Preeclampsia and Prematurity: Balancing the Odds for Maternal and Perinatal Outcomes in a Low-middle Income Country

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Abstract

Objective: To evaluate the maternal and perinatal outcomes of pre-eclampsia in accordance with the World Health Organization (WHO) prematurity criteria in a Low-Middle Income Country.

Methods: This cross-sectional study was conducted between January 2017 and December 2019 at Aga Khan University Hospital, Pakistan. All women with preterm preeclampsia were included. Pregnant women with fetal anomalies or incomplete medical records were excluded. The participants were divided into three groups based on the WHO prematurity classification: I. extremely preterm (EPB-24-27+6 weeks), II. very preterm (VPB- 28 and 31+6 weeks), III. moderate to late preterm (MLPB 32-36+6 weeks). Data was analyzed using SPSS 19.0.

Results: Out of 324 women, 27%, 10.8%, and 61.7% were delivered as extremely preterm, very preterm, and moderate to late preterm respectively. 13.9% of women developed serious maternal complications. Intrauterine death occurred in 5.6% of cases, and the rate of IUD was not statistically significant among groups. The median birth weight was significantly lower in the EPB and VPB groups in comparison to the MLPB group. Out of the total, 6.3% of neonates expired, with all deaths in the extremely premature group except for one neonatal death which occurred after 28 weeks.

Conclusion: The neonatal death rate is high when delivery is expedited before 28 weeks of gestation. Maternal complications are more common in pregnancies affected by preeclampsia before 32 weeks. However, the maternal and perinatal outcomes can be improved with vigilant surveillance and appropriate referrals.

Keywords: Preeclampsia, Preterm, Neonatal outcome, Perinatal, Neonatal Death, Low-middle income countries

Introduction

Preeclampsia is a disease of placenta, responsible for the annual death of 30,000 women (1) and 500,000 infants (2, 3). It is defined as new-onset hypertension (≥140/90 mmHg) after 20 weeks of gestation in a previously normotensive woman, accompanied by proteinuria (≥300 mg/24h, protein/creatinine ratio ≥0.3, or dipstick ≥1+) or evidence of end-organ dysfunction. End-organ involvement includes thrombocytopenia (platelet of <100,000/μL),

renal insufficiency (serum creatinine >1.1 mg/dL or doubling of baseline), elevated liver enzymes (≥2× normal) with or without severe epigastric pain, pulmonary edema, or persistent neurological symptoms such as headache or visual disturbances (6). This multiorgan disorder can lead to maternal seizures, and intracranial hemorrhage, and can cause death of the mother and fetus. It is associated with the highest morbidity and mortality in middle- and low-income countries (4). Thirty-four percent of maternal deaths were attributed to the complications of preeclampsia in Pakistan (5).

To prevent complications of pre-eclampsia, delivery is the definite treatment. However, the timing of delivery is a challenge considering maternal and neonatal outcomes. The World Health Organization (WHO) recommends expectant management till 37 weeks of pregnancy with close maternal and fetal surveillance using clinical, biochemical, and hematological markers (6). However, delivery is indicated when there is evidence of severe pre-eclampsia or impending eclampsia regardless of gestational age. Hence in such cases, preterm birth (PTB) is a frequent complication (7) contributing to about 25 to 30% of all preterm deliveries (8, 9).

Healthcare in developing countries with limited resources is burdened by high maternal and perinatal mortality (10). In comparison to high-income countries, the management of preeclampsia may differ in these settings as the risk of premature termination of pregnancy with associated reduced neonatal survival has to be balanced against the risk of increased maternal and fetal morbidity and mortality.

Our study aims to evaluate the maternal and perinatal outcomes of preeclampsia in accordance with the WHO prematurity criteria in a low-resource country. The result of our study will enable obstetricians to better counsel the expected parents to make an informed decision based on the local data from a tertiary care hospital. This may also help policymakers formulate national guidelines on referral pathways and the allocation of resources to accommodate these patients.

Methods

This cross-sectional study was conducted between January 2017 and December 2019 in the Department of Obstetrics and Gynecology at Aga Khan University Hospital, Pakistan. The study included all women in whom preeclampsia was diagnosed between 24^{+0} and 36^{+6} weeks of pregnancy. Pregnant women with fetal anomalies or incomplete medical records were excluded from the study.

The newborn outcomes were divided into three groups based on the WHO prematurity classification: I. extremely preterm (EPB group comprising women who delivered between 24-27+6 weeks of gestation), II. very preterm (VPB group comprising women delivered between 28 and 31+6 weeks of gestation), III. moderate to late preterm (MLPB group including women delivered between 32 and 36+6 weeks of gestation).

Demographic details of the mothers were collected from the hospital medical records and labor room management system database. Details of the newborn were obtained from hospital medical records, labor room medical record system, and neonatal intensive care unit (NICU) records.

The following outcomes were examined and considered: gestational week at delivery, mode of delivery, development of maternal complications (e.g., eclampsia, stroke, pulmonary edema, abruptio placenta and maternal mortality etcetera), fetal growth restriction, newborn birth weight, Apgar score, NICU admission, neonatal death (NND) and intrauterine death (IUD).

All statistical analyses were performed using SPSS 19.0 (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA). Numeric data were expressed as mean ± standard deviation (SD) or median with interquartile ranges (IQR). Categorical data were reported as proportions and percentages. The continuous variables were evaluated using visual (histograms) and analytical methods (Shapiro-Wilks test) to determine whether they were normally distributed or not. One-way analyses of variance were used for normally distributed data, and the Kruskal-Wallis's test and Mann-Whitney U test were performed for comparison of non-normally distributed metric data. A chi-square test or exact test was used to analyze the difference between categorical data. Variables with $P < 0.20$ in the univariate analysis were subjected to a multivariable model to explore independent risk factors. Multinomial logistic regression analysis was used to determine independent predictors for EPB and VPB. Statistical significance was accepted as $p \leq 0.05$.

This study was exempted for full review by Aga Khan University- Ethical Review Committee under study number 2020-3531-11013, dated 2nd July, 2020. Consent was waived off due to retrospective nature of study and no direct involvement with patients.

Results

During the study period, our institution recorded a total of 16,229 deliveries, averaging approximately 5,400 deliveries per year. As a private-sector tertiary care teaching hospital, we receive referrals not only from within the city but also from other catchment areas. The prevalence of preeclampsia during this time was around 6.7% which is based on data from the departmental annual report on morbidity and mortality statistics. A total of 324 women with pre-eclampsia were analyzed. The average age of the women was 29.84±5.13 years. Almost 63% were booked, and 70% were primiparous. A history of miscarriage was found in 106 of 324 (32.7%) cases. The most common maternal co-morbid was Diabetes Mellitus (25.6%) and thyroid disease (5.2%). In 23 (7.1%) women were pregnant with multiple gestation. A total of 285 (88%) underwent cesarean sections, whereas 39 (12%) had vaginal births. In this cohort, 89 of 324 women (27.47%) were delivered between 24-27+6 weeks of gestation, which is referred to as extremely preterm birth (EPB); 35 (10.8%) were delivered between 28 and 31+6 weeks of gestation, which is known as very preterm birth (VPB) group; and 200 (61.7%) were born between 32 and 36+6 weeks of gestation, which is referred to as moderate to late preterm birth (MLBP) group.

Demographic characteristics for EPB, VPB and MLPB are shown in **Table 1.** The mean age, history of miscarriage, parity, and multiple pregnancies were not statistically significant among the groups. Only 10 (3.1%) women conceived through in vitro fertilization and no significant difference was observed among the groups ($p = 0.848$). The rate of un-booked cases was significantly higher in EPB as compared to MLPB ($P<0.01$).

Fetal growth restriction was diagnosed in 127 (39.2%) of the women. The rate of IUGR was also significantly higher in women with EPB (59.6% vs. 27.5%, p <0.01) and VPB (54.3% vs. 27.5%, p <0.01) as compared to MLPB. However, no significant difference was observed between EPB and VPB (p = 0.687). Out of 324, forty-five (13.9%) preeclamptic women developed serious maternal complications, including eclampsia, pulmonary edema, abruptio placenta, postpartum hemorrhage, and HELLP syndrome, as reported in **Table 2.** The overall rate of maternal complications was also significantly higher in VPB as compared to MLPB (31.4% vs. 10%, p<0.01). The frequency of HELLP syndrome was significantly higher in the VPB group as compared to EPB and MLPB (17.1% vs. 3.5%; p<0.01) and (17.1% vs. 4.5%; p<0.01). Intrauterine death(IUD) was found in 18 (5.6%) of pregnancies, and the rate of IUD was not statistically significant among groups (p = 0.836). The unadjusted and adjusted odd ratios for the independent risk factor were investigated using multinomial logistic regression analysis. In comparison to EPB and MLPB, HELLP syndrome was the most important risk factor for VPB. Similarly, IUD was a significant risk factor for EPB and VPB in comparison to MLPB in univariate and also in multivariate analyses after controlling the effect of booking status, parity, HELLP syndrome, diabetes women and preexisting hypertension. **(Table 3)**

A comparison of neonatal outcomes among the groups is presented in Table 4. The median birth weight was significantly lower in the EPB and VPB groups in comparison to the MLPB group. The rate of very low BW ≤1.5 kg was significantly higher in EPB than MLPB (89% vs. 12.9%; p<0.01) and higher in VPB than MLPB (76.9% vs. 12.9%; p<0.01). Ventilatory support need and Apgar score <7 was significantly greater in EPB groups as compared to VPB and MLPB groups. Out of 331 neonates, 21 (6.3%) expired, and most of the neonatal deaths were significantly higher in EPB groups as compared to VPB and MLPB.

Table 1: Comparison of characteristics of women among the preterm groups (n=324).

Variables	**EPB n=89**	**VPB n=35**	**MLPB n=200**	**P-Value**
Age (Years)	29.44±5.63	29.63±4.62	30.06±5.00	0.622
Booking Status Booked Un-Booked	42(47.2%) 47(52.8%) †	18(51.4%) 17(48.6%) ‡	142(71%) 58(29%)	0.005
Previous Miscarriage	35(39.3%)	11(31.4%)	60(30%)	0.292
Parity Nullipara Multipara	68(76.4%) 21(23.6%)	23(65.7%) 12(34.3%)	134(67%) 66(33%)	0.244
IVF Pregnancy	2(2.2%)	1(2.9%)	7(3.5%)	0.848
Multiple Pregnancy	8(9%)	4(11.4%)	11(5.5%)	0.324

Extremely Preterm Birth (EPB), Very Preterm Birth (VPB) and Moderate to Late Preterm Birth (MLPB)

† $p<0.01$ vs. MLPB ‡ $p<0.01$ vs. MLPB.

Table 2: Comparison of maternal characteristic of women among preterm birth groups (n=324).

Variables	**EPB n=89**	**VPB n=35**	**MLPB n=200**	**P-Value**
Mode of delivery				0.307
Vaginal Delivery	9(10.1%)	2(5.7%)	28(14%)	
Caesarean Section	80(89.9%)	33(94.3%)	172(86%)	
Pregnancy Complications				
Overall*	**14(15.7%)**	**11(31.4%) ‡**	**20(10%)**	**0.003***
Cerebrovascular Accident	1(1.1%)	0	1(0.5%)	0.728
Eclampsia	3(3.4%)	0	1(0.5%)	0.098
Pulmonary edema	1(1.1%)	2(5.7%)	5(2.5%)	0.333
Cardiomyopathy	3(3.4%)	0	0	0.052
Acute renal failure	0	1(2.9%)	0	0.383
Abruption Placenta	2(2.2%)	3(8.6%)	7(3.5%)	0.460
Postpartum Hemorrhage	3(3.4%)	2(5.7%)	2(1%)	0.115
HELLP Syndrome	4(4.5%)	6(17.1%) ‡ ¥	7(3.5%)	0.004*
Maternal Mortality	0	0	0	NA
IUD	6(6.7%)	2(5.7%)	10(5%)	0.836
IUGR	53(59.6%) †	19(54.3%) ‡	55(27.5%)	0.0005*

Extremely Preterm Birth (EPB), Very Preterm Birth (VPB) and Moderate to Late Preterm Birth (MLPB)

† $p<0.01$ vs. MLPB; ‡ $p<0.01$ vs. MLPB; ¥ $p<0.01$ vs. EPB

Table 3: Multinomial Logistic regression applied for the risk factor of EPB, VPB.

Factors	EPB vs. VPB		EPB vs. MLPB		VPB vs. MLPB	
	Unadjusted OR [95%CI]	Adjusted aOR[95%CI]	Unadjusted OR [95%CI]	Adjusted aOR[95%CI]	Unadjusted OR [95%CI]	Adjusted aOR[95%CI]
Booking Status						
Un-booked	1.19[0.54-2.59]	1.40[0.61-3.22]	2.74[1.63-4.59] ‡	2.31[1.32-4.45] †	2.31[1.11-4.79] ‡	1.64[0.75-3.61]
Booked	Ref	Ref	Ref	Ref	Ref	Ref
Parity						
0-1	1.69[0.72-3.96]	1.69[0.69-4.12]	1.59[0.90-2.82]	1.48[0.81-2.78]	0.94[0.44-2.01]	0.88[0.39-2.00]
≥2	Ref	Ref	Ref	Ref	Ref	Ref
HELLP Syndrome						
Yes	0.27[0.06-0.86] †	0.23[0.53-0.95] †	1.29[0.37-4.55]	1.81[0.48-683]	5.70[1.79-18.16] †	8.06[2.24-28.04] †
No	Ref	Ref	Ref	Ref	Ref	Ref
Diabetic Mellitus						
Yes	1.14[0.41-3.18]	1.17[0.40-3.43]	0.55[0.30-1.01]	0.77[0.39-1.52]	0.48[0.19-1.22]	0.66[0.25-1.77]
No	Ref	Ref	Ref	Ref	Ref	Ref
Pre-existing Hypertension						
Yes	1.52[0.69-3.34]	1.52[0.67-3.48]	1.57[0.95-2.59]	2.16[1.23-3.81] †	1.03[0.5-2.12]	1.42[0.65-3.12]
No	Ref	Ref	Ref	Ref	Ref	Ref
IUGR						
Yes	1.24[0.56-2.72]	0.96[0.40-2.29]	3.88[2.29-6.56] †	3.76[2.13-6.64] †	3.13[1.50-6.52] †	3.91[1.72-8.86] †
No	Ref	Ref	Ref	Ref	Ref	Ref

† $p<0.01$ ‡$p<0.05$ Multinomial Logistic regression applied

Table 4: Comparison of neonatal outcome among women with EPB, VPB and MLPB

Variables	**Total n=331**	**EPB n=91***	**VPB n=39****	**MLPB n=201*****	**P-Value**
Birth Weight (kg)$	**1.77±0.77 [0.3-8]**	1.12±0.82 [0.3-8]	1.28±0.35 [0.6-5]	2.16±0.53 [1-3.9]	0.0005
NICU Admission	**202(61%)**	88(96.7%) †	39(100%) ‡	75(37.3%)	0.0005
Ventilator Support	**51(15.5%)**	39(42.9%) †	3(7.7%)	9(4.5%)	0.0005
Apgar score <7	**13(3.9%)**	11(12.1%) †	2(5.1%)	0	0.0005
Neonatal Death	**21(6.3%)**	20(22%) †	0	1(0.5%)	0.0005

Extremely Preterm Birth (EPB), Very Preterm Birth (VPB) and Moderate to Late Preterm Birth (MLPB) † $p<0.01$ vs. MLPB; ‡ $p<0.01$ vs. MLPB. $ Mean ± SD [Range: Min-Max]

Mann-Whitney U test for median comparison; Chi-square test for proportion comparation

* 81 had singleton, **8 twin pregnancies** and **6 were IUD** so

n= 81+16=**97**-6= **91.**

** 31 women had singleton, **two had twin** and **two had triplet**, 2 were IUD so,

n=31+4+6 =41-2= **39**

*** 189 women had singleton, **11 had twin** and 10 were IUD so,

n=189+22= 211 - 10= **201**

Discussion

The findings of our study revealed an elevated incidence of maternal complications, particularly within the EPB and VPB cohorts. The VPB group exhibited a complication rate twice as high as the EPB group and three times greater than that of the MLPB group. This suggests that early-onset type (onset before 34 weeks), is a more severe form of preeclampsia with a much higher complication rate. This findings are in agreement with prior results of other studies that early-onset type when compared to its counterpart late-onset preeclampsia (34-37 weeks) has a worse prognosis(11, 12). This was also concluded in the systematic review by Guida JP et al. (13). According to the type of preeclampsia, both EPB and VPB are categorized as early-onset, yet the VPB group exhibits a twofold higher rate of maternal complications. We believe that this discrepancy is attributed to physicians adopting a more interventionist approach in the EPB group, where delivery decisions are influenced by maternal factors only and not perinatal factors as the gestational age is considered too low for a favorable perinatal outcome. Moreover, maternal and perinatal outcomes in the Pakistani population are worse compared to other low and middle-income countries(14). Pakistan has a neonatal mortality rate (NMR) of 41 deaths per 1000 live births (15). Given one of the highest neonatal mortality rates, cases of severe preeclampsia diagnosed before 28 weeks of gestation prioritize maternal health(6). This might explain a lower maternal complication rate in EPB group in comparison to the VPB group. However, when preeclampsia is diagnosed after 28 weeks, a more conservative approach is employed, considering the gestational age, with prolongation of pregnancy associated with a higher chance of survival for the neonate, and delivery is only decided when impending maternal or perinatal complication is developed or anticipated. In a systematic review by G. Scott et al. also recommended that severe preeclampsia warrants delivery irrespective of gestational age (16). While for late-onset preterm preeclampsia, straightforward evidence exists supporting elective planned preterm birth to prevent severe maternal morbidity (17). Our data confirm findings of other studies that preeclampsia causes severe organ dysfunction, highlighting the fact that no form of preeclampsia is benign (11), and hence delivery should be expedited particularly if signs or symptoms of severe preeclampsia develop.

Half of the women in EPB and VPB were un-booked referred cases, while 71% of women in MLPB were booked cases as more complicated cases were referred to our hospital for the intensive care needs of the mother and baby from the primary and secondary care facilities. Studies have shown that the interval between diagnosis and delivery is usually short in cases of preeclampsia even among women where less severe symptoms are observed and expectant management is employed, hence in such situations, the decision to transfer the patient should not be delayed (18).

Most women in our study were delivered by cesarean section. There was no statistically significant difference in all three groups (89.9% in EPB, 94.3% in VPB and 86% in MLPB). Unlike term preeclampsia, where vaginal delivery is the aim (19). Evidence is lacking regarding recommendations on the mode of delivery for preterm preeclampsia. When preterm birth is indicated, cesarean section is opted by many given severity of maternal conditions, prolonged induction to delivery time, and the possibility of fetal tolerance of trial of labor (20). Like ours, a study on Chinese women with preeclampsia also reported a very high cesarean delivery (21). In another study, a 92.76% cesarean

delivery rate was reported in preterm preeclampsia (22). This has to be understood that cesarean delivery is associated with a high rate of maternal complications in women with severe preeclampsia (23). In one study, nearly half of women were delivered vaginally after induction of labor, even in preterm preeclampsia with less maternal morbidity and without any difference in neonatal outcomes (24). However, the rate of normal delivery is very variable as shown in other studies (25) hence it is recommended to consider induction of labor in carefully selected cases.

Our results show that Fetal Growth Restriction (FGR) is the most common complication observed with preeclampsia. We observed that 59% and 54% of pregnancies were complicated in the EPB and VPB groups respectively, while 27% were in the MLPB group. A similar trend was observed by other researchers who found a strong association of FGR with a severe form of preeclampsia and with early-onset preeclampsia (26). This can be attributed to the shared pathophysiology of fetal growth restriction with preeclampsia, especially with early-onset type (27, 28). This has led some experts and groups, to include FGR as one of the diagnostic criteria of preeclampsia being one the organ dysfunction (29). Our results show the rate of FGR to be almost double in the EPB and VPB groups in comparison to the MLPB group, supporting the hypothesis that preeclampsia has different subtypes based on etiology, one associated with placental dysfunction and FGR, while the other with normal or even enhanced placental function (30).

Our study finds that neonatal outcomes were primarily dependent on gestational age at delivery, and mainly were prematurity related. This was evident with a significant difference in the weight at birth, the need for neonatal intensive care unit (NICU) admission, and the requirement for ventilatory support among the groups. The rate of neonatal death was highest in the EPB group i.e. before 28 completed weeks. Among women delivered after 28 weeks of pregnancy, one neonatal death was observed. This favors expectant management in extreme preterm pregnancies as the conservative approach may reduce the incidence of adverse perinatal outcomes. After 28 weeks, if maternal condition warrants delivery, good neonatal survival can be expected. In fact, in a randomized controlled trial, pregnancies with severe preeclampsia after 28 weeks gestation, conservative management did not improve perinatal mortality and many other morbidities supporting our findings (31). Expectant management of preeclampsia is recommended by several international guidelines up to at least 34 weeks to improve neonatal outcomes with vigilant monitoring (13). In the LMIC, due to difficulty in access to care and complex cultural and social issues , many women with preeclampsia are diagnosed late and situation is compounded by limited resources (32). If optimal expectant management cannot be provided, then prompt delivery should be considered for maternal safety.

Strength and limitation of study

A key strength of this study is that it is the first from a low- and middle-income country (LMIC) to evaluate maternal and perinatal outcomes of preeclampsia based on the WHO classification of prematurity, providing valuable insights into neonatal outcomes in the presence of a well-equipped NICU and timely early referrals. The findings highlight the potential for improved neonatal survival with access to specialized care. However, a limitation of this study is its cross-sectional design, which restricts the ability to establish causal relationships. Additionally,

the lack of data on unbooked cases limits the assessment of the impact of pre-existing hypertension on the onset and progression of preeclampsia.

Conclusion

Pre-eclampsia is a critical and potentially life-threatening condition. After diagnosis of preterm preeclampsia, the only reason to prolong the pregnancy is to improve neonatal outcomes. Our study concludes that neonatal death is high when delivery is expedited before 28 weeks with expectant management improving outcomes for the neonate. Maternal complications are high in the pregnancies complicated with preeclampsia before 32 weeks, attributable to the nature of a more severe disease type in early-onset preeclampsia. This study adds that prioritizing early delivery based on maternal condition after 28 weeks can substantially enhance maternal outcomes along with better expectation for neonatal survival. It highlights the need for timely decision-making in the context of available neonatal care resources. Future research should focus on a prospective study with a more detailed analysis that accounts for all potential confounding factors on these maternal and perinatal outcomes related to this important disorder of pregnancy.

Disclosure

The authors declare no conflicts of interest. No funding was received for this study.

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