

ORIGINAL ARTICLE**Clinical and Biomarkers Difference in Prepartum and Postpartum Eclampsia****Yifru Berhan¹, Gezahegn Endeshaw¹****ABSTRACT**

BACKGROUND: *There is a large body of literature which assessed the incidence and risk factors of eclampsia, but little was done in assessing the association of clinical features and biological markers with prepartum and postpartum eclampsia.*

METHODS: *A total of 361 eclamptic women admitted to three teaching hospitals between 2008 and 2013 were included in this analysis. A comparative analysis was done for several clinical and biological variables to assess their association with prepartum and postpartum eclampsia.*

RESULTS: *The overall incidence of eclampsia was 1.2% (prepartum 71% and postpartum 29%). The majority of women with prepartum eclampsia were young, primigravida, more hypertensive, symptomatic and proteinuric. Conversely, the majority of the women with post-partum eclampsia were adult, multiparous, carrying pregnancy to term, anemic, thrombocytopenic, and with hepatic dysfunction. The commonest severity symptom (headache) was less common in postpartum eclamptic women.*

CONCLUSION: *The incidence of eclampsia was among the highest in the world. And, the analysis has shown that the clinical and biochemical spectrum of prepartum and postpartum eclampsia were apparently different. The majority of the women who developed postpartum eclampsia were multiparous and adult. Derangement of biomarkers was also more common in women with postpartum eclampsia.*

KEYWORDS: *clinical features, comparative analysis, Ethiopia, incidence, organs dysfunction, prepartum, postpartum*

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INTRODUCTION

Eclampsia is one of the commonest causes of maternal and perinatal morbidity and mortality worldwide, the majority being in developing countries (1,2). It may complicate 2% to 3% of severely preeclamptic women not given anticonvulsant prophylaxis, and about 0.6% of those women receiving the anticonvulsant prophylaxis (3,4). The overall incidence of eclampsia in developed and developing countries is estimated to be 1.6 to 10 and 6 to 157 per 10,000 deliveries, respectively (3,5,6).

Eclampsia is characterized by the occurrence of generalized tonic-clonic seizure and/or coma in pregnant or postpartum women with preeclampsia, and is not caused by epilepsy or other convulsive disorders (7-9). It is well known that eclampsia can occur during pregnancy (antepartum), during

labor and delivery (intrapartum), and after delivery (postpartum) (10,11).

To date, however, there are no reliable biological tests to predict which pregnant or postpartum women will have preeclampsia/eclampsia (12). Clinical features and laboratory findings are also nonspecific but commonly used as a surrogate marker for the effect of the disease on organs/systems and as a warning sign for eclampsia (13). The challenge is that eclampsia can occur without clinical or biological evidences of preeclampsia (14-16).

There is a large body of literature on eclampsia, which described its incidence before, during and after delivery, factors associated with its occurrence and the risks of maternal and perinatal mortality taking the overall eclampsia as a denominator (7,17-21). However, there is a

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paucity of data that assessed the risk factors and its complications disaggregated by onset of eclampsia.

One study investigated maternal and obstetric factors associated with delayed and early postpartum eclampsia (22). Only delayed eclampsia cases were also compared with preeclamptic mothers with no eclampsia in the postpartum period (23). Other studies assessed only the magnitude of fetal and/or maternal mortality by type of eclampsia (24,25). In another study, some clinical features and proteinuria were compared in 46 antepartum and postpartum eclamptic women (26). Recurrence of convulsion in different types of anticonvulsant was assessed by different types of eclampsia (27). Antepartum and intrapartum eclampsia were also assessed for mode of delivery (28). Relatively, better characterization of eclampsia by type was done in a Scandinavian study (29).

To our knowledge, this is the first study that investigated several variables in relation to prepartum and postpartum eclampsia. Thus, the objective of the study was to assess the association of selected clinical features and biological markers with prepartum and postpartum eclampsia.

METHODS

Study design, setting and participants: The current analysis was performed from a six year retrospective cohort study database, which was collected from three university teaching hospitals (Hawassa, Hosanna and Yirgalem) in the South regional state of Ethiopia. A comparative analysis (prepartum vs postpartum eclampsia) was done for several clinical and biological variables. All eligible women with eclampsia admitted to the study hospitals during the study period (2008 to 2013) were included. The exclusion criterion was lost or incomplete data.

The study hospitals were functioning as referral centers for the region and teaching center for public universities and private health colleges. In these hospitals, eclampsia was diagnosed with the onset of generalized tonic-clonic seizure and/or coma in pregnant or postpartum women commonly with clinical and/or laboratory features of preeclampsia. The most senior person's (gynecologist, resident or general practitioner) clinical assessments and decisions were taken as a final source of data for this analysis.

The commonly assessed clinical features for women with eclampsia were hypertension, headache, blurring of vision, epigastric pain, vomiting, urine output, bleeding tendency and generalized body swelling. Among others, dipstick and microscopic examination of urine, liver and renal function tests, and complete blood count were routinely performed in all study hospitals.

Variables and data collection: Some of the variables assessed in association with the onset of eclampsia were: maternal age, parity, gestational age, prenatal care, number of fetuses, severity symptoms of HDP, degree of hypertension, episodes of convulsion, urine output, proteinuria, hemoglobin level, platelet count, creatinine level, serum oxaloacetic transaminase (SGOT) level, type of anticonvulsant or antihypertensive given, mode of delivery, fetal birth weight, perinatal and maternal outcome.

The detail data were retrieved from patients' charts. Each patient's chart was accessed after identifying the eclampsia cases by their card number in the delivery log book. A structured data collecting format was prepared and used to abstract relevant data from the included patients' charts. The data were abstracted by nine trained nurse data collectors (three for each hospital).

Data analysis: Data were entered into a computer data analysis software program (Epi Info 7) to perform a comparative analysis. We used frequencies and proportions to describe the characteristics of the included variables with stratification by total eclampsia, prepartum and postpartum onset of eclampsia. A statistically significant association was considered when the p-value was < 0.05 . A flow diagram was used to select the study participants and a bar graph was constructed to show the proportion of eclampsia stratified by onset.

Operational definitions: Onset of eclampsia was classified based on occurrence of first convulsion as antepartum (before onset of labor), intrapartum (during labor and delivery), and postpartum (after delivery and before end of puerperium). It was also reclassified as early onset (< 34 weeks of gestation) and late onset (≥ 34 weeks of gestation). The postpartum eclampsia cases were also reclassified as early postpartum (< 48 hours after delivery) and late postpartum (≥ 48 hours and < 6 weeks after delivery).

For the purpose of this analysis, however, the antepartum and intrapartum onset of eclampsia were merged to prepartum eclampsia. This was done taking into account that the baby and placenta were still in utero in both antepartum and intrapartum onset of eclampsia. One of the etiologies incriminated for occurrence of preeclampsia/eclampsia is placental pathology (8). As a result, this study defines prepartum eclampsia in women who developed generalized tonic-clonic seizure before the delivery and after 28 weeks of gestation. Women included as postpartum eclampsia were those who developed generalized tonic-clonic seizure after the delivery of at least a 28 week gestational age fetus and before 6 weeks of the postpartum period.

Eclamptic women's systolic and diastolic blood pressures (BP) after admission were grouped as <160 and ≥ 160 mmHg, and <110 and ≥ 110 mmHg, respectively. The laboratory results were also dichotomized in order to determine their association with prepartum and postpartum eclampsia. Significant proteinuria defined that the qualitative test revealed +2 and above or +1 if the specific gravity was <1.020 . Serum glutamic-oxaloacetic transaminase (SGOT) level raised by ≥ 2 -fold from the baseline and creatinine level ≥ 1 mg/dl were considered as significantly raised. Platelet count $<100,000/\text{mm}^3$ and hemoglobin level <12 gm/dl were taken as severe thrombocytopenia and anemia, respectively.

Women with an age range of 15-24 years and 25-49 years were categorized as youth and adult,

respectively (30). Youth and young women, primigravida and nulliparous were used interchangeably. The term prepartum and pre-delivery, postpartum and post-delivery were also used interchangeably.

Ethical consideration: Hawassa University College of Medicine and health sciences, institutional review board (IRB) gave us the ethical clearance to conduct and publish this research. Since the study was retrospective by design, written consent from patients was not required. Patient records were anonymized and de-identified by excluding identifiers from data collection format prior to analysis. Furthermore, anonymity was secured by analyzing and presenting the data in aggregate.

RESULTS

During the study period, there were 30,750 deliveries in all study hospitals (Figure 1). Of which, 1098(3.6%) women were diagnosed to have hypertensive disorders of pregnancy (HDP). Out of the total HDP cases, 373 were registered as eclampsia. Twelve cases of eclampsia were excluded from analysis due to incomplete or lost data. Finally, 361 women with eclampsia were included for this analysis (1.2% of the total deliveries and 33% of the total HDP). These women were again regrouped as prepartum and postpartum eclampsia, 256 (71%) and 105 (29%), respectively.

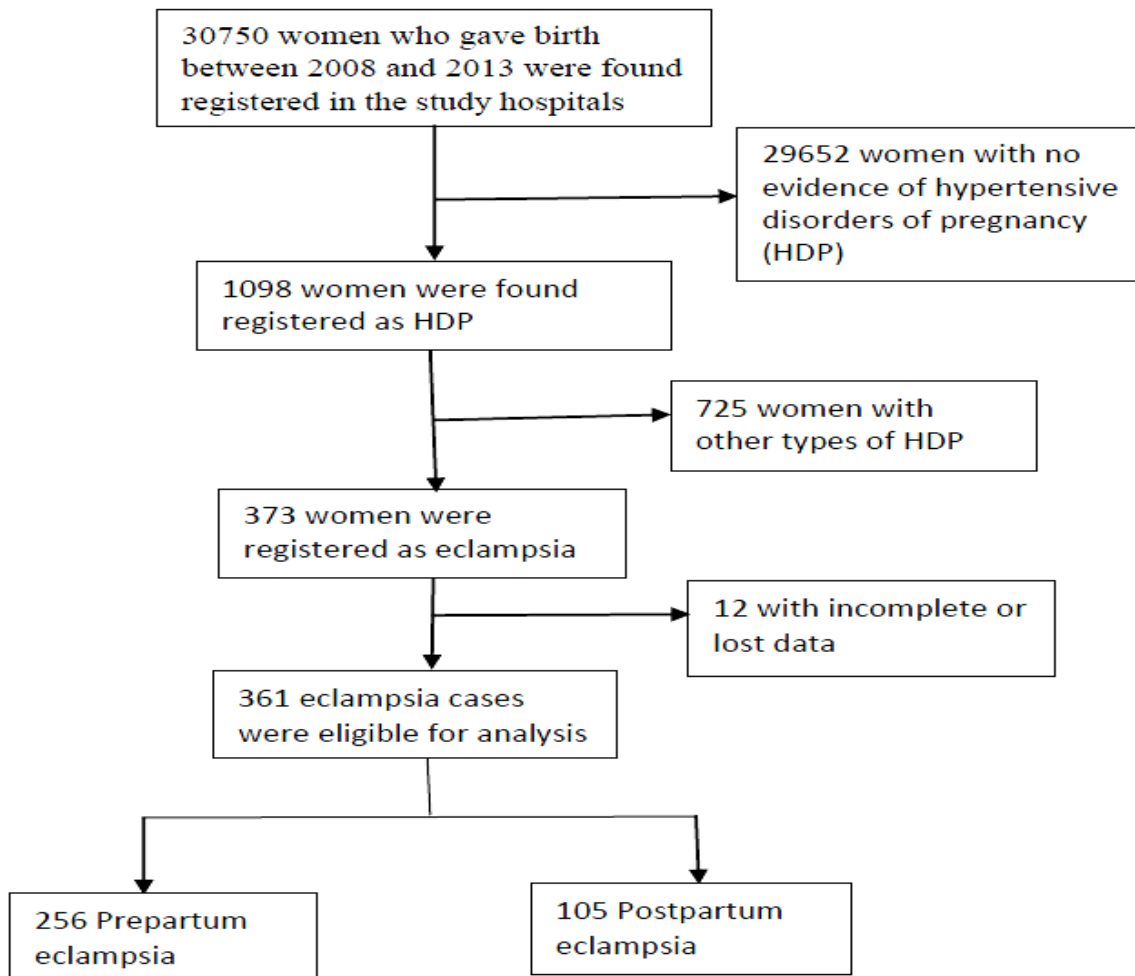


Figure 1: Flow diagram showing the study population selection

Figure 2 shows the summary of the included eclamptic women as categorized by occurrence of first convulsion in relation to the gestational age and delivery. Out of 361 eclamptic women, the proportion of antepartum, intrapartum and postpartum eclampsia was 47%, 24% and 29%, respectively. In terms of gestational age, the early (<34 weeks) and late (\geq 34 weeks) onset eclampsia cases were 18% and 82%, respectively.

Specific to postpartum eclampsia, early (<48 hours after birth) and late/atypical (\geq 48 hours after birth) onset accounted for 79% and 21%, respectively. The range of late onset eclampsia was 60 hours to 10 days from the time of delivery; five patients developed eclampsia on the 10th postpartum day. In 97% of the total eclamptics, the convulsion occurred at home or on the way to the study hospitals.

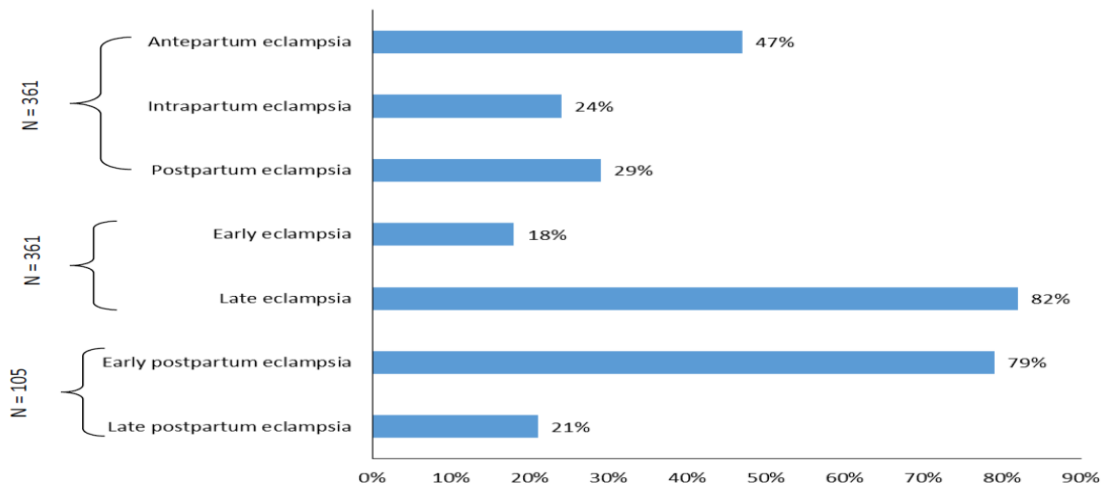


Figure 2: The distribution of eclampsia by timing of onset in relation to gestational age and delivery, 2008-2013.

Note. Onset of eclampsia was defined based on occurrence of first convulsion as:

- 1) Antepartum (during pregnancy), intrapartum (during labor and delivery) and postpartum (after delivery)
- 2) Early (< 34 weeks of gestation) and late (\geq 34 weeks of gestation)
- 3) Early postpartum (< 48 hours after delivery) and late postpartum (\geq 48 hours after delivery)

Table 1 shows the proportion of prepartum and postpartum eclampsia in relation to maternal age, selected clinical features and biomarkers. The ratio of eclampsia in youth and adults was almost 1:1. However, the proportion of postpartum eclampsia was significantly higher in adults than in youths (63.8% vs 36.2%; $P = 0.001$). In terms of gestational age, more than two-thirds of the women with postpartum eclampsia (69.7%) experienced it at term. In other words, preterm eclampsia was significantly higher in prepartum than in postpartum eclampsia ($P < 0.0001$).

The overall incidence of eclampsia was a little bit higher in multigravida than in primigravida women (53.2% vs 46.8%). Of interest, this analysis has strongly demonstrated that prepartum and postpartum eclampsia were mainly the diseases of primigravida and multigravida, respectively ($P < 0.0001$). Out of the total primigravida eclamptic women, 96.4% (163/169) developed it during the prepartum period. Similarly, out of the total postpartum eclampsia cases, 94.3% occurred in multigravida women.

Among selected clinical features, severe systolic hypertension (≥ 160 mmHg) were characteristics of prepartum eclampsia (60.2%). In other words, the majority of postpartum eclamptic women were having mild to moderate systolic hypertension (53.3%; $P < 0.05$). However, the difference in diastolic hypertension in the two

groups was not statistically significant. In the majority of both the prepartum and postpartum eclamptic women, the commonest severity symptom was headache (80.5% and 66.7%, respectively), with statistically significant difference between the two groups ($P = 0.004$). Epigastric pain was an uncommon symptom among postpartum eclamptic women ($P < 0.0001$). There were no statistically significant differences between the two groups in relation to other clinical features like urine output and episodes of convulsion before and after initiation of anticonvulsants.

In the majority of selected biomarkers, this analysis has demonstrated statistically significant difference between women with prepartum and postpartum eclampsia. Significant proteinuria ($P < 0.001$) and severe thrombocytopenia ($P = 0.009$) were more common in women with prepartum than postpartum eclampsia. On the other hand, a high proportion of anemia ($P < 0.001$) and ≥ 2 -fold raised in SGOT level was observed among women with postpartum eclampsia ($P = 0.005$). The ≥ 1 mg raised in creatinine level in both prepartum and postpartum eclampsia was proportional, and occurred in nearly three-fifths of the total eclamptic women (59.6%).

In terms of place of delivery, the proportion in one group was the mirror image of the other: 82% of prepartum eclamptic women gave birth in a health facility; 81.6% of postpartum eclamptic

women gave birth at home without the assistance of skilled persons ($P < 0.0001$). Almost all women with postpartum eclampsia and nearly three-fourths of women with prepartum eclampsia delivered vaginally ($P < 0.0001$).

The fetal birth weights in prepartum and postpartum eclamptic group were also significantly different: 75% of newborns of prepartum eclamptic women were having low

birth weight; whereas, 87.6% of postpartum eclamptic women gave birth to newborns with normal birth weight ($P < 0.0001$). As one of the outcome indicators, the proportion of perinatal death in women with prepartum eclampsia was significantly higher than the postpartum eclampsia ($P < 0.0001$). With regard to the mothers, there was no statistically significant difference in maternal death and maternal hospital stay in the two groups.

Table 1: Clinical and biomarker features of prepartum and postpartum eclampsia, 2008-2013

Variables	Total N = 361	Prepartum (%) N = 256	Postpartum (%) N = 105	P-value
Age in years: 15 – 24 25 – 49	179(49.6) 182(50.4)	141 (55.1) 115 (44.9)	38(36.2) 67(63.8)	0.001
Gestational age: Preterm (< 37 weeks) Term (≥ 37 weeks)	110(30.3) 251(69.7)	96 (37.5) 160 (62.5)	14(13.3) 91(86.7)	< 0.0001
Parity: Primigravida Multigravida	169(46.8) 192(53.2)	163 (63.4) 93 (36.6)	6(5.7) 99(94.3)	<0.0001
Prenatal care: Yes No	181(50.1) 180(49.9)	138 (53.9) 118 (46.1)	43(40.9) 62(59.1)	< 0.05
Fetuses number: Singleton Twins	330(91.4) 31(8.6)	234 (91.4) 22 (8.6)	96(91.4) 9(8.6)	0.9
Systolic hypertension (ever): < 160 mmHg ≥ 160 mmHg	158(43.8) 203(56.2)	102 (39.8) 154 (60.2)	56(53.3) 49(46.7)	< 0.05
Diastolic hypertension (ever): < 110 mmHg ≥ 110 mmHg	191(52.9) 170(47.1)	134 (52.3) 122 (47.7)	57(54.3) 48(45.7)	0.8
Headache: Yes No	276(76.5) 85(23.5)	206 (80.5) 50 (19.5)	70(66.7) 35(33.3)	0.004
Visual disturbance: Yes No	161(44.6) 200(55.4)	121 (47.3) 135 (52.7)	40(38.1) 65(61.9)	0.1
Epigastric pain: Yes No	129(35.7) 232(64.3)	110 (43.0) 146 (57.0)	19(18.1) 86(81.9)	<0.0001
Total episodes of convulsion before arrival: < 10 ≥ 10	277(76.7) 84(23.3)	200(78.1) 56(21.9)	77(73.3) 28(26.7)	0.4
Any convulsion after initiation of anticonvulsant: Yes No	35(9.7) 326(90.3)	25(9.8) 231(90.2)	10(9.5) 95(90.5)	0.9
Aspiration pneumonia: Yes No	64(17.7) 297(82.3)	53(20.7) 203(79.3)	11(10.5) 94(89.5)	< 0.05
Urine output: Normal Oliguria/Anuria	156(43.2) 205(56.8)	113(44.1) 143(55.9)	43(41.0) 62(59.0)	0.5
Proteinuria (qualitative): Insignificant Significant	122(33.8) 239(66.2)	73(28.5) 183(71.5)	49(46.7) 56(53.3)	< 0.001

Table 1. Cont...

Variables	Total N = 361	Prepartum (%) N = 256	Postpartum (%) N = 105	P-value
Anemia (Hgb < 12 gm/dl):				
Yes	85(23.5)	48(18.8)	37(35.2)	< 0.001
No	27 (76.5)	208(81.2)	68(64.8)	
Severe thrombocytopenia (< 100, 000/mm3):				
Yes	122(33.8)	76(29.7)	46(43.8)	0.009
No	239(66.2)	180(70.3)	59(56.2)	
Raised creatinine (>= 1gm/dl):				
Yes	215(59.6)	153(59.8)	62(59.1)	0.9
No	146(40.4)	103(40.2)	43(40.9)	
Highest SGOT level:				
< 2-fold raised	186(51.5)	144(56.3)	42(40.0)	0.005
>=2-fold raised	175(48.5)	112(43.7)	63(60.0)	
Required antihypertensive:				
Yes	256(70.9)	190(74.2)	66(62.9)	< 0.05
No	105(29.1)	66(25.8)	39(37.1)	
Anticonvulsant given:				
MgSo4	228(63.2)	168(65.6)	60(57.1)	0.1
Diazepam	133(36.8)	88(34.4)	45(42.9)	
Place of delivery:				
Health facility	229(63.4)	210(82.0)	19(18.4)	< 0.0001
Home	132(36.6)	46(18.0)	86(81.6)	
Mode of delivery:				
Vaginal	287(79.5)	183(71.5)	104(99.0)	< 0.0001
Caesarean	74(20.5)	73(28.5)	1(1.0)	
Newborns sex:				
Male	222 (61.5)	153 (59.8)	69(65.7)	0.3
Female	139 (38.5)	103 (40.2)	36(34.3)	
Newborn birth weight (kg):				
< 2.5	205 (56.8)	192 (75.0)	13(12.4)	< 0.0001
>=2.5	156 (43.2)	64 (25.0)	92(87.6)	
Maternal outcome:				
Discharged alive	320 (88.6)	227 (88.7)	93(88.6)	0.9
Dead	41 (11.4)	29 (11.3)	12(11.4)	
Perinatal outcome:				
Discharged alive	228 (63.2)	139 (54.3)	89(84.8)	< 0.0001
Dead	133 (36.8)	117 (45.7)	16(15.2)	

DISCUSSION

The incidence of eclampsia in this study was more than four-fold higher than a global estimate (1.2% vs 0.28%) (7). Yet, our report was nearly in line with other reports from Nepal and Tanzania (31,32), and more than 3-fold lower than the reports from some centers in Nigeria and Pakistan (24,33,34). Specifically, the incidence of postpartum eclampsia (more than a quarter of the total) is consistent with several reports from both high and low income countries (26,29,35,36). The proportion of late postpartum eclampsia (21%) was also in between some previous reports, 14% and 15% (22,37) and 28% and 56% (36,38).

Of interest, this analysis has shown that the clinical and biochemical spectrum of prepartum

and postpartum eclampsia were different. Our main findings were that women with prepartum eclampsia were relatively young age, and the majority were primigravida, more hypertensive, symptomatic and proteinuric. Conversely, the majority of women who were at increased risk for post-partum eclampsia were adult, multiparous, having term pregnancy, anemic, thrombocytopenic, and with hepatic dysfunction.

The association of prepartum eclampsia with young age and primigravida is consistent with one previous report that assessed only antepartum and intrapartum eclampsia (39). Several other studies also showed the increased risk of eclampsia among primigravid and young women. However, none of these studies compared the predictor

variables by stratifying the type of eclampsia as pre- and post-delivery; they reported that eclampsia is common in primigravida, age <25 years by including either all types of eclampsia or only postpartum eclampsia as a denominator (5,21,27,37,38,40).

The increased risk of prepartum eclampsia among young and nulliparous women may not be as such controversial. As this study showed, however, the postpartum eclampsia was strongly associated with women who were multiparous and aged 25 years and above. Nevertheless, this finding is not in line with two previous studies, which assessed only postpartum eclampsia and reported the increased risk to primigravida and young age (37,38). As a result, we recommend further study to verify the age and parity spectrum in prepartum and postpartum eclampsia.

The significant association of prepartum and postpartum eclampsia with preterm and term pregnancies, respectively, was expected. This is because the majority of prepartum eclampsia cases (47%) were antepartum by onset; and antepartum eclampsias in turn were reported as being strongly associated with preterm pregnancies (Douglas and Redman, 1994) (40). This study also showed that about 38% of prepartum eclampsia occurred in preterm pregnancies while the proportion of preterm postpartum eclampsia was nearly three-fold lower (13%). As a complimentary evidence, three-fourths of babies born to prepartum eclampsia were having low birth weight while the reverse was true for postpartum eclampsia.

Similarly, the significantly increased anemia, thrombocytopenia and evidence of hepatic dysfunction in women with postpartum eclampsia could be explained in two ways. Since the majority of women with postpartum eclampsia gave birth at home with no skilled person attendant, the possibility of more blood loss during delivery was probably unavoidable. Secondly, the relatively low proportion of headache and the lowest proportion of epigastric pain and blurring of vision among postpartum eclamptic women might have increased the chance for the disease to buy more time which might have resulted in more organs damage.

In this study, headache was the commonest prodromal symptom in both prepartum and postpartum eclampsia, which is consistent with several other studies (21,26,40). The relatively

low proportion of epigastric pain and visual disturbance in women with postpartum eclampsia was also reported in Onuh *et al* study (40). The low proportion of severity symptoms in women with postpartum eclampsia might have contributed to failure of preventive actions prior to its occurrence.

Lastly, the significantly increased risk of perinatal mortality in women with prepartum eclampsia may not only be associated with the hypertensive disease itself. Since the majority of babies in preeclamptic women were born preterm and with low birth weight, the chance of survival in the early neonatal period might be low, which was also observed in other studies (7,31,40).

This study is not without limitation. Since our study is based on referral hospitals data, where the majority of eclamptic women were likely to come, the reported incidence may not represent the actual incidence of eclampsia in the general population. The denominator in the community is expected to be high due to the large number of deliveries at home and in the referring health facilities. Furthermore, since the majority of the included women were admitted to the study hospitals after the onset of convulsion, we were unable to assess their pre-convulsion status. Because of the delay in reporting, patients or relatives might not recall the exact time of onset of convulsion. As a result, some of the early onset postpartum eclampsia might be grouped as late onset. The documented histories, physical examinations and laboratory findings may not be always accurate.

In conclusion, the incidence of eclampsia in this study was high, but not as high as some other reports. More than a quarter of the total were postpartum eclampsia. This analysis demonstrated that prepartum eclampsia was mainly the disease of nulliparous and young women. On the other hand, the majority of women who developed postpartum eclampsia were multiparous and adult. The commonest severity symptom was headache, but was less common in postpartum than prepartum eclamptic women. Derangement of biomarkers was more common in postpartum eclampsia. Since this is probably the first study that assessed the association of several variables with prepartum and postpartum eclampsia, similar studies are highly recommended.

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