ORIGINAL ARTICLE

MATERNAL MORTALITY PREDICTORS IN WOMEN WITH HYPERTENSIVE DISORDERS OF PREGNANCY: A RETROSPECTIVE COHORT STUDY

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ABSTRACT

BACKGROUND: Hypertensive disorders of pregnancy (HDP) are multisystem disorders unique to human pregnancy. They are becoming the leading causes of maternal mortality worldwide, with the majority of deaths occurring in low income countries. However, little is known about the predictors of maternal mortality in women with HDP.
METHODS: A retrospective cohort study was conducted between 2008 and 2013 in three university teaching hospitals among 1015 women admitted with a diagnosis of HDP. Statistically significant associations were assessed by the hazard ratio (HR) with 95% confidence using the Cox proportional hazards model and by the Log Rank test using the Kaplan-Meier survival analyses.
RESULTS: There were 51(5%) maternal deaths and the majority died after they developed eclampsia. The median delay in arrival among the deaths was longer than the survivors. The multivariate survival analyses showed an increased risk of maternal mortality among women with eclampsia (HR=8.4), no antenatal care (HR=2.3), being grand multiparous (HR=2.8), having low diastolic blood pressure (HR=4.5), high creatinine level (HR=9.9), use of diazepam as anticonvulsant (HR=2.7) and untreated with antihypertensive drug (HR=4.2).
CONCLUSIONS: The case fatality rate of HDP was among the highest in the world and a delay in initiation of treatment because of delay in health care-seeking contributed to the majority of maternal deaths.
KEYWORDS: Ethiopia, hypertensive disorders, maternal mortality, predictors, retrospective cohort

INTRODUCTION

Hypertensive disorder of pregnancy is commonly used to describe a broad spectrum of hypertension related diseases during pregnancy. These disorders can appear for the first time during pregnancy (preeclampsia, eclampsia, gestational hypertension, HELLP syndrome) or may result from already established medical disorders (chronic hypertension, renal disease, systemic disease) (1). In general, hypertensive disorders of pregnancy (HDP) may complicate 5%-10% of pregnancies in the general population and are known to increase the risks of maternal and perinatal morbidity and mortality (2).

A recent literature review has shown that the incidence of HDP is increasing mainly due to increasing obesity trend, and these disorders are becoming the leading causes of maternal mortality worldwide (3,4). An author estimated that HDP have contributed to 10% to 15% of direct maternal deaths globally (5). However, there is a significant variation in the proportion of maternal mortality due to these disorders between the low and high income countries. It was noted that the majority of maternal deaths associated with hypertensive disorders occur in the low-and middle-income countries (6).

In South Africa, for instance, hypertensive disorders were the commonest direct causes of

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maternal deaths; in some areas, these disorders contributed to 19%-32% of all maternal deaths (7, 8). Similar studies in India and Pakistan revealed a high maternal mortality associated with HDP (9, 10). Few hospital based studies in Ethiopia have also shown that hypertensive disorders are among the top three causes of maternal mortality (11, 12). Furthermore, a national survey in Ethiopia demonstrated that 11% of all maternal deaths and 16% of direct maternal deaths occurred due to HDP and the cause-specific case fatality rate was 3.6% (13).

However, these studies were limited to describing the magnitude of maternal mortality due to HDP. Even in the international arena, literature on predictors of maternal mortality in women with HDP are scarce. Therefore, the purpose of the current study was to assess the predictors of maternal mortality in three teaching hospitals in Ethiopia among women diagnosed to have HDP.

METHODS

Study design and setting: A retrospective cohort study was conducted from 2008 to 2013 in three university teaching hospitals in the Southern Regional State of Ethiopia (Hawassa referral hospital, Hosanna hospital and Yirgalem hospital). In these hospitals, a total of 30,750 babies was delivered during the study period. All women with HDP admitted to the study hospitals during the study period were included unless they were categorized as ineligible for this study (gave birth before 28 weeks of gestation, lost or incomplete data, or died on arrival). For each patient, the included data were from onset of HDP to the time end of treatment declared (mother discharged as cure or dead).

Variables and data collection: Maternal mortality was taken as dependent or outcome variable. The independent variables were: maternal age, parity, gestational age, antenatal care, onset and type of HDP, severity symptoms, blood pressure, selected renal and liver function tests, types of medications and mode of delivery.

Nine nurse (three for each hospital), who were working in the department of Obstetrics and Gynecology, were recruited and trained as data collectors. Since every woman with HDP was found registered in the delivery logbook, their card number documented in the delivery logbook was

used as an initial entry to access their chart (where the detailed data is documented) in the hospital record office. Data collections were performed using a structured data collecting format prepared only for this purpose. The data collection format was designed to include all the relevant information starting from the onset of signs and symptoms of HDP to the time end date was declared.

Data processing & analysis: Data were coded, entered, and analyzed using computer data analysis software program (SPSS version 20). Whisker and Box plotting was performed to assess the contribution of gestational age and delay in arrival to maternal mortality. We used Kaplan-Meier survival analyses for cumulative mortality rates in relation to parity, type of HDP, onset of HDP and type of anticonvulsant drug. Cox proportional hazards regression model was used to estimate associations between selected predictor variables/covariates and maternal mortality taking the onset of HDP illness to death or discharge from the hospital as time period. A statistically significant association was considered when the hazard ratio (HR) 95% confidence interval did not include the number 1. Variables which did not show statistical significance in the univariate analysis were excluded in the multivariate analysis.

Operational definitions: Pregnant or postpartum women were grouped as normotensive [systolic blood pressure (BP) <140 mmHg and diastolic BP<90 mmHg], mild to moderate hypertension (systolic BP≥140 mmHg and diastolic BP≥90 mmHg) and severe hypertension (systolic BP≥160 mmHg and diastolic BP≥110 mmHg).

Presence of hypertension or severity symptoms with significant proteinuria was enough to diagnose preeclampsia. Eclampsia was defined as the occurrence of convulsion or coma not attributable to other causes. Presence of hypertension before the occurrence of pregnancy or that was diagnosed before 20 weeks of gestation was taken as chronic hypertension. Superimposed preeclampsia was diagnosed when a new onset or worsening of proteinuria and/or worsening of hypertension occurred during pregnancy in women with a known chronic hypertension. Gestational hypertension was defined as the development of an elevated blood

pressure during the second half of pregnancy without proteinuria and severity symptoms. In this article, other HDP include all women with chronic hypertension, gestational hypertension and superimposed preeclampsia.

Severity symptoms of HDP include headache, blurred vision, epigastric pain and vomiting. Proteinuria was considered as significant when the qualitative test (dipstick) revealed +2 and above or +1 if the specific gravity was <1.020. Creatinine level <1 and 1+ mg/dl and Serum glutamic-oxaloacetic transaminase (SGOT) level raised by < or >2-fold from the base line were included in the analysis as proxy indicators for status of renal function and liver function, respectively. Platelet count was also dichotomized as < or >100,000/mm3. Degree of anemia was categorized as severe to moderate (< 10gm/dl), mild (10-11.9 gm/dl) and no anemia (12+gm/dl).

Ethical consideration: Ethical clearance was obtained from the Institutional Review Board of Hawassa University, College of Medicine and Health Sciences. Since the study was retrospective by design, written consent from patients was not required. Patient records were de-identified prior to data analysis. Furthermore, anonymity was secured by analyzing and presenting the data in aggregate.

RESULTS

The logbook review identified 1098 women registered as HDP. After excluding 83 ineligible cases that were diagnosed to have HDP (38 patients chart lost, 36 with incomplete data, 6 delivered before 28 weeks and 3 died on arrival), we analyzed data for 1015 women. The mean age of the included women was 25.8±5.2 years (range of 15-46 years). The distribution of HDP by type was: 612(60.3%) preeclampsia, 346(34.1%) eclampsia and 57(5.6%) other type of HDP (chronic hypertension, gestational hypertension and superimposed preeclampsia). Six hundred thirty-three (62.4%) of these women had antenatal care (ANC) in a health facility and 847(83.4%) presented with one or more of the severity symptoms of HDP (headache, blurred vision, epigastric pain and/or vomiting). Out of 60 women with systolic BP<140 mmHg, and out of 39 women diastolic BP<90 mmHg, 62% and 64% were eclamptic mothers, respectively. A separate analysis presented the detail description of socio-demographic and obstetric data of the included women.

Of the total women included in this analysis, 51 died in the hospital after initiation of treatment, making the case fatality rate of HDP 5%. The majority of maternal deaths (78.4%), however, occurred in women with eclampsia. As a result, the case fatality rates of eclampsia, preeclampsia and other type of HDP were 11.6%, 1.1% and 7.0%, respectively.

Figure 1 shows the relation of maternal deaths with the gestational age as stratified by type of HDP. In women with eclampsia, the median gestational ages of deaths and survivors were equivalent (38 weeks each). However, it should be noted that several outliers of survivors with low gestational age were excluded from this Figure. The median gestational ages for preeclampsia and other type of HDP were found to be lower in maternal deaths than the survivors, 30 vs 37 weeks and 32 vs 37 weeks, respectively. The interquartile range (IQR) of the gestational age for maternal deaths due to preeclampsia and other type of HDP were also 30-34 and 28-34 weeks, respectively.

The relation of maternal deaths with delay in arrival as stratified by type of HDP is presented in Figure 2A-D. In the overall assessment, the median delays in arrival among the maternal deaths and survivors were 24 (IQR 12-48) and 48 (IQR 12-96) hours, respectively. The range of delay was also 4-720 hours for deaths and 2-1440 hours for survivors. However, when the data were stratified by type of HDP, a marked delay was observed among the deaths.
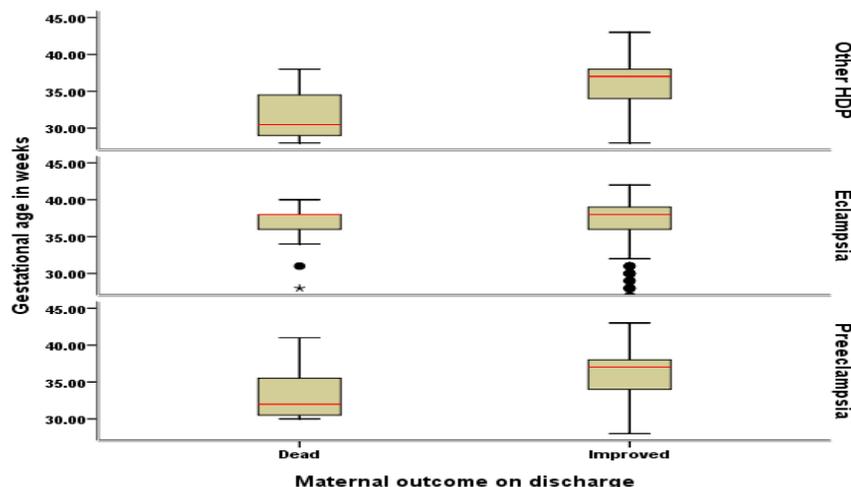
Figure 1: The relation of maternal death with gestational age at the onset of the illness in different type of hypertensive disorders of pregnancy (HDP), Ethiopia, 2008-2013 (Outliers were excluded)

Specifically, the median delay in hours among maternal deaths was twice of the survivors in eclamptic women (24 vs 12), and about two and half-fold longer than the survivors in women with preeclampsia (168 vs 72) or other type of HDP (120 vs 48). Of interest, the delays in all maternal deaths among the preeclamptic and the other HDP group were not beyond the median value.
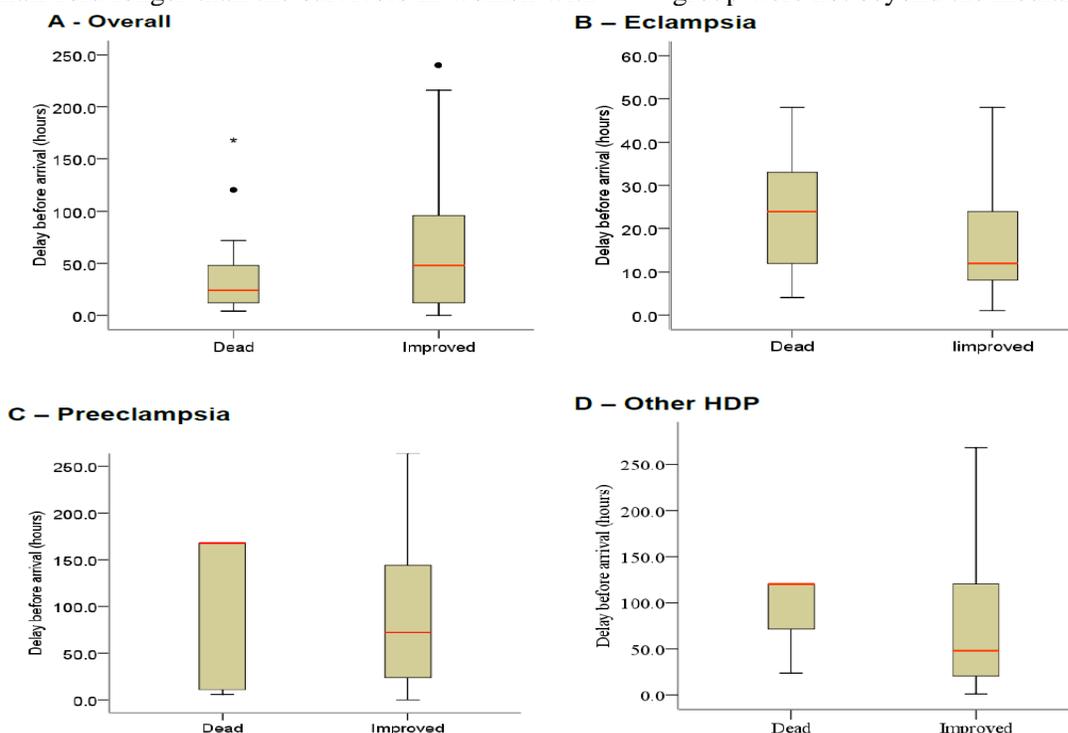

Figure 2 A-D: The maternal outcome on discharge in relation to delay in arrival as stratified by type of hypertensive disorders of pregnancy (HDP), Ethiopia, 2008-2013 (Outliers were excluded)

Table 1 shows the Cox regression survival analysis of maternal deaths with selected demographic and clinical findings. In the univariate analysis, maternal death was strongly associated with grand multiparity (Crude Hazard ratio = 3.6), lack of ANC (CHR=3.5), eclampsia (CHR=11.3), other type of HDP (CHR=6.5), intrapartum (CHR=2.6) and postpartum onset of

HDP (CHR=3.5), ever highest systolic blood pressure (BP)<140 mmHg (CHR=2.8), and ever highest diastolic BP<90 mmHg in the current illness (CHR=4.3). The univariate model did not show association of maternal mortality with previous history of HDP, diabetes mellitus and renal disease. Helou G, Alassas N,

In the multivariate analysis, grand multiparous women had 2.8 times increased risk of mortality as compared with multiparous and primigravid women. Similarly, those women with no ANC were 2.3 times more likely to die than their counterparts. The risk of dying in eclamptic women had also increased by 8.4-fold as compared to preeclamptic women. Women having highest diastolic BP<90 mmHg were also at higher risk of death than women with severe diastolic hypertension (AHR=4.5). Onset of HDP and highest systolic BP<140mmHg in the multivariate analysis, and age, severity symptoms and gestational age in the univariate analysis did not show association with maternal death.

Table 1: Cox regression survival analysis of women with hypertensive disorders of pregnancy (HDP) in relation to selected clinical findings as predictors, Ethiopia, 2008-2013.

Variables	Total HDP	Maternal deaths (%)	Crude HR (95% CI)	Adjusted HR (95% CI)
Age in years:				
15 – 19	57	8.8	1.9(0.74 - 4.78)	
20 – 34	876	4.7	1	
35 – 49	82	6.1	1.3 (0.51 - 3.24)	
Parity:				
Primigravida	536	4.3	1	1
Multipara (I – IV)	400	4.3	1.0 (0.52 – 1.88)	0.8 (0.38 – 1.84)
Grandmultipara (V+)	79	13.9	3.5 (1.69 – 7.10)‡	2.8 (1.13 – 6.78)¥
Gestational age (weeks)*				
Very preterm (< 34)	228	4.4	1.4 (0.56 – 3.39)	
Preterm (34 – 36)	168	5.9	1.1 (0.55 – 2.38)	
Term + (> = 37)	619	5.0	1	
Antenatal care:				
Yes	633	2.8	1	1
NO	382	8.9	3.5 (1.95 - 6.43)†	2.3 (1.19 - 4.38)¥
Type of HDP:				
Preeclampsia	612	1.1	1	1
Eclampsia	346	11.6	11.3(1.85 – 22.99)†	8.4(3.48 – 20.15)†
Other HDP	57	7.0	6.5(5.00 – 25.52)‡	5.0(1.35 – 18.64)‡
Onset of HDP:				
Antepartum or before	721	3.3	1	1
Intrapartum	183	8.2	2.6 (1.33 - 5.05)‡	1.8(0.86 - 3.72)
Postpartum	111	10.8	3.5 (1.71 - 7.26)‡	1.0(0.40 - 2.57)
Severity symptoms:				
Yes (one or more)	847	4.7	0.7 (0.36 – 1.41)	
None	168	6.5	1	
Highest systolic BP:				
< 140 mmHg	60	11.7	2.8 (1.17 – 6.63)¥	0.8 (0.21 – 3.06)
140 – 159	270	4.8	1.1 (0.55 – 2.07)	0.7 (0.33 – 1.67)
160+	685	4.5	1	1
Highest diastolic BP:				
< 90 mmHg	39	17.9	4.3 (1.72 – 10.49)‡	4.5 (1.11 – 18.65) ¥
90 – 109	425	4.0	0.8 (0.44 – 1.51)	1.0 (0.47 – 2.12)
110+	551	4.9	1	1

¥ P < 0.05; ‡ P = 0.001; † p < 0.0001. HR = Hazard ratio. BP = Blood pressure. * Gestational age at the onset of the HDP.

The association of maternal deaths with selected laboratory findings and treatment modalities is presented in Table 2. In the univariate analysis, some of the laboratory findings which showed a statistically significant association with maternal death were hemoglobin <12gm/dl (CHR=2.3 - 3.7), platelet count <100,000/mm3 (CHR=7.0), creatinine ≥1mg/dl (CHR=3.7), and SGOT ≥ 2-fold raised (CHR=2.7). Proteinuria was not associated with maternal death.

Table 2: Cox regression survival analysis of women with hypertensive disorders of pregnancy (HDP) in relation to selected laboratory findings and treatment modalities as predictors, Ethiopia, 2008-2013.

Variables	Total HDP	Maternal deaths (%)	Crude HR (95% CI)	Adjusted HR (95% CI)
Hemoglobin level (gm/dl):				
<10.0	158	10.1	3.7(1.82 - 7.35)†	1.6 (0.38 - 6.69)
10-11.9	255	6.7	2.3(1.17 - 4.57)¥	2.1 (0.64 - 6.86)
≥12	602	3.0	1	1
Platelet count in mm3:				
< 100	223	14.3	7.0 (3.35 - 14.51)†	2.3(0.73 – 7.18)
>=100	792	2.4	1	1
Proteinuria (qualitative):				
Insignificant	266	4.1	1	
Significant	749	5.3	1.3 (0.66 – 2.59)	
Highest creatinine (gm/dl):				
< 1.0	494	6.1	1	1
1.0+	521	9.2	3.7(1.49 – 9.24)‡	9.9(1.26–78.26)¥
Highest SGOT:				
< 2-fold raised	689	3.3	1	1
>=2-fold raised	326	8.6	2.7 (1.09 – 6.64)¥	1.7 (0.58 – 5.24)
Antihypertensive drug given:				
Yes	811	3.9	1	1
No	204	9.3	2.5 (1.39 – 4.51)‡	4.2(1.46 - 11.91)‡
Anticonvulsant given:				
MgSo4	641	2.8	1	1
Diazepam	374	8.8	3.4(1.86 – 6.04)†	2.7 (1.1 – 8.08)¥
Mode of delivery:				
Vaginal	597	6.5	2.4 (1.22 - 4.57)¥	2.8(0.70 - 10.90)
Caesarean section	418	2.9	1	1

¥ P < 0.05; ‡ P = 0.001; † p < 0.0001. HR = Hazard ratio. SGOT = Serum glutamic-oxaloacetic transaminase

Women who were not given any antihypertensive drug were at higher risk for death (CHR=2.5). Diazepam as anticonvulsant (CHR=3.4) and vaginal delivery of any type (CHR = 2.4) had also increased the risks of maternal death. In the multivariate analysis, however, only high creatinine value (AHR=9.9), failure to take antihypertensive drug (AHR=4.2) and use of diazepam as anticonvulsant (AHR=2.7) were strong and independent predictors of maternal death.

In general, the majority of maternal deaths occurred before 48 hours (65%), and nearly half occurred before 24 hours (47%) of onset of illness.

However, there were 10(20%) maternal deaths that occurred between 4 and 31 days of onset of illness.

As a complement to the findings in Table 1 and 2, Kaplan-Meier survival analyses of maternal mortality were performed taking the period of onset of HDP to discharge or death as time frame; and parity, onset of HDP, type of HDP and type of anticonvulsant as independent factors. As the time of hypertensive illness increased, the survival of grand multiparous women was lesser than multiparous and primigravid women (Log Rank: P=0.001). Similarly, the survival of eclamptic mothers was lower than that of mothers with

preeclampsia or other type of HDP as the duration of illness advanced (Log Rank: P<0.0001). In terms of timing, women with antepartum onset of HDP had better survival than intrapartum and

postpartum onset of HDP (Log Rank: P<0.0001). Hypertensive mothers who were given magnesium sulphate were better protected from death (Log Rank: P<0.0001).
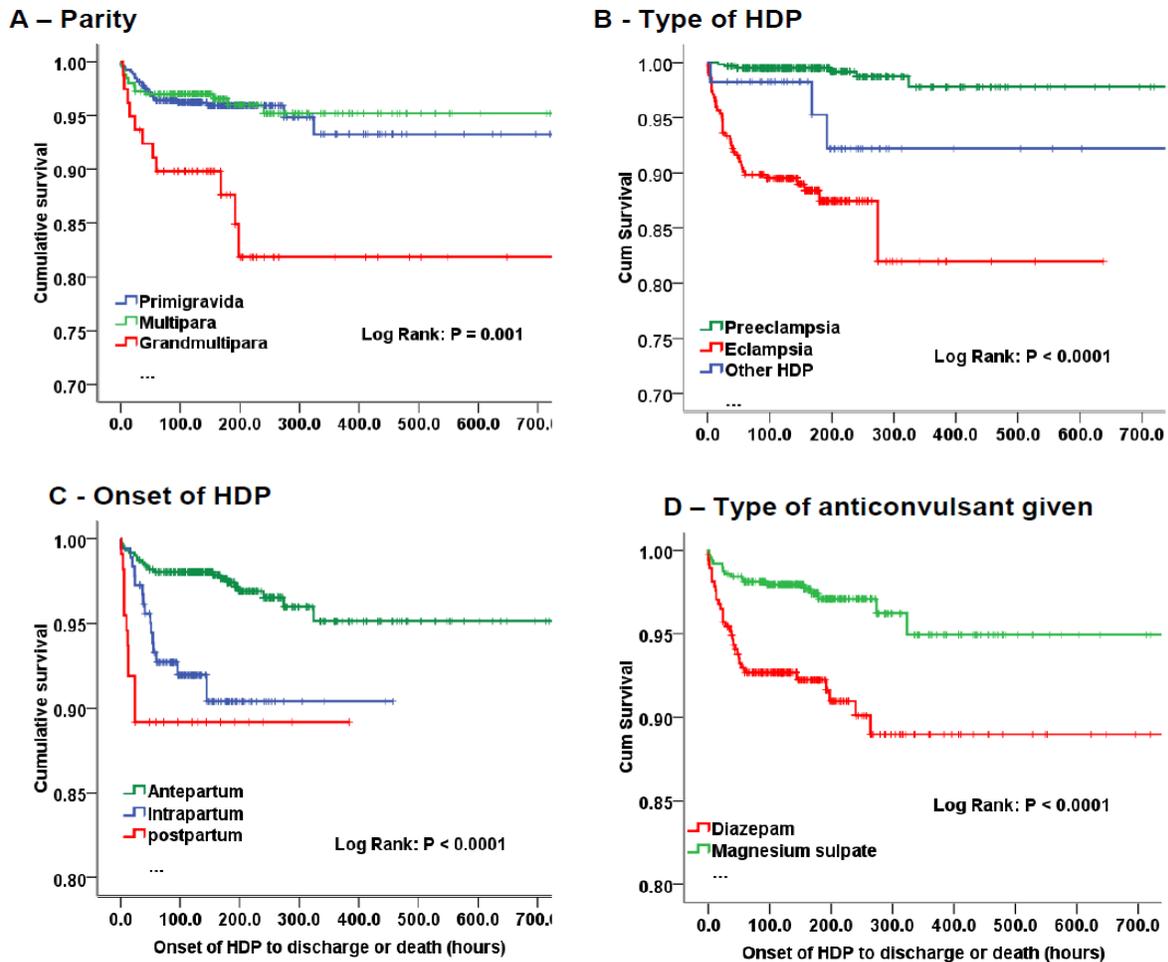

Figure 3 A-D. Survival of women with hypertensive disorders of pregnancy (HDP) across the course of illness as stratified by type of HDP, onset of HDP, parity and type of anticonvulsant, Ethiopia, 2008-2013

DISCUSSION

The overall maternal mortality of HDP in this study was similar to a study report from Pakistan (5.5%) (10), but higher than other studies reports (13-15). Specifically, the contribution of eclampsia for the overall maternal deaths (78%) was more than 3-fold higher than a report from a tertiary hospital in Ghana (24%) (14). The proportion of eclampsia related maternal mortality reports from a population based study in South Africa (57%) (16) and from a tertiary hospital based study in India (67%) (15) were also somehow lower than our report. Similar to our finding (11.6%), high case fatality rates of

eclampsia were reported from Tanzania (7.9%) and Nigeria (10.7%) (17, 18). However, our finding was less than the report from Northern Nigeria (23.2%) (19) by half.

The high maternal mortality among eclamptic mothers in this study was probably the result of the big delay in health care-seeking before (lack of ANC) and after the onset of the illness. As it was noted in the Whisker and Box plot graph, the median time delay before arrival among deaths was longer than that of the survivors in all types of HDP. Furthermore, it was noted that some mothers developed eclampsia in normotensive and symptom free-state, which was also reported in

several other studies (20-22). However, being eclampsia nearly one-third of the included cases (34%) and the very high maternal mortality in this group of women may still indicate the significant delay in initiating anticonvulsant prophylaxis and antihypertensive drugs, among other lifesaving interventions.

Consistent with the finding of a previous study (14), most of the maternal deaths occurred within the first 24 hours of admission, which may further strengthen the contribution of delay in initiating treatment or the ineffectiveness of treatment modalities. Specifically, it is known that eclampsia cases are likely to deteriorate fast unless further convulsions are aborted as early as possible. In other words, we surmise that those mothers who were died critically ill at admission or there were further delays in initiating treatment modalities after admission, for which we were not able to get data on the time interval between arrival and initiation of treatment. Previous authors also noted that the most important factor contributing to high maternal mortality due to HDP in developing countries is late arrival to hospital in irreversible stage of disease (23).

On the other hand, as the multivariate and survival analyses showed, the use of diazepam as anticonvulsant probably contributed much to the high maternal mortality due to eclampsia. This is because, as authors observed, before the magnesium sulphate was instituted in 2010 to the study hospitals as anticonvulsant for women with HDP, diazepam was the sole anticonvulsant agent. The ineffectiveness of diazepam as anticonvulsant for hypertensive pregnant women has also been shown in several other studies (24-26).

The multivariate analyses have also shown more than 2-fold increased risk of maternal mortality among women with no ANC, being grand multipara, having low diastolic BP, high creatinine level and untreated with antihypertensive drug. The association of lack of ANC follow up with high maternal mortality was also noted in several other studies (2-4, 24). Similarly, other studies showed the strong association of maternal mortality with grand multiparity (1-3), probably due to their additional susceptibility to other obstetric complications (1).

The independent association of high creatinine level with increased risk of maternal mortality may indicate the severity of the HDP.

However, the strong association of maternal mortality with low blood pressure, failure to get antihypertensive drugs and intrapartum and antepartum onset of HDP after admission to one of the study hospitals seem to show that one factor was interrelated with another one.

Since the protocol (27) for initiation of antihypertensive drug require the finding of blood pressure in the severe state (>160/110 mmHg), which is also the recommendation of other literatures (28, 29), women in normotensive or mild to moderate hypertension state were unlikely to get antihypertensive drug. Similarly, the majority (56%) of women who died with intrapartum and antepartum onset of HDP were not eligible for antihypertensive drug.

Nevertheless, the association of maternal mortality with low blood pressure needs to be interpreted very cautiously. Firstly, the majority of women with normal blood pressure during their hospital stay were eclamptic, who have probably already developed further complications including multiple organ failure. This was partly evidenced by the strong association of maternal mortality with low platelet count, severe to moderate anemia, elevated creatinine and liver enzyme level. Secondly, because of the exactly unknown nature of these diseases course (30, 31), some women might still have low blood pressure record while the systemic effect of the disease was in the worst state.

Otherwise, the increased maternal mortality observed in women with early onset of HDP among preeclamptic and other type of HDP was not verified by the Cox proportional hazards models and Kaplan Meier survival analyses. This observation needs further investigation. Similarly, the observed increased risk of maternal mortality in the univariate analysis among women who gave birth vaginally needs to be interpreted very cautiously. Caesarean delivery is known to result in expeditious delivery and probably has reduced the risk of HDP related mortality. However, till a randomized clinical trial demonstrates the significance of caesarean delivery to reduce maternal mortality, the current evidence should be taken as inadequate.

This study was not without limitation. The retrospective nature of the study design could not give us room to find some data on social and service related factors. As a result, we were not

able to control all potential determinants of maternal mortality in women with HDP. Furthermore, since our data relied on record review, which might not be accurately recorded, the comparisons made on temporal relationship between exposed and non-exposed may be biased. Because of physiologic drop of blood pressure in the second trimester and decreased blood urea nitrogen and creatinine (32), some of the women who were diagnosed to have new onset hypertension probably had preconception hypertension.

In conclusion, the case fatality rate of HDP was among the highest in the world, and the analysis indicated that the majority of maternal deaths were linked to delay in providing obstetric care because of lack of antenatal care, delay in arrival, or delay in initiation of appropriate treatment. Therefore, health promotion should be provided to pregnant women focusing on awareness creation on the importance of antepartum and intrapartum care, and risk preparedness to seek health care when they experience HDP severity symptoms. Furthermore, the strong association of maternal mortality with low blood pressure is an area of investigation to redefine the threshold for initiation of antihypertensive drug.

ACKNOWLEDGEMENT

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