COMPARATIVE STUDY OF MATERNAL AND PERINATAL OUTCOME IN EARLY ONSET AND LATE ONSET PREECLAMPSIA

Sreedevi Atluri[1], Nandish S. Manoli[2]

[1]Postgraduate, Department of Obstetrics and Gynaecology, J. S. S. Medical College and Hospital, Mysore.
[2]Professor and Unit Chief, Department of Obstetrics and Gynaecology, J. S. S. Medical College and Hospital, Mysore.

ABSTRACT

BACKGROUND

Preeclampsia is the leading cause of maternal and perinatal morbidity and mortality worldwide, the exact aetiology of which is still unknown. The concept of early and late pre-eclampsia depending on gestational age at onset is more modern and is widely accepted that these two entities have different aetiologies and should be considered as different forms of the disease. Even though the presenting features overlap, these two entities of preeclampsia differ by biochemical markers, maternal and foetal outcomes.

Aim of the Study**-** This study compares early-onset preeclampsia and late-onset preeclampsia with respect to their clinical presentation, laboratory parameters, management options, maternal and foetal outcomes which gives us an idea that these two preeclampsia subtypes have different pathological processes and a need for varied clinical approach to prevent adverse outcomes.

METHODS

This is a prospective comparative study conducted in JSS Hospital, Mysore from November, 2014 to June, 2016. All Antenatal cases (both booked and unbooked) with gestational age ≥20 weeks between 18 yrs. and 40 yrs. of age diagnosed as preeclampsia as per the inclusion and exclusion criteria attending the outpatient department or admitted were selected and divided in to two groups, early onset preeclampsia (EOP) group if gestational age at onset of preeclampsia is before 34 weeks and late onset preeclampsia if gestational age at onset is at 34 weeks or later were observed until delivery and early postpartum period and babies till early neonatal period.

RESULTS

A total of 158 patients at >20 weeks of gestation with preeclampsia were enrolled for this study. Early-onset Preeclampsia (EOP) and Late-onset Preeclampsia (LOP) had 75 and 83 pre eclamptic women respectively. Early onset group had severe clinical picture with deranged laboratory findings (Thrombocytopenia, altered liver enzymes, lactic dehydrogenase (LDH) levels, urea and creatinine levels) compared to late onset group ($p<0.001$). High BMI values were noticed in late onset preeclampsia (LOP) group compared to early onset preeclampsia (EOP) ($p<0.001$). The maternal HELLP syndrome incidence, usage of number of anti-hypertensives, $MgSO_4$ therapy, length of intensive care unit (ICU) and hospital stay were statistically significant in early onset preeclampsia (EOP) group. The incidences of intrauterine growth retardation (IUGR), oligohydramnios, abnormal uterine artery Doppler were significantly different between the groups. Low Apgar score at 5th min, increased requirement for neonatal intensive care unit (NICU) stay, still births and perinatal mortality were significantly higher in early onset preeclampsia (EOP) group.

CONCLUSION

This study confirms that early onset preeclampsia is more severe entity with adverse maternal and perinatal outcomes compared to late onset. The implication of these findings might lead to understanding of different pathophysiological mechanisms underlying these entities and the need for prevention, follow-up and early treatment to prevent adverse outcomes of pre-eclampsia.

KEYWORDS

Preeclampsia, Early Onset, Late Onset, Maternal Outcome, Perinatal Outcome.

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Corresponding Author:
Dr. Sreedevi Atluri,
Department of Obstetrics and Gynaecology,
J. S. S. Medical College and Hospital,
M. G. Road, Mysore, - 570004, Karnataka.
E-mail: srideviredddya@gmail.com
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BACKGROUND

Hypertensive disorders in pregnancy are common and their incidence appears to be on rise, Preeclampsia is a major pregnancy complication that becomes clinically apparent after 20 weeks of gestation or within the first 4-6 weeks of postpartum, it can affect both the mother and the unborn baby and is estimated to affect between 5% and 8% of healthy pregnancies[1] and is responsible for about 76,000 maternal deaths and 50,000 infant deaths per year worldwide.[2]

The exact pathogenesis of pre-eclampsia (PE) is not clearly understood and is most likely multi-factorial, it is clear that pathological processes at the interface of the foetal and maternal circulation leading to generalized endothelial cell dysfunction contribute to the spectrum of the disease.[3] Preeclampsia is a clinical diagnosis and is graded in to mild and severe forms according to specific clinical findings.[4] However, in recent times a new concept of gestational age at clinical presentation has gained interest and pre-eclampsia is classified based on the timing of disease onset: early-onset preeclampsia occurring before 34 weeks gestation and late-onset preeclampsia that occurs at 34 weeks gestation or later.[5, 6]

Differences between two types of PE are due to pathophysiological variations, effects on mother and foetus as well as their long-term impacts, studies comparing clinical parameters or biomarkers between times of onset for preeclampsia are limited. Recently a study proposed that early onset and late onset preeclampsia have different aetiologies, clinical parameters and laboratory biomarkers suggesting early onset and late onset preeclampsia may be a different form of the disease, especially in cases of severe preeclampsia.[7] Early-onset disease, in particular, leads to life-threatening maternal complications and foetal demise.[8-10] Conversely, late-onset is associated with minor placental involvement and milder clinical disease.[11] Intrinsic placental factors are more frequently altered in early onset preeclampsia, while late onset preeclampsia is usually associated with predisposing maternal factors.[12,13] Approaching preeclampsia as early onset and late onset will help us to anticipate the disease severity, maternal and fetal outcomes as they do vary in their pathogenic mechanisms.

Aim of the Study

This study is to analyse the similarities and differences in the clinical parameters, laboratory biomarkers, severity of early and late onset pre-eclampsia including management options, timing of delivery, maternal and perinatal outcomes.

MATERIALS AND METHODS

A total number of 158 cases of pre-eclampsia admitted to JSS Hospital, Mysore from November, 2014 to June, 2016 were taken in this study after obtaining clearance from hospital ethical committee. Informed consent was obtained from all participating patients, clinically evaluated and the final diagnosis of preeclampsia was derived according to American College of Obstetrics and Gynecology (ACOG) criteria.[14] Exclusion criteria include pregnant women with essential hypertension or hypertension <20 weeks gestation, preexisting renal disease, multiple pregnancies, liver disorder, and epilepsy.

Included patients (n=158) were divided into two groups: Early onset preeclampsia (EOP) group consisting of 75 patients diagnosed before 34 weeks of gestation, Late onset preeclampsia (LOP) group (n=83) consisting of patients who were diagnosed at or after 34 weeks gestation.

The two groups would be matched according to age, gravidity, parity, maternal basal metabolic index, clinical findings (systolic blood pressure, diastolic blood pressure, mean blood pressure and imminent signs of eclampsia-epigastric pain, headache, visual disturbance), USG findings, laboratory findings at admission [haemoglobin (g/dL), haematocrit (%), platelet count, aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactic dehydrogenase (LDH), total bilirubin, uric acid, blood urea nitrogen (BUN), creatinine, spot urine dipstick proteinuria]. Evaluated maternal characteristics include number of anti-hypertensive drugs used and duration, $MgSO_4$ therapy and mode of delivery.

Maternal outcomes like duration of stay in intensive care unit (ICU), length of hospital stay, any maternal complications (Severe preeclampsia, Eclampsia, haemolysis elevated liver enzymes low platelets (HELLP) syndrome, Renal failure/Oliguria, Posterior reversible encephalopathy syndrome (PRES), Abruptio placenta) and foetal outcomes like gestational age at delivery, birth Weight, small for gestational age (SGA), intra uterine death (IUD), Still birth, early neonatal death, neonatal intensive care unit (NICU) admission, Perinatal mortality (still birth and early neonatal death) were compared using SPSS 21.0 software for all calculations.

Continuous variables for early onset preeclampsia (EOP) group and late onset preeclampsia (LOP) groups were compared using the student's t-test according to their distribution and were expressed as mean ± SD, median, maximum and minimum values. Categorical values were compared between the groups using the chi-square test, and were calculated as n and rate (%). $P<0.05$ was considered statistically significant. The inferential statistics are done using chi- square test, independent t test. $P<0.05$ is considered as significant.

RESULTS

A total of 158 patients at >20 weeks of gestation with preeclampsia were enrolled for this study. Early onset preeclampsia (EOP) and late onset preeclampsia (LOP) groups had 75 and 83 preeclamptic women respectively. The mean maternal age in years was 26.01±4.5 in early onset preeclampsia (EOP) group and 25.83±3.5 in late onset preeclampsia (LOP) group, the mean basal metabolic index (BMI) was 26.31±3.13 in early onset preeclampsia (EOP) and 28.53±1.72 in late onset preeclampsia (LOP) group ($P<0.001$) which is statistically significant and the mean gestational age was 31.66±2.25 wks. in early onset preeclampsia (EOP) group and 35.93±3.37 weeks in late onset preeclampsia (LOP) group. Among the total 158 patients with preeclampsia, 75 had severe preeclampsia (47.4%), 11 patients had eclampsia (6.9%), 37 patients had HELLP syndrome (23.4%) and five patients had diagnoses of HELLP syndrome plus eclampsia (3.1%). The rates of severe preeclampsia, HELLP syndrome were significantly higher in patients from the early onset preeclampsia (EOP) group than from the late onset preeclampsia (LOP) group ($p <0.0001$).

There were no statistically significant differences between the groups with respect to maternal age, parity, presence of pedal oedema. Even though eclampsia is not statistically significant in either groups, imminent signs of eclampsia like headache, epigastric pain and visual disturbances were more in EOP group (p <0.0001). In our study, systolic blood pressure, diastolic blood pressure and mean blood pressure were significantly higher in early onset pre-eclampsia (p <0.0001).

Laboratory values like Mean haemoglobin and haematocrit values were different between the groups (p <0.0001). Mean platelet counts, lactic dehydrogenase(LDH), aspartate amino transferase (AST), alanine amino transferase (ALT), total bilirubin, uric acid, blood urea nitrogen (BUN) and creatinine values also differ between the groups, higher values were present in early onset pre-eclampsia than late onset preeclampsia which were statistically significant. Spot urinary dipstick proteinuria were significantly different between the groups.

Ultrasound findings like abnormal uterine artery Doppler (61.3 vs. 9.6%) (p <0.0001), oligohydramnios (amniotic fluid index [AFI] <5), IUGR (48 vs. 9.6%) (p <0.0001) were statistically different in the study groups. The incidence was significantly higher in early onset preeclampsia (EOP) than late onset preeclampsia (LOP). Two or more types of antihypertensive drugs including MgSO4 therapy were often used in early onset preeclampsia (EOP) than late onset preeclampsia (LOP) group.

The mean gestational age at delivery in weeks was 33.57±3.61 in early onset preeclampsia (EOP) group and 36.90±0.37 in late onset preeclampsia (LOP) group which is statistically significant (p <0.0001), birth weight in grams were 1805.05±720.93 in early onset preeclampsia (EOP) and 2568.55±338.24 in late onset preeclampsia (LOP), incidence of small for gestational age newborns (57.3 vs. 12%) (p <0.0001) were statistically significant. The incidence of Apgar score <7 at 5 min, stillbirth, neonatal intensive care unit (NICU) admission, perinatal mortality were significantly higher in early onset preeclampsia (EOP) group (p = 0.001).

Incidence of maternal complications like renal failure/oliguria, eclampsia, posterior reversible encephalopathy syndrome (PRES), Abruptio placenta were not statistically significant, length of intensive care unit (ICU) stay and overall hospital stay was higher in early onset preeclampsia (EOP) group which was statistically significant. Three maternal deaths in late onset preeclampsia (LOP) group and one maternal death in early onset preeclampsia (EOP) group (not statistically significant) occurred in our study due to eclampsia complicated with haemolysis elevated liver enzymes low platelet (HELLP) syndrome resulting in disseminated intravascular coagulation (DIC).

Perinatal mortality was significantly higher in early onset preeclampsia (EOP) group (24% vs. 4.8%) which can be explained by viz. termination of pregnancy before the period of viability (<28 weeks), complications of prematurity and increase in incidence of intra uterine growth retardation (IUGR).

Sl. No.	Category	Early onset group (n=75)	%	Late onset group (n=83)	%	Total (n=158)	p value
1.	Severe pre- eclampsia	48	64.0	27	32.5	75	0.0001
2.	Eclampsia	3	4.0	8	9.6	11	0.3
3.	HELLP syndrome	33	44.0	4	4.8	37	<0.0001
4.	ECLAMPSIA+HELLP syndrome	2	2.7	3	3.6	5	0.9
	1+2+3+4	2	2.7	3	3.6	5	0.9

Table 1. Categories of the Preeclamptic Patients in Study Groups

		Early onset Preeclampsia (75)		Late onset Preeclampsia (83)		p-value
		Count	Column N %	Count	Column N %	
AGE (yrs.)	<25 yrs.	36	48.0	46	55.4	0.4
	26-30 yrs.	26	34.7	28	33.7	
	>31	13	17.3	9	10.8	
GRAVIDA	Primi	45	60.0	36	43.4	0.3
	Multi	30	40.0	47	56.6	
PARA	Nulliparity	52	69.3	51	61.4	0.6
	>1	23	30.6	32	38.5	
	<34 wks.	75	100	0	0	
	>34 wks.	0	0	83	100	
BMI (kg/m^2)	<25	27	36.0	0	.0	<0.001
	25.1-30	40	53.3	63	75.9	
	>30.1	8	10.7	20	24.1	
	Pedal Oedema	71	97.3	81	100.0	0.3
IMMINENT SIGNS	Epigastric pain	13	17.8	1	1.2	<0.0001
	headache	30	41.1	8	9.9	<0.0001
	Visual disturbance	4	5.5	0	.0	<0.0001

Table 2. Demographics and Clinical Findings of the Patients According to Onset of Pre-Eclampsia

	Early onset Preeclampsia		Late onset Preeclampsia		
	Mean	**SD**	**Mean**	**SD**	**p**
Systolic BP mm of Hg	163.87	12.63	156.94	5.86	<0.0001
Diastolic BP mm of Hg	107.69	4.87	100.67	4.64	<0.0001
MAP mm of Hg	126.47	6.67	119.41	4.57	<0.0001

Table 3. Blood Pressure Measurements in Two Groups

	Early onset Preeclampsia		Late onset Preeclampsia		
	Mean	**SD**	**Mean**	**SD**	**p**
Haemoglobin gm/dl	11.68	1.29	10.66	.94	< 0.0001
Haematocrit	36.19	3.48	33.07	3.53	< 0.0001
Platelet count cu/mm	161973.05	53727.71	242007.23	55681.70	< 0.0001
LDH U/L	749.57	350.34	460.99	152.43	< 0.0001
AST U/L	81.67	43.15	50.17	14.94	< 0.0001
ALT U/L	57.48	32.90	31.20	11.14	< 0.0001
Total bilirubin mg/dl	1.04	.36	.80	.16	< 0.0001
Uric acid mg/dl	5.41	1.12	4.20	.78	< 0.0001
Urea mg/dl	34.05	6.04	31.07	5.79	0.002
Creatinine mg/dl	.91	.16	.83	.12	0.001

Table 4. Laboratory Findings of Patients According to Onset of Pre-Eclampsia

		EOP group		LOP group		
		n	**%**	**n**	**%**	**p**
No. of Antihypertensive drugs used	None	0	.0	5	6.0	0.001
	One	31	41.3	60	72.3	
	Two	27	36.0	12	14.5	
	Three	17	22.7	6	7.2	
Mgso4 therapy	No	25	33.3	49	59.0	0.0001
	Yes	50	66.7	34	41.0	
Route of delivery	Hysterotomy	1	1.3	0	.0	0.02
	LSCS	38	50.7	26	31.3	
	Vaginal delivery	36	48.0	57	68.7	

Table 5. Patient Management Characteristics

Maternal Outcomes	Early Onset Preeclampsia		Late Onset Preeclampsia		
	n	**%**	**n**	**%**	**p**
Eclampsia	3	4.0	8	9.6	0.2
Renal failure/Oliguria	14	18.7	7	8.4	0.06
PRES	3	4.0	0	.0	0.06
Abruptio placenta	2	2.7	0	.0	0.1
Maternal mortality	1	1.3	3	3.6	0.3

Table 6. Maternal Complications in Each Group

	Early onset preeclampsia			Late onset preeclampsia			
	Mean	**SD**	**Median**	**Mean**	**SD**	**Median**	**p**
Length of ICU stay in days	1.84	1.87	2.00	.89	1.83	.00	0.002
Length of hospital stay in days	9.41	2.24	9.00	6.72	1.73	6.00	<0.0001

Table 7: Length of ICU / Hospital Stay in Two Groups

Fetal Outcome	Early onset Preeclampsia		Late Onset Preeclampsia		
	n	%	n	%	p
Small for gestational age	43	57.3	10	12.0	<0.0001
APGAR 7 at 5 minutes	17	22.7	4	4.8	0.001
Intra uterine deaths	3	4.0	1	1.2	0.3
Still births	12	16.0	1	1.2	0.001
Early neonatal death	4	5.3	2	2.4	0.3
Neonatal ICU(NICU) admission	35	46.7	9	10.8	0.001
Perinatal mortality	18	24.0	4	4.8	0.001
Intra uterine growth retardation (IUGR)	36	48.0	8	9.6	<0.0001

Table 8. Neonatal Outcomes

DISCUSSION

There is a growing evidence that preeclampsia has two different forms of disease depending on gestational age at onset, the heterogeneity of preeclampsia shows that the timing of disease onset is one important indicator of disease severity and possibly of disease aetiology resulting in different maternal and perinatal outcomes. Approaching as an early onset and late onset pre-eclampsia gives us better idea about understanding of the complex aetiopathogenesis of this medical enigma.

Few studies have reported that signs of poor early placentation are more frequently observed in early onset preeclampsia (EOP) than in late onset preeclampsia (LOP) and stated that exaggerated systemic inflammatory response as the origin for late onset preeclampsia (LOP).[15] Early onset preeclampsia (EOP) is associated with increased risk of multi organ involvement including hepatic, hematologic, nervous, arterial, renal and adverse maternal and fetal outcomes as compared with late onset preeclampsia (LOP). There are limited number of studies and reviews that have compared characteristics of early onset and late onset pre-eclampsia.

In our study the incidence of pre-eclampsia was 5.8%, more in late onset preeclampsia (LOP) than early onset preeclampsia (EOP) group (52.5 vs 47.4 %). Clinical characteristics like systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean arterial pressure (MAP) were significantly higher in early onset (EOP) group suggesting increased maternal total vascular resistance which strengthens abnormal placentation as the probable cause for early onset subtype. Impaired trophoblastic invasion of the maternal spiral arteries was shown to be associated with increased impedance to flow in the waveforms obtained by Doppler ultrasound examination of the uterine arteries.[16] In our study, oligohydramnios and uterine artery (UtA) Doppler abnormality was demonstrated to be more prevalent in early onset preeclampsia (EOP) compared to late onset preeclampsia (LOP) (20 vs. 7.2%; 61.3 vs. 9.6%, respectively), chronic placental insufficiency leading to intra uterine growth retardation (IUGR) was higher in early onset preeclampsia (EOP) (48 vs 9.6%) (p <0.0001). Consistent with our findings, Meler et al[17] had also reported uterine artery (UtA) Doppler abnormality to be more prevalent in early onset preeclampsia (EOP) (62 vs. 27%).

Late onset of the disease ($\geq$34 weeks gestation) on the other hand has been linked to maternal factors and maternal immunogenic (inflammatory) reaction to pregnancy.[18] Valensise et al[6] reported that patients who were diagnosed with late onset preeclampsia (LOP) had higher pre-pregnancy basal metabolic index (BMI) which supports our study where pre-pregnancy BMI was higher in late onset preeclampsia (LOP) group (p<0.0001).

The laboratory parameters like platelet count, liver enzymes, lactic dehydrogenase (LDH), renal function tests were significantly elevated in early onset preeclampsia (EOP) group which suggests multi organ involvement and increased severity in early onset preeclampsia (EOP) group. Assessment of dipstick proteinuria is not statistically significant between the two groups which in turn supports the fact that proteinuria cannot be considered in classifying the severity of pre-eclampsia.

We observed more severe preeclampsia (64 vs 32.5%) (p<0.0001), HELLP syndrome (44 vs 4.8%) (p<0.0001) in the early onset preeclampsia (EOP) group than in the late onset preeclampsia (LOP) group, however there is a increased incidence of eclampsia and maternal mortality in late onset preeclampsia (LOP) group (p<0.3). HELLP syndrome and eclampsia can be considered complications of preeclampsia and higher rates of admission to the critical care unit observed in patients with early onset preeclampsia (EOP) may result from the increased incidence of HELLP syndrome and severe pre-eclampsia found in this group.

Our study results confirmed that early onset preeclampsia (EOP) is a more severe clinical entity. Imminent signs of eclampsia (headache, blurring of vision, epigastric pain and vomiting), the number and duration of antihypertensive drug usage, MgSO4 therapy were statistically significant (p<0.0001), the increased length of intensive care unit (ICU) and hospital stay were also statistically significant (p<0.0001) in early onset preeclampsia (EOP) group, but the rates of other maternal complications due to pre-eclampsia, such as abruption of the placenta, acute renal failure (ARF)/oliguria, posterior reversible encephalopathy syndrome (PRES) were not sufficient to show differences between the groups.

Gestational age at birth had a major impact on perinatal morbidity and mortality. Early onset group had early termination of pregnancy due to uncontrolled blood pressure, derangement of laboratory parameters and clinical

worsening. Mean gestational age at delivery for the early onset preeclampsia (EOP) and late onset preeclampsia (LOP) was 33.57±3.61, 36.90±.37 respectively (p<0.0001). Perinatal mortality and still birth rates were significantly different with 24% and 16% in early onset preeclampsia (EOP) group, 4.8% and 1.2% in late onset preeclampsia (LOP) group.

Small for gestational age babies were more in early onset preeclampsia (EOP) with average birth weight of 1805.05±720.93 vs. 2568.55±338.24 in late onset preeclampsia (LOP) group (p<0.0001). Low Apgar score at 5^{th} minute, small for gestational age and increased requirement for neonatal intensive care unit (NICU) stay were higher in early onset preeclampsia (EOP) group which can be explained by premature termination of pregnancies. Intra uterine foetal demise was 4% in early onset preeclampsia (EOP) group and 1.2% in late onset preeclampsia (LOP) group (p = 0.3).

CONCLUSION

Our results revealed that early onset pre-eclampsia is a distinct and severe clinical subtype than late onset pre-eclampsia with higher risk for life-threatening maternal complications and foetal mortality, late onset pre-eclampsia is associated with minor placental involvement and milder clinical disease. As the prediction and prevention of pre-eclampsia is not possible, approaching pre-eclampsia as early onset and late onset depending on gestational age at onset with anticipation of maternal and perinatal outcomes in these preeclamptic subtypes will help us in initiating an appropriate treatment in a timely manner.

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