and analysed immediately for serum calcium and magnesium levels.

Obstetric management was done (spontaneous/ induced labour) as per the unit protocols and patients were delivered either by vaginal route or by caesarean section. Neonatal care was provided by pediatrician from delivery onwards. The patients with uncontrolled hypertension were managed in collaboration with physician and anesthetist.

Results and Discussion

Pre-eclampsia is characterized by new-onset hypertension and proteinuria at ≥20 weeks of gestation. Pre-eclampsia can progress to eclampsia, which is characterized by new-onset grand mal seizures and affects 2.7–8.2 women per 10,000 deliveries. Complications of pre-eclampsia or eclampsia include cerebrovascular accidents, liver rupture, pulmonary oedema or acute renal failure that can result in maternal death.3 Adverse perinatal outcomes of pre-eclampsia and eclampsia are mainly attributed to preterm delivery, which occurs secondary to maternal or fetal complications, intrauterine growth restriction (IUGR) and fetal death.

Hypertension is one of the most common medical complication of pregnancy. It contributes significantly to the cause of maternal and perinatal morbidity and mortality. Hypertensive disorders of pregnancy predispose women to acute or chronic uteroplacental insufficiency, resulting in ante or intra partum asphyxia that may lead to fetal death, intrauterine growth retardation and/or preterm delivery.

Hypertensive disorders of pregnancy have been identified as a major world wide health problem, associated with increased perinatal morbidity and mortality. Various authors have found the frequency of hypertensive disorders of pregnancy between 7-10% which is comparable to the present study [15].

Table 1: Comparison of Clinical Findings

Group	Group I	Group II
Group of	**Cases Females**	**Control Females**
Cases of	Pre-eclampsia Females	Normal Females
No, of Cases	25	25
Age	25 – 33	23 – 34
Systolic Blood Pressure (mmHg)	126 – 150	108 – 124
Diastolic Blood Pressure (mmHg)	89 – 100	71 – 83
Haemoglobin (gm %)	11.5- 14.1	11.1 – 13.6

Table 2: Maternal Parameters

Group	Group I	Group II
Group of	**Cases Females**	**Control Females**
Cases of	Pre-eclampsia Females	Normal Females
No, of Cases	25	25
Age of mother (years)	25 – 33	23 – 34
Socio-economic status		
Lower class	18	16
Middle class	7	9
Maternal education		
Illiterate	10	12
primary	15	13
Pre pregnancy weight > 45 kg	5	18
Spacing < 2years	18	14
Primigravida	15	13
Bad obstetrics history	8	13
Maternal Infections	1	2
History of infertility	2	1
Tobacco consumption	1	2
Heavy physical activity	14	11
Pregnancy Induced Hypertension	4	5
Anaemia	12	9
Caesarean section delivery	11	13

Table 3: Maternal Outcome

Group	Group I	Group II
Group of	Cases Females	Control Females
Cases of	Pre-eclampsia Females	Normal Females
No, of Cases	25	25
Maternal deaths	2	0
Maternal near miss	4	1
Maternal severe outcomes	12	3

Table 4: Fetal Outcome

Group	Group I	Group II
Group of	Cases Females	Control Females
Cases of	Pre-eclampsia Females	Normal Females
No, of Cases	25	25
Fetal death	3	1
Early neonatal death	2	0
Perinatal death	3	2
Preterm birth	4	2
NICU admission	3	2

The ultimate treatment for pre eclampsia in order to prevent potential maternal complication is to deliver the patient. However, delivery is not always in best interest of fetus. The rational for delaying delivery in these pregnancies, is to reduce perinatal morbidity and mortality by delivery of more mature fetus and to lesser degree to achieve more favorable cervix [16]. In India, maternal mortality and morbidity from eclampsia is very high. The figure ranges

from 8- 14%. The perinatal mortality ranges from 14.6% to 47.4% [17-18] the incidence of eclampsia can be reduced by better antenatal care, early reorganization and treatment of severe pre eclampsia [19].

While preeclampsia has the potential for serious complications, most cases of preeclampsia are mild and require minimal clinical treatment. Management of preeclampsia may include increased maternal and fetal surveillance, blood pressure control, and seizure prophylaxis, but ultimately delivery of the infant is the only definitive treatment [20]. There have been limited studies examining the role of maternal symptoms in predicting outcomes. Menzies *et al*. [21]. have stated that the preeclampsia severity criteria identified by both the Canadian Hypertension Society and the National High Blood Pressure Education Program were not predictive of maternal or perinatal morbidity. Current guidelines that make use of these severity criteria, such as those written by the Society of Obstetricians and Gynecologists of Canada [22]. and the American College of Obstetricians and Gynecologists [23], for evaluating the severity of preeclampsia are not uniform and have not been proven effective.

Maternal morbidity includes severe bleeding from abruption placentae with its resulting coagulopathy, pulmonary edema, aspiration pneumonia, acute renal failure, cerebrovascular haemorrhage, retinal detachment and PRES. Perinatal mortality and morbidity is another impact factor in eclampsia patients, as the definitive treatment is the only termination of pregnancy irrespective of gestational age. The primary target in eclampsia is achieving control of convulsions, control of blood pressure and terminating pregnancy within optimal time frame. At all health providing levels appropriate use of anticonvulsants, anti-hyper tensives along with safe culmination of pregnancy should be encouraged for these patients. If need is felt referral to a well-equipped higher center should be done promptly without wasting time along with by appropriate emergency obstetric care. Preeclampsia has remained a significant public health threat in both developed and developing countries contributing to maternal and perinatal morbidity and mortality globally. 1 Preeclampsia, a human pregnancy-specific disorder is defined as the occurrence of hypertension and significant proteinuria in a previously healthy woman on or after the 20th week of gestation. Risk factors for preeclampsia include nulliparity, multifetal gestations, previous history of preeclampsia, obesity, diabetes mellitus, vascular and connective tissue disorders like systemic lupus erythematous and antiphospholipid antibodies, age >35 years at first pregnancy and smoking.

Conclusion

The data generated from the present study concludes that Eclampsia is associated with significant maternal and perinatal morbidity and mortality. The higher death is due to high percentage of the patient being unbooked; majority receive no therapeutic intervention until admission. Good antenatal care, nutrition, health education, early diagnosis, good control of BP, early referral to higher center, multidisciplinary approach will reduce morbidity as well as mortality in mother and baby.

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