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Maternal and perinatal outcomes in early onset and late onset preeclampsia

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Summary

Purpose: This study was performed to compare the clinical findings and identify differences in risk factors between early-onset preeclampsia (EO-PE) and late-onset preeclampsia (LO-PE). *Materials and Methods:* This retrospective study included 516 women with singleton pregnancies and preeclampsia (none of them had superimposed preeclampsia on chronic hypertension) who delivered in a tertiary care center. Clinical findings, and maternal and perinatal outcomes were compared between early (< 34 weeks' gestation) and late (≥ 34 weeks' gestation) onset of the disease. *Results:* Incidences of nulliparity, previous preterm births, stillbirths, and first trimester abortions were significantly higher in women with EO-PE ($p < 0.05$). History of disease other than chronic hypertension (especially diabetes mellitus) and previous term births were significantly higher in women with late-onset disease ($p < 0.05$). The mean gestational week at delivery and mean birth weight were significantly lower in early-onset disease ($p < 0.05$). Stillbirths, early and late neonatal deaths, and cases where the mother's life at risk were significantly higher in women with early-onset disease ($p < 0.05$). *Conclusions:* EO-PE appears to be mediated by the placenta and associated with higher incidence of perinatal, neonatal and maternal deaths, and maternal near-miss cases.

Key words: Preeclampsia; EO-PE, LO-PE; Maternal mortality; Perinatal mortality.

Introduction

In the past, preeclampsia has been defined as a syndrome characterized by hypertension and proteinuria. In 2013, American College of Obstetricians and Gynecologists (ACOG) removed proteinuria as an essential criteria for diagnosis of preeclampsia with severe features. Thus, preeclampsia refers to the new onset of hypertension and either proteinuria or end-organ dysfunction after 20 weeks of gestation in a previously normotensive woman. ACOG also removed massive proteinuria (5 grams/24 hours), oliguria ,and fetal growth restriction as possible features of severe disease [1].

Preeclampsia has been classified into early (< 34 weeks' gestation) and late (≥ 34 weeks' gestation) onset groups, according to the gestational week at diagnosis [2]. Although some of the etiological features similar in both groups, they differ with regards to several risk factors, and often lead to different outcomes [3].

This study was performed to compare the clinical findings and identify differences in risk factors between early-onset preeclampsia (EO-PE) and late-onset preeclampsia (LO-PE).

Materials and Methods

This retrospective study included 516 women with singleton pregnancies and preeclampsia (none of them had superimposed preeclampsia on chronic hypertension) who delivered in a tertiary care center over a ten-year period. Clinical findings and maternal and perinatal outcomes were compared between early and late onset of disease.

Preeclampsia and features of severity were defined according to criteria provided by ACOG in 2013; blood pressure elevation after 20 weeks of gestation with proteinuria or any of the severe features of preeclampsia [1]. Diagnostic criteria for severe preeclampsia were: 1) hypertension: systolic BP >160 mmHg or diastolic BP >110 mmHg on two occasions at least four hours apart while the patient is on bed rest (unless antihypertensive therapy is initiated before this time), 2) thrombocytopenia (platelet count <100.000/microliter), 3) impaired liver function (elevated blood levels of liver transaminases to twice the normal concentration), severe persistent right upper quadrant or epigastric pain unresponsive to medication and not accounted for alternative diagnosis, or both, 4) new development of renal insufficiency (elevated serum creatinine greater than 1.1 mg/dl, or doubling of serum creatinine in the absence of other renal disease), 5) pulmonary edema and 6) new-onset cerebral or visual disturbances [1].

Gestational age was determined according to the last menstrual period and/or to the crown-rump length at first trimester ultrasound. Intrauterine growth restriction (IUGR) was defined as a birth weight < 10^{th} percentile for gestational age. Perinatal mortality was defined as the number of stillbirths and deaths in the first week of life. Maternal deaths and maternal near-miss cases were defined in respect of World Health Organization/International Classification of Diseases-10 (WHO/ICD-10) definitions. The flow chart recommended by Say *et al.* was used in the selection of maternal near-miss cases [4]. Only maternal deaths and maternal near-miss cases caused by hypertension were accepted as

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Table 1. — *Clinical characteristics and obstetric outcomes of women with EO-PE and LO-PE.*

	EO-PE (n=235)	LO-PE (n=281)
Nulliparity*	141 (60)	145 (51.6)
History of term delivery*	74 (31.5)	129 (45.9)
History of preterm delivery*	21 (8.9)	10 (3.6)
History of immature delivery*	12 (5.1)	3 (1.1)
History of in utero ex (28-37 gw)*	12 (5.1)	5 (1.8)
History of in utero ex (20-28 gw)*	8 (3.4)	2 (0.7)
History of abortion before the 12th gw*	47 (20)	36 (12.8)
Systemic disease*	25 (10.6)	52 (18.5)
Diabetes mellitus*	4 (1.7)	15 (5.3)
Maternal mortality and maternal near-miss*	91 (38.7)	63 (22.4)
Eclampsia*	49 (20.9)	24 (8.5)
HELLP syndrome*	45 (19.1)	29 (10.3)
Severe symptoms*	191 (81.3)	205 (73)
Gestational age at delivery (week)*	30.3 ± 2.4	36.8 ± 1.9
Birth weight (g)*	1280 ± 459	2541 ± 748
Stillbirth*	52 (22.1)	18 (6.4)
Early neonatal death*	21 (9.2)	6 (2.1)
Perinatal mortality*	73 (31.9)	24 (8.5)
Late neonatal death*	3 (1.3)	-
Neonatal mortality*	24 (10.5)	6 (2.1)

*$p < 0.05$

maternal deaths and maternal near-miss cases.

All women with severe symptoms were hospitalized. Women without severe symptoms were also hospitalized if they had fetal indications, such as non-reassuring fetal status according to cardiotocography and umbilical artery Doppler assessment with an absent or reversed end-diastolic flow, IUGR/oligohydramnios, fetal demise, etc. Magnesium sulfate for eclamptic seizure prophylaxis and acute antihypertensive therapy were administered to women with severe preeclampsia when it is deemed necessary within the indications. Antenatal steroid was administered for fetal lung maturity to all pregnancies less than 34 weeks of gestational age. Indications for delivery were severe preeclampsia, uncontrollable blood pressure, diagnosis of hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome, eclamptic seizures or non-reassuring fetal status according to cardiotocography and umbilical artery Doppler assessment with an absent or reversed end-diastolic flow, fetal demise. Spontaneous labor was also an indication for delivery.

Statistical Package of the Social Sciences (SPSS) 17.0 software was used for the statistical analyses. Data were expressed as n (%) and mean with standard deviation. Quantitative variables were tested for normal distribution (by Kolmogorov–Smirnov Test) and homogeneity (by One-Way Anova Test). For those variables not distributed normally, two groups were compared with Mann–Whitney U Test. Chi-square test for independence was used for the analysis of categorical variables. A p value < 0.05 was considered as significant.

Five different logistic models were also set up to describe the relationship between maternal–perinatal (stillbirth and early neonatal)–neonatal outcomes, and variables associated with maternal-perinatal–neonatal outcomes. Chi-square test for independence and univariate logistic regression analysis were used for the selection of variables ($p < 0.05$). Significant variables were included in the multivariate logistic regression analysis. Before multivariate logistic regression analysis, significant variables were analyzed by bivariate correlation test to determine whether the relationship between independent variables was significant. Backward stepwise elimination (likelihood ratio) was used in the logistic regression. Entry and removal significance levels for the backward selection were 0.05 and 0.1, respectively. Significance level of 0.05 was used for the assessment of model. Classification table and pseudo R2 statistics were applied to assess the adequacy of the model. Box-Tidwell test was used to determine the presence of linear correlation between the continuous variables and the logit. Odds ratios were used in the interpretation of the last model. Likelihood ratio test was used for assessment of model. Likelihood ratio and Omnibus tests were used for the assessment of variable coefficients. The goodness of fit of the model was performed by Hosmer-Lemeshow test.

The study was conducted in accordance with the ethical principles stated in the Declaration of Helsinki, and an approval was obtained from the Human Ethics Committee of the Institution.

Results

In EO-PE cases, the mean gestational age at delivery was 30.3 ± 2.4 weeks and mean birth weight was 1280 ± 459 grams. Ratios of antenatal, perinatal, and neonatal mortality were, respectively, as follows: 22.1%, 31.9%, and 10.5%. Maternal life threatening conditions (maternal mortality+maternal near-miss) occurred in 38.7% of cases. In LO-PE cases, the mean gestational age at delivery was 36.8 ± 1.9 weeks and mean birth weight was 2541 ± 748 grams. Ratios of antenatal, perinatal, and neonatal mortality were, respectivelym as follows: 6.4%, 8.5%, and 2.1%. Maternal life threatening conditions occurred in 22.4% of cases.

Incidence of nulliparity, previous preterm births, stillbirths, and first trimester abortions were significantly higher in women with EO-PE. The incidences of history of disease other than chronic hypertension (especially diabetes mellitus) and previous term birth were significantly higher in women with LO-PE. The mean gestational week at de

Table 2. — *Obstetric outcomes of women with EO-PE and LO-PE according to the severity of symptoms.*

	EO-PE without severe symptoms (n: 44)	EO-PE with severe symptoms (n=191)	LO-PE without severe symptoms (n=76)	LO-PE with severe symptoms (n=205)
Maternal mortality and maternal near-miss*	2 (4.5)	89 (46.6)	1 (1.3)	62 (30.2)
Eclampsia*	-	49 (25.7)	-	24 (11.7)
HELLP syndrome*	-	45 (23.6)	-	29 (14.1)
Birth weight	1251 ± 444	1287 ± 460	2525±790	2559±741
IUGR	18 (40.0)	77 (40.3)	35 (46.1)	71 (34.6)
Stillbirth	12 (27.3)	40 (20.9)	7 (9.2)	11 (5.4)
Early neonatal mortality	1 (2.3)	20 (10.8)	-	6 (2.9)
Perinatal mortality	13 (30.2)	60 (32.3)	7 (9.2)	17 (8.3)
Late neonatal mortality	-	3 (1.6)	-	-
Neonatal mortality	1 (2.3)	23 (12.4)	-	6 (2.9)
Gestational week at birth	30.8 ± 1.8	30.2 ± 2.5	36.9 ± 2	36.8 ± 2

*$p < 0.05$

Table 3. — *The most relevant variables effecting on maternal and fetal outcomes according to the multivariate analysis.*

		p	OR	OR 95% CI
Maternal mortality and maternal near-miss	HELLP syndrome	0.000	297.203	40.159-2199.504
	Eclampsia	0.000	9.150	4.834-17.319
	Severe symptom	0.001	7.479	2.272-24.624
Perinatal mortality	Early or late onset	0.000	0.236	0.140-0.396
	Antenatal care	0.000	0.255	0.157-0.413
Stillbirth	Antenatal care	0.000	0.220	0.127-0.380
	Early or late onset	0.000	0.310	0.172-0.560
	History of in utero ex	0.030	2.753	1.101-6.882
Early neonatal mortality	Early or late onset	0.03	0.240	0.094-0.614
	Gravidity	0.024		
	Multigravidas (1)	0.424	0.688	0.275-1.719
	Grand multigravidas (2)	0.028	3.351	1.139-9.862
	Severe symptom	0.68	6.589	0.873-49.744
Neonatal mortality	Early or late onset	0.001	0.207	0.082-0.524
	Gravidity	0.007		
	Multigravidas (1)		0.593	0.242-1.453
	Grand multigravidas (2)		3.552	1.272-9.922
	Severe symptom	0.055	7.252	0.962-54.674

livery and mean birth weight were significantly lower in the EO-PE cases. The incidences of stillbirths, early and late neonatal deaths, and cases where the mother's life at risk were significantly higher in women with EO-PE (Table 1).

Table 2 illustrates obstetric outcomes of women with EO-PE and LO-PE according to the severity of symptoms. There were no significant differences between the incidences of stillbirth and early neonatal and neonatal death rates between EO-PE cases, with or without severe symptoms. This was also true for LO-PE cases with or without severe symptoms. However, in cases where the mother's life at risk there was a significant difference between the groups. Maternal deaths and complications were more common in groups with severe symptoms whether early or late onset.

There were five maternal deaths. Deaths were occurred due to intraventricular hemorrhage (IVH) in two women with eclampsia, multiple organ failure (MOF) in a woman with HELLP syndrome, subarachnoid hemorrhage (SAH), and MOF in a woman with HELLP syndrome and eclampsia and hypertensive encephalopathy and acute renal failure (ARF) in a woman with HELLP syndrome and eclampsia.

In univariate analysis maternal age, eclampsia, HELLP syndrome, severe symptoms, highest blood pressure (systolic-diastolic-mean arterial pressure), antenatal care, early or late onset of disease were significantly associated with cases where the mother's life at risk ($p < 0.05$). Antenatal care, early or late onset of disease, and previous stillbirth were significantly associated with perinatal mortality and stillbirth ($p < 0.05$). Severe symptoms, birth weight, gravidity, previous first trimester abortion, HELLP syndrome, cases where the mother's life at risk, and early or late onset of disease were significantly associated with early neonatal and neonatal deaths ($p < 0.05$). In multivariate analysis the most relevant variables that contribute to cases where

the mother's life at risk, in descending order, were as follows: HELLP syndrome, eclampsia, and severe symptoms. The most relevant variables that contribute to perinatal deaths, in descending order, were as follows: early or late onset of disease, antenatal care. The most relevant variables that contribute to stillbirths, in descending order, were as follows: antenatal care, early or late onset of disease, and previous stillbirth. The most relevant variables that contribute to early neonatal deaths, in descending order, were as follows: early or late onset of disease, gravidity, and severe symptoms. The most relevant variables that contribute to neonatal deaths, in descending order, were as follows: early or late onset of disease, gravidity, and severe symptoms.

Women with HELLP syndrome had a 297-fold increased risk of life-threatening conditions, whereas eclampsia had a nine-fold increased risk and severe symptoms had 7.4-fold increased risk. Perinatal mortality increased 3.9-fold in women without antenatal care, whereas it increased 4.2-fold in EO-PE. Stillbirth ratio increased 4.5-fold in women without antenatal care, 3.2-fold in EO-PE, whereas 2.7-fold increase in women with a history of intrauterine fetal demise. Early neonatal deaths increased 6.5-fold in women with severe symptoms, 3.3-fold in grand multigravidas, and 4-fold in EO-PE. Neonatal deaths increased 7.2- fold in women with severe symptoms, increased 3.5-fold in grand multigravidas and 4.8-fold in EO-PE (Table 3).

Discussion

Not being population-based, this study included highly selected cases. As a tertiary referral center, disproportionate representation of cases was an expected result. Women were hospitalized not only for maternal indications but also for fetal indications. Cesarean section rate, incidence of delivery before 34 week, and cases with severe symptoms were high. The ratio of EO-PE to LO-PE was also higher than that of other studies [3, 5].

In this study 2.7-fold increased effect of previous history of intrauterine fetal demise on stillbirth was detected. It was also detected that previous stillbirths and first trimester abortions were significantly higher in women with EO-PE. These results reinforce the concept that pregnancy would not be expected to reach until term with an improperly formed placenta and the severity of the impairment in placentation would lead the clinical manifestations to develop at earlier gestational weeks. The incidences of nulliparity and previous preterm births were significantly higher in EO-PE cases whereas previous term births were significantly higher in LO-PE cases. Previous history of pregnancies unreached the term was more common in EO-PE, whereas previous history of pregnancies successfully reached the term was more common in LO-PE. The present authors believe some factors impeding successful pregnancy may also be in a causal pathway for EO-PE. Diseases other than hypertension, especially DM were also significantly higher in LO-PE. These results supports other studies declaring late onset of disease is associated with maternal factors rather than being associated with abnormal placentation. [6, 7]. Unlike several studies this study did not include women with superimposed preeclampsia on chronic hypertension but only ones with preeclampsia. In those studies it was stated that previous hypertension had a significant effect on early onset disease [3, 5]. So, potential risk of chronic hypertension on preeclampsia and/or early onset of symptoms was eliminated.

Boyd *et al.* stated previous history of EO-PE was associated with 25-fold increased risk of recurrence of preeclampsia with the same timing onset. They suggested although that genetics play a role in preeclampsia regardless of the timing of onset; EO-PE appears to have the largest genetic component and large numbers of rare mutations that may contribute to genetically determined preeclampsia [8]. Because this study did not included= normotensive women, the authors do not know whether previous history of EO-PE is associated with more recurrence of preeclampsia. However, they can state that incidence of previous history of preeclampsia is not significantly different between EO-PE and LO-PE.

Similar to several studies, perinatal and neonatal mortalities were higher in EO-PE [3, 9]. Some authors suggested that perinatal mortality and morbidity rates substantially increased in women with severe preeclampsia [9, 10]. This study showed that severity of symptoms did not correlate with perinatal outcomes in some aspects. Perinatal outcomes such as mean gestational weight at birth, incidences of IUGR, stillbirth, and early neonatal and neonatal death rates were not significantly different between women with and without severe symptoms, whether with early or late onset. Mean gestational week at birth was either not significantly different between women with and without severe symptoms. This is partly due to the fact that deliveries occurred not only according to maternal indications, but also for fetal indications. ACOG removed fetal growth restriction as a possible feature of severe disease because fetal growth restriction is managed similarly, whether or not preeclampsia is diagnosed. In this study fetal growth restriction was not a criteria for categorizing symptom severity. Confirming previous statements, this study showed that gestational age at birth had a major impact on perinatal outcome [7, 11]. On the other hand, when the present authors performed multivariate analysis, they detected no stillbirths but early neonatal and neonatal deaths (especially the first one) were also influenced by severity of the disease, but to a lesser extent than gestational age at onset of the disease. Antenatal care, gestational age at onset of the disease, and previous history of intrauterine fetal demise had more important effect on stillbirths. Gestational age at onset of the disease, gravidity, and severity had more important effect on early neonatal and neonatal deaths. In cases where fe-

tuses were dead, deliveries were carried out promptly, whereas in cases where fetuses were alive, deliveries were postponed with expected management. In these cases managed expectantly gestational age at birth could be higher than the gestational age at onset of the disease. So, neonatal outcome could be more favorable. However, in women with severe symptoms, deliveries were performed mainly for maternal indications. That was why severe symptoms were among the predominant factors effecting on early neonatal and neonatal deaths.

In concordance with previous studies, EO-PE had significantly higher rates of maternal mortality and morbidity compared to LO-PE [3, 12]. The severity of symptoms was significantly associated with maternal outcomes. HELLP syndrome was the most relevant factor that contribute to cases where the mother's life is at risk.

Conclusions

EO-PE appears to be mediated by the placenta and associated with higher incidence of perinatal, neonatal and maternal deaths, and maternal near-miss cases.

This study has some limitations. In cases without antenatal care, gestational age at onset of disease were estimated based on hospital admission. The present authors were not able to know exact onset time of disease, especially in women with severe symptoms if they were not admitted before. Other potential weaknesses of the study include limited information about risk factors, such as body mass index, family history of preeclampsia, etc.

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