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Comparative study of clinical and biochemical parameters in early and late onset preeclampsia

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Abstract
Objective: To compare clinical and biochemical parameters in cases of early and late onset pre-ecclampsia and compare maternal and perinatal outcomes in both the study groups.
Study design: This was a prospective observational study. All antenatal patients presenting in the Department of Obstetrics and Gynaecology, PGIMS, Rohtak with features of preeclampsia requiring admission were included and divided into 2 groups on the basis of period of gestation. All women were subjected to routine antenatal investigations and specific investigations pertaining to preeclampsia. The subjects were followed during their hospital stay and the maternal outcome and fetal outcome and biochemical were observed and compared in both the study groups.
Results: A total of 120 patients were enrolled in the study and divided into 2 equal groups of 60 each. The early onset group had more severe preeclampsia at the time of admission in comparison to late onset group (p<0.001).The hematological parameters did not show any stastistical difference when compared between the groups.The EOPE had a significantly larger proportion of patients with significant albuminuria as compared with LOPE (p<0.01).)The mean gestational age at termination of pregnancy was 33.03(±3.08) weeks in early onset group and 38.17(±2.08) in the late onset group. The mean APGAR score at 5 minutes was significantly lower in early onset group(5.93±3.54) when compared to late onset group(8.40±1.68) (p<0.001).There was a significant difference between the groups in terms of NICU admissions with the early onset pre-eclampsia having a significantly higher proportion NICU admissions(51.67%) as compared to the late onset group(16.67%).
Conclusion: The present study reveals that the women having early onset preeclampsia were more likely to develop a more severe form of the disease. The biochemical parameters were significantly deranged in women who developed preeclampsia before 34 weeks of gestation. It can be concluded that careful vigilance is required in all women presenting with preeclampsia especially with early onset preeclampsia, where utmost clinical expertise and decision making is required keeping in mind the increased severity of the disease as well as prematurity of the baby.

Keywords: Preeclampsia, early onset, late onset, maternal outcomes, perinatal outcomes

Introduction
Preeclampsia is a pregnancy specific hypertensive disorder that may lead to serious maternal and fetal complications. It is a multisystem disease that is commonly, but not always accompanied by proteinuria [1]. It is defined by new development of hypertension and proteinuria after 20 weeks of gestation, sometimes leading to a multiorgan disease of varying clinical features. The incidence of preeclampsia ranges from 5% to 8% of healthy pregnancies [2]. Preeclampsia has been characterised by some investigators as two different diseases on the basis of gestational age as early-onset preeclampsia (EOPE) and late-onset preeclampsia (LOPE) [3, 4]. EOPE is usually defined as preeclampsia that develops before 34 weeks of gestation, while LOPE develops at or after 34 weeks of gestation. Although the diagnostic criteria are the same in each of these phenotypic variants of preeclampsia, they are characterised by different clinical features and are associated with different maternal and fetal outcomes [3]. EOPE and LOPE have different implications for the fetus and neonate, with approximately 10-fold higher risk of perinatal death observed among mothers with early-onset disease, and a two fold increased risk evident among mothers with late-onset disease (compared with mothers without preeclampsia) [5].

Materials and methods
This was a prospective observational study. All antenatal patients presenting in the Department of Obstetrics and Gynaecology, PGIMS, Rohtak with features of preeclampsia requiring

admission were included in this study.

Cases having multiple pregnancy, gestational diabetes mellitus, chronic kidney disease, liver disease, heart disease were excluded from the study. A written informed consent was taken from all the subjects. The subjects who choose to be included in the study were divided into 2 groups on the basis of period of gestation. Gestational age was estimated by the last menstrual period or ultrasonography (if not sure of dates). The groups thus divided were:

Group 1: Early onset preeclampsia((EOPE) POG<34 weeks) (n=60)
Group 2: Late onset preeclampsia (LOPE) (POG>34 weeks) (n=60)

All the subjects underwent detailed history taking. History of headache, blurring of vision, epigastric discomfort, pedal edema, decreaesed urine output was asked. General physical examination and obstetric examination of the patients was done.

All women were subjected to Hb, ABORh, viral markers, TSH, urine complete examination. Specific investigations pertaining to preeclampsia such as complete hemogram with Absolute Platelet Count(APC), coagulation profile, kidney function tests (blood urea, serum creatnine, serum uric acid,24 hour urinary protein), liver function tests(SGOT, SGPT, ALP, serum proteins, serum bilirubin), plasma nitric oxide levels, fundus examination and ultrasound scan for fetal maturity, growth, liquor was done. The subjects were followed during their hospital stay and the maternal outcome and fetal outcome were observed in both the study groups.

Statistical analysis: The data thus obtained was statistically analysed using SPSS software version 20.0. Continuous variables for EOP and LOP were compared using student's t test. Categorical values were compared between the groups using the chi-square test. A $p<0.05$ was considered statistically significant.

Results

The present study was conducted on 120 pregnant females with preeclampsia divided according to gestational age at onset of disease into early onset (EOPE) (<34 weeks) and late onset (LOPE)(≥34weeks).The clinical and biochemical parameters were compared in both the groups and results were analysed. In this study the mean matrernal age of EOPE group was 24.5(±4.04) years whereas the mean age in LOPE group was estimated to be 24.47(±4.29) years but there was no statistical difference between the two groups. In our study, EOPE showed significantly higher values of systolic, diastolic and mean blood pressures ($p<0.001$).

Laboratory values were deranged more in the early onset group in comparison to late onset group.

There was a significant difference between the two groups in terms of Urinary Albumin (Spot), with the early onset pre-eclampsia group having a significantly larger proportion of patients with higher urine albumin (spot) as compared to the late onset pre-eclampsia group ($p<0.010$).

Maternal complications like HELLP, abruptio placentae and renal impairment were higher in the early onset group in contrast to eclampsia which showed higher incidence in the late group. Higher rate of ICU admissions were seen in early onset group (8.33%) and no admissions in the late onset group. 3 maternal mortalities occured in our study; one of the patient died of multiple organ failure due to sepsis in a critical care unit after developing DIC. 1 patient had a cardiac arrest secondary to development of deep venous thrombosis and another patient suffered severe neurologic deficits due to multiple brain infarcts developing after multiple episodes of eclamptic fits.

The mean Fetal Maturity at Delivery of the Early Onset Pre-eclampsia group was 33.03 (±3.08) and the late Onset Pre-eclampsia group was 38.17 (±2.08). There was a significant difference between the two groups (t = -8.608, $p < 0.001$). The mean birth weight was higher in EOPE ($P<0.001$). The incidence of lower APGAR score at 1 and 5minutes was higher in EOPE ($p<0.001$). There were higher number of NICU admissions (51.67% vs16.67%), neonatal deaths (20.00% vs 3.33%) in the EOPE group.

Table 1: Demographic and clinical findings according to onset of preeclampsia

	Early Onset Pre-eclampsia		Late Onset Pre-eclampsia		P value
	Mean	SD	Mean	SD	
Age (Years)	24.50	4.04	24.47	4.29	0.965
Period of gestation	31.96	2.16	37.54	2.45	< 0.001
Systolic BP	160.6	14.15	151.40	10.45	< 0.001
Diastolic BP	106.20	9.64	100.90	8.38	< 0.002

Table 2: Laboratory findings of the patients according to onset of preeclampsia

	Early Onset Pre-eclampsia		Late Onset Pre-eclampsia		P value
	Mean	SD	Mean	SD	
Hemoglobin (gm/dl)	9.84	2.01	9.68	2.02	0.658
Platelet Count (LACS)	2.21	1.01	2.27	0.99	0.743
INR	1.00	0.23	0.97	0.21	0.542
Blood Urea (mg/dl)	38.43	20.53	27.40	15.24	0.001
Serum Uric Acid (mg/dl)	7.16	2.27	6.56	1.72	0.108
Serum Creatinine (mg/dl)	0.92	0.70	0.77	0.56	0.195
SGOT Levels	49.12	51.16	50.83	54.13	0.859
SGPT Levels	40.80	36.89	51.37	79.34	0.352
ALP Levels	226.90	102.38	230.03	124.08	0.880
24 Hour Urinary Protein (grams)	2.03	1.03	1.41	0.84	< 0.001
Nitric Oxide Levels (µmol/lt)	51.07	45.72	86.83	93.60	0.009

Table 3: Maternal complications according to onset of preeclampsia

	Early Onset Pre-eclampsia		Late Onset Pre-eclampsia		Total		Chi-Square Test	
	N	%	N	%	N	%	$\chi 2$	p value
Eclampsia								
Present	3	5.0%	4	6.7%	7	5.8%	0.152	1.000
Absent	57	95.0%	56	93.3%	113	94.2%		
HELLP syndrome								
Present	5	8.3%	1	1.7%	6	5.0%	2.807	0.207
Absent	55	91.7%	59	98.3%	114	95.0%		
Abruptio placentae								
Present	10	16.67%	3	5.00%	13	10.83%	4.227	0.075
Absent	50	83.33%	57	95.00%	107	89.17%		
Renal impairment								
Present	2	3.33%	1	1.67%	3	2.50%	0.342	1.000
Absent	58	96.67%	59	98.33%	117	97.50%		

	Early Onset Pre-eclampsia		Late Onset Pre-eclampsia		P VALUE
	Mean	SD	Mean	SD	
Fetal Maturity at Delivery (Weeks)	33.03	3.08	38.17	2.08	< 0.001
Birth Weight (Kgs)	1.49	0.65	2.56	0.63	< 0.001
APGAR Score at 1 minute	4.72	2.67	6.52	1.16	< 0.001
APGAR Score at 5 minutes	5.93	3.54	8.40	1.68	< 0.001

Table 4: Neonatal outcomes according to onset of preeclampsia

	Early onset Pre-eclampsia		Late onset Pre-eclampsia		Total		Chi-square test	
	N	%	N	%	N	%	$\chi 2$	p value
NICU admission	31	51.67%	10	16.67%	41	34.17%	16.338	< 0.001
Neonatal death	12	20.00%	2	3.33%	14	11.67%	8.086	0.008
Intrauterine death	13	21.67%	1	1.67%	14	11.67%	11.644	0.001
Small for gestational age	27	50.0%	18	34.0%	45	42.1%	2.823	0.118

Discussion

The modern concept divides preeclampsia into two categories as early onset preeclampsia (EOPE) (<34 weeks of gestation) and late onset preeclampsia (LOPE) (≥ 34 weeks of gestation). Approaching as an EOPE and LOPE gives us better idea about understanding of the complex etiopathogenesis of this medical enigma. Generally preeclampsia is considered a disease of first pregnancy and its incidence is 2 to 7% in healthy nulliparous women.. Many studies have reported nulliparity as a risk factor for severe preeclampsia. In this study incidence of nulliparous women was 50% in early onset group versus 56.67% in late onset group. The difference in the groups was not statistically significant. Similar findings where nulliparity was 43.6% in EOPE and 43% in LOPE group were reported by Gulec *et al.* [6]

In our study the mean gestational at presentation was 31.96(±2.16) weeks in EOPE whereas mean gestational age in LOPE group was 37.54(±2.45) weeks. The difference was statistically significant between the two groups (p<0.001, t= -13.227). Alturi *et al.* reported the mean gestational age in early onset group as 31.66 (±2.25) weeks and 35.93(±3.37) weeks [7]. The mean systolic BP in EOPE was 160.6(±14.15) mmHg in comparison to LOPE where the mean BP was 151.4(±10.45) mmHg which is a statistically significant (p<0.001, t= 4.051). In early onset group 55% women had blood pressure levels >160mmHg whereas only 21.7% women had blood pressure levels > 160mmHg. The mean diastolic BP was 106.2(±9.64) mmHg in EOPE in comparison to LOPE where mean was 100.9(±8.38) mmHg. There was significant difference between the two groups (p<0.002, t= 3.214). In early onset there were more women who had more severe preeclampsia. This data is consistent with study by Odegard *et al.* reporting 65% of the patients diagnosed with EOP had severe preeclampsia while only 22% of those with LOP were classified as severe cases [8].

In kidney function tests the blood urea levels in EOPE group were 38.43(±20.53) mg/dl which were elevated in comparison to the LOPE group having the mean blood urea levels as 27.4 (±15.24) mg/dl. This difference is statistically significant in both the groups (p<0.001) suggesting increased severity of the disease in the EOPE group. The mean 24-hour urinary protein excretion in early onset group was 2.03(±1.03) grams/dl compared to 1.41 (±0.84) grams/dl in the late onset group. This difference is statistically significant (p<0.001). Gulec *et al.* reported similar difference in 24 hour proteinuria in EOPE group when compared with LOPE group(p=0.012) [6]. The mean gestational age at delivery was 33.03(±3.08) weeks in early onset group when compared to late onset onset group where mean gestational age was 38.17(±2.08) weeks. (p<0.001). Madazali *et al.* reported the mean gestational age at delivery to be 29.3 (±2.5) weeks in EOP group versus 36.3(±2.2) in LOP group.[9] 66.67% of the early onset group babies had APGAR <7 and only 30% of the late onset group babies had APGAR<7 at 1 minute. This difference in APGAR scores at 1 minute of delivery was significant (p-<0.001). Gulec *et al.* reported similar data in which 34.9% of the early group babies had low APGAR score when compared to late onset group where only 2.4% of the neonates had low APGAR scores [6]. The mean birth weight in the early onset group was estimated to be 1.49(±0.65) kgs whereas it was 2.56 (±0.63) kgs in the late onset group. This difference in the birth weight is significant (p<0.001, t= -9.206). Gomathy *et al.* also reported similar results where 91.6% babies in early onset group had birth weight <2 kgs and 54.8% of babies in late onset group had birth weight> 2.5 kgs [10].

Conclusion

The present study reveals that the women having early onset preeclampsia were more likely to develop a more severe form of the disease. The biochemical parameters were significantly deranged in women who developed preeclampsia before 34 weeks of gestation. Also, a higher incidence of maternal complications was observed in early onset patients, although eclampsia was observed to be more common in the late onset group. The women with early onset preeclampsia had early termination of pregnancy due to uncontrolled hypertension or worsening of the biochemical parameters. There were significant number of preterm deliveries and NICU admissions in the early onset group. Overall the perinatal morbidity and mortality was increased in early onset preeclampsia. Thus, it can be concluded that careful vigilance is required in all women presenting with preeclampsia especially with early onset preeclampsia, where utmost clinical expertise and decision making is required keeping in mind the increased severity of the disease as well as prematurity of the baby.

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