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Impact of Social and Clinical Attributes Of Patients on Outcome of Eclampsia in a University Hospital, Benin City, Nigeria

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Abstract:
Background*: Case fatality of eclampsia remains high in our environment, probably from the impact of factors in the individual patient and sociocultural or institutional factors.*
Objective*: We sought to examine the influence of some identifiable factors on maternal and perinatal outcome.*
Method*: The case records of patients managed for eclampsia in University of Benin Teaching Hospital, Benin City, Nigeria from June 2012 to May 2013 were retrospectively studied. Data on sociodemographic characteristics, clinical management and outcome were extracted and analyzed.*
Results*: The incidence of eclampsia was 3.6% with case fatality of 11%. Mean age was 28.67±5.75 years, mean parity was 2.63±1.55 and 67% were unbooked. Anaemia and severe proteinuria increased risk of maternal mortality (33.3% vs 9.5; p=0.018 and 27.3% vs 6.3; p=0.001). Organ-system dysfunctions, ICU admission and stillbirth were more likely in women who died (100% vs 8.9, p=0.001; 36.4% vs 7.8, p=0.018; and 45.5% vs 5.6, p=0.001, respectively). Maternal mortality ratio was 0.4% and perinatal mortality rate was 14.9%.*
Conclusion*: Anaemiaand kidney injury increase the risk of adverse outcome in eclampsia, hence the need for early screening and increased vigilance. A prospective and larger scale study is recommended to identify other associated factors.*
Key words: *eclampsia, severe proteinuria, anaemia, near miss, maternal mortality*

I. Introduction

Preeclampsia and eclampsia are important contributors to morbidity and mortality in pregnancy, childbirth and puerperium. Preeclampsia affects 2-7% of healthy nulliparous women, with 1-2% of affected women developing eclampsia[1]. Deaths due to a combination of preeclampsia and eclampsia remain high in our environment, with acute renal failure (ARF), aspiration pneumonia, abruptio placentae, cerebrovascular accident (CVA), disseminated intravascular coagulopathy (DIC) and hemolysis, elevated liver enzymes, low platelets (HELLP) syndrome being the most reported causes of maternal mortality[2-4]; while perinatal mortality occurs from birth asphyxia, prematurity and intrauterine growth restriction[4-6].

Most deaths attributable to preeclampsia occur when it progresses to eclampsia, especially in the face of recurrent fits. This observation emphasizes the need to prevent the occurrence of eclampsia through early diagnosis and appropriate management of preeclampsia. The use of magnesium sulphate (MgSO4) is currently the standard of care in the treatment of eclampsia[7,8]. Recent trials have also confirmed the beneficial role of antenatal exposure to magnesium sulphate[9,10].

Eclampsia and its associated adverse outcome have been dramatically reduced in advanced economies, where the use of MgSO4 is widespread. However, this effect has not been replicated in many parts of the developing world where the drug was used in managing eclamptic seizures. Elsewhere, factors noted to influence outcome have included young age, nulliparity, anemia and presence of heart disease[11,12]. Others are long distance from healthcare centre, poverty, night time arrival to the hospital, substandard care, inadequate monitoring and delayed delivery[12-14].

Consequently, despite the availability and utilization of MgSO4 in many hospitals in Nigeria today, documented case fatality of eclampsia has consistently been over 20%, though few reports have been encouraging. Similarly, perinatal mortality from eclampsia remains high. At the University of Benin Teaching Hospital (UBTH), diazepam was the drug used to treat preeclampsia and eclampsia until 2006 when magnesium sulphate was introduced. Empirical data suggests a reduction in maternal deaths but eclampsia remains high on the list of causes of maternal mortality in this hospital[3]. Therefore, this study aims to highlight individual and/or clinical management influences on the outcome of treatment of eclampsia in UBTH.

II. Materials And Methods

A retrospective study of all patients managed for eclampsia at the Department of Obstetrics and Gynecology, UBTH, Benin City, was conducted between June 2012 and May 2013 (both inclusive), with Institutional Research and Ethics Committee approval. This period was identified because it coincided with the time a one-year National Survey on Maternal Near Miss was conducted with our hospital as one of the participating centers. All patients had been managed based on our standardized labor ward protocol[15]; Cesarean section was done for obstetric indications or unfavorable Bishop Score.

The UBTH is a tertiaryhealth facility located in Edo State which serves as a major referral center in Nigeria, attracting patients from neighboring states, and from both public and private hospitals. Within the hospital, the major portal of entry for pregnant women is the general practice clinic (GPC) from where they are referred to the antenatal clinic for booking, but in emergency situations, patients are admitted via the emergency unit of the hospital to the labor ward. On the average, between 100 and 150 patients are booked for antenatal care every week in the hospital, while follow up attendance rate is between 250 and 400 patients per week. The delivery rate in the hospital in the last five years has been around 2,700 per year, which gives an average monthly delivery rate of 225. The hospital has a total antenatal and postnatal bed capacity of 82 spaces, and 8 delivery rooms in the labor ward. There are 2 operating theatres attached to the labor ward.

Medical Management of the Patients:

In this study, women who had antenatal care in UBTH were referred to as 'booked' and those not registered in UBTH as 'unbooked'. The diagnosis of eclampsia was entertained when the patient was admitted to the labor ward either after a seizure or in coma in association with clinical evidence of the syndrome of preeclampsia, without any other obvious cause of coma or seizure. Severe hypertension was defined as a single reading of 180/120mmHg or more, or occurrence of 160/110mmHg or more on two occasions at least 4 hours apart. Severe proteinuria was defined as dipstick report of proteinuria 3+ or more (24-hour urine collection for protein estimation was not done for diagnosis because of the emergency nature of eclampsia).

At admission, seizure was aborted or repeat seizure prevented with MgSO4, blood pressure was controlled with labetalol, and blood was drawn for full blood count and platelets, electrolytes, urea and creatinine estimation, liver function test and clotting time; and abnormalities were identified for correction. Antenatal monitoring of the fetuses was done with a fetal stethoscope, hand-held Doppler or cardiotocography. Following this initial resuscitation and stabilization, preparation was made for delivery.

Intravenous fluid regimen was instituted with Ringer's lactate or normal saline at a rate of 80ml per hour. MgSO4 use was based onZuspanregimen.[16] Monitoring for toxicity was by clinical assessment of respiratory rate, deep tendon reflexes and urinary output. MgSO4 treatment was withheld when deep tendon reflex was depressed, respiratory rate was below 16cycles/min, or urine output was lower than 100ml in previous 4 hours. Intravenous labetalol was used for control of acute rise in blood pressure up to a cumulative dose of 300mg in 24 hours.

Outcome Measures and Confounders:

The ultimate goal in the management of eclampsia is the prevention ofmaternalmortality. Hence, in this study, primary outcome measure was "maternal death". Features of severe disease alone or in combination viz. pulmonary edema, acute renal failure, HELLP syndrome, CVA, adult respiratory distress syndrome (ARDS), abruptio placentae, fetal growth restriction (IUGR), fetal death (IUFD) and neonatal death (ENND), admission to intensive care unit (ICU), need for dialysis, need for transfusion of blood products, and hospital stay in excess of 14 days were considered secondary outcome measures. Any patient who survived was described as "near miss" in this study.

Factors considered as possible determinants of poor outcome included patient-specific characteristics (like age, parity, social status of the patient, distance to hospital, packed cell volume (PCV) at admission, severity of blood pressure at admission, severity of proteinuria, degree of thrombocytopenia, place where seizure first occurred); and hospital-related events (like time of day to arrive hospital, duration of time between onset of eclampsia and commencement of MgSO4 in hours, the number of seizures before commencement of MgSO4, duration of time from arrival in labor ward to commencement of MgSO4 in minutes, onset of eclampsia to delivery interval in hours, admission time to consultant review time in minutes, route of delivery, length of hospital stay, presence of organ-system dysfunctions, need for dialysis, need for ICU admission, need for special care baby unit (SCBU) admission, availability of space in ICU, availability of blood products, and availability of senior medical staff viz. anesthesia, hematology, medicine, and ophthalmology).

Data Collection and Management:

The medical details of these patients were collected into data extraction sheets from their case notes as well as records of theatre, intensive care unit, renal unit and SCBU. Information about the babies was retrieved up till one week of life while the mothers' records were collected up till the point of discharge from hospital or occurrence of mortality. Socio-demographic and clinical information retrieved were used to generate a database for analysis. The data was subjected to statistical analysis with a personal computer using SPSS version 20.0 (SPSS IBM Corp, Armonk, NY) and GraphPadInStat 3 (GraphPad Software Inc., San Diego, CA). Univariate analysis was conducted using Chi-square test or Fisher's Exact Test as appropriate. Cross tabulations and binary logistic regression were conducted to determine associations and the contributions of confounders. P value < 0.05 was considered significant.

III. Results

Of the 2,780 women who delivered during the 12-month study period, 101 had eclampsia. Thus the incidence of eclampsia was 3.6%.

The mean age of the subjects was 28.67±5.75 years (range: 18 to 43), and 85.1% of the women were younger than 35 years**.** The mean parity was 2.63±1.55 (range: 0 to 6), with 2% of them nulliparous. The median gestational age at delivery was37 weeks, and 90% of the women were more than 33 weeks (Information not in table). Majority of the women were unbooked (88%), had low social class (72.3%), and lived over 5km from the hospital (84.2%). The mean packed cell volume (PCV) at admission was 35.38±4.90% (range: 20 to 48). And 18.8% of the eclampsia occurred in women without proteinuria (Table 1).

All the patients had fitted before arrival to the labor and delivery unit, with the majority (65.7%) presenting as intrapartum eclampsia**.**Repeat seizures during MgSO4 therapy was observed in 4 (3.96%) of the patients in this series. The association of a mean arterial blood pressure (MABP) of at least 140mmHg and severe proteinuria with eclampsia was statistically significant (Chi-square=14.127, p=0.003, and Chi-square=25.619, p=0.000 respectively). We found 40.6% of the women arrived hospital after 6pm, while 95% of them got their initial dose of MgSO4 within 10min of arrival. Consultant review in 60.4% of the women occurred within 4h of arrival to hospital, and 47.5% of them delivered within 6h of commencing MgSO4.Cesarean delivery occurred in 64.4% of the women**(**Table 2).

Only one woman (1%) had dialysis but 11% of them required admission into the intensive care unit (ICU). Hospital stay in excess of 15 days occurred in 25.7%, and 18.8% had varying proportions of organ-system dysfunctions. Live birth occurred in90.1% of the babies.The mean birth weight was 2.25±0.88kg (range: 0.4 to 4.7), 87.1% had Apgar score of more than 6 in the first minute but 56.4% had to be admitted to SCBU for varying combinations of indications. By the end of one week in hospital, 5.5% of babies delivered alive had suffered ENND. Perinatal mortality rate was 14.9% (Table 3).

There were 11 maternal deaths in this series of eclamptics, with a case fatality of 10.9%. The surviving 90 women were regarded as "near misses". The majority (53.3%) died from renal failure (Figure 1). The overall maternal mortality ratio attributable to eclampsia during the study period was 395.7 per 100,000 deliveries. Teenage mothers were 1.9-fold more likely to suffer mortality than older women (20% vs 10.4, p=0.702). Grandmultiparas were 2.3-fold more likely to experience mortality than lower parity women (21.4% vs 9.2, p=0.173). Similarly, low social class was 1.7-fold more associated with maternal mortality (12.2% vs 7.4, p=0.497). The booking status and the distance to hospital did not significantly contribute to the occurrence of maternal mortality (11.4% vs 7.7, p=1.00 and 12.5% vs 10.6, p=0.685, respectively). PCV of less than 30% and more than 40% at admission were 3.5-fold and 3-fold, respectively more associated with maternal mortality (33.3% vs 9.5, and 25% vs 8.2; p=0.018).

The time of day to arrive hospital; the timeliness of MgSO4 therapy; the promptness of consultant review; and the length of time spent before delivery did not significantly differ between near misses and those who died (p=0.754, p=0.828, p=0.107, and p=1.000 respectively). Vaginal delivery was 2-fold more associated with mortality than Cesarean section (19.4% vs 9.5, p=0.051). Women with severe proteinuria were 4.3-fold more likely to die (27.3% vs 6.3, chi-square=15.810 with df=3 and p=0.001), but MABP ≥ 140mmHg was not significantly associated with maternal death (p=0.744). Hospital stay in excess of 15 days was 3-fold more likely in patients who were near misses (27.7% vs 9.1%, p=0.002). ICU admission, stillbirth and occurrence of organ-system dysfunctions were 4.7-fold, 8.1-fold, and 11.2-fold, respectively more associated with mortality than near miss {(36.4% vs 7.8, p=0.018; 45.5% vs 5.6, p=0.001; and 100% vs 8.9, p=0.001, respectively). Neonatal admission was 1.3-fold more associated with babies born to women who died (72.7% vs 55.6, p=0.346).

Logistic regression analyses conducted to predict the occurrence of maternal mortality using a combination of patient-specific characteristics and hospital-related events showed that the sets of predictors could not reliably distinguish a patient who would suffer mortality from those who would survive (Chi-square=11.749, p=0.163 with df=9; and chi-square=3.223, p=0.358 with df=3 respectively). The Wald criterion

showed that none of the predictors made a significant contribution to the occurrence of maternal mortality (Table 4). In the "Variables Not in the Equation" tables, only PCV and proteinuria improved the prediction (p=0.042 and p=0.001 respectively).

IV. Discussion

Eclampsia-related mortality and morbidity continue to plague women in resource-constrained environments. The present study gives an overt expression to this long observed calamity which is already being curtailed in more advanced economies of Europe and North America. The incidence of eclampsia in this study was 3.6%. Eclampsia was observed to be more common in women younger than 35 years, unbooked patients, those living more than 5km from the hospital, low social class women, and those with severe hypertension and severe proteinuria. Maternal death was more associated with young age, grandmultiparity and low social class. Anemia, severe proteinuria and vaginal delivery were also associated more with maternal mortality.

The 3.6% incidence of eclampsia in our study is higher than the 1.32% previously reported from Benin City by Onuh and Aisien;[6] the present figure probably reflects the perceived increase in the number of patients referred to our center since the introduction of magnesium sulfate, as well as the observed increase in utilization of intrapartum care services. This 3-fold increase may also be due to the higher delivery rate in the present study as well as the longer duration of the previous study. This rate is also four times higher than the 0.9% reported by Bhalerao**et** al,[17] but slightly lower than the 4.4% found by Adamuet al.[18] The higher contribution of the unbooked patients to our population of eclamptics is consistent with reports of other studies, [4,6] and this observation demonstrates that inadequate antenatal care and monitoring together play a key role in disease progression to eclampsia. At the present time, clear quality protocols to facilitate preconception, antenatal, intrapartum and postpartum care are lacking; hence there is need to create guidelines for improved quality of obstetric care.

The risk of developing eclampsia was found to be significantly higher with severe hypertension and severe proteinuria, which agrees with the findings of Al-Mulhim and colleagues.[19] Nulliparous women constituted only 2% of our patients. This finding is a dramatic drift from the established pattern as reported by several authors.[5,6,20-23] Our finding probably represents an overriding effect of other associated factors like coexisting medical conditions, obesity and recurrence of eclampsia, which predispose many higher parity women to eclampsia. In agreement with previous reports, [6,18]intrapartum eclampsia was seen in the majority of our patients. This findingagain reflects poor antenatal surveillance leading to inadequate diagnosis, such that severe disease is not discovered until eclampsia or other complications make it obvious to the patient, attending healthcare provider or traditional birth attendant.

Many studies from Europe and North America have documented a decreasing pattern in the incidence of eclampsia but there seems to be only little change in the frequency of adverse maternal and perinatal outcome.[11-14,20] Worse still in our environment, the mortality from eclampsia remains worrisome;[4,18,24] thus, eclampsia is now largely regarded as a disease of developing countries. The 10.9% case fatality from eclampsia in this study is higher than 2.3% reported by Okerekeet al,[25]but similar to reports of previous authors.[3,6,21] It is, however, lower than 29.4% found by Adamuet al.[18] Again, this observation is disturbing considering the relative improvement in the availability of MgSO4 over the years. This further underscores the pressing need to continue the efforts toward making MgSO4 easily accessible where it is most needed. One quick explanation for the high fatality may be that many patients are being referred late to teaching hospitals now, and often in very critical condition, following multiple seizures, such that outcome appears to suggest non-improvement in our statistics.

The mainstay of treatment of eclampsia is the control of seizures. The superiority of MgSO4 in this regard informed its introduction in our hospital, to replace diazepam. Despite the availability and utilization of MgSO4 in this hospital and several other health facilities around us, the contribution of eclampsia to maternal and perinatal mortality and morbidity remains enormous. Patient-specific characteristics found to be significantly associated with higher rates of maternal mortality in our study were anemia and severe proteinuria. Previous studies have also associated these factors with adverse outcome.[12,26] In contrast to the findings of other authors,[4,13,18,27] maternal age, parity, booking status, social class and distance travelled to reach hospital, did not significantly influence the rate of maternal mortality in our study. Similarly, the increased risk of mortality documented for patients arriving hospital at night, patients who received delayed or no consultant review, and patients who delivered beyond 12h after commencing MgSO4,[13,18,27] was not shown in this study. The lack of association in our study is perhaps explained by the small size of patients studied.

It is instructive to note that mortality was more likely with vaginal delivery in our study. Other researchers have also made similar observation,[28] though some have reported otherwise.[29] Higher rates of mortality found with vaginal delivery may reflect the tendency to allow longer periods from onset of eclampsia to delivery, while Cesarean sections are more likely to be done within a shorter time.The increased risk of mortality in our patients with severe hypertension, severe proteinuria, and patients with higher rates of organ-system dysfunctions is consistent with the findings of previous workers who identified timing and quality of

care received, presence of comorbidities or severity of the condition as contributors to the disparity in fatality rate between individuals.[30] Long stay in hospital was expectedly a characteristic of patients who recovered from eclampsia, whereas those who succumbed did so rapidly. However, patients with eclampsia associated with mortality also had significantly higher rates of ICU admission, stillbirth and early neonatal deaths.

The major causes of maternal death highlighted in this study have been previously documented by many authors.[6,21,23] The high contribution of renal failure would suggest a higher need for dialysis than the less than 1% revealed in our study. Even so, observation has revealed that since the introduction of MgSO4 to our practice, fewer numbers of our patients have had need for renal dialysis, and this was further shown by the findings of this study, with only one patient undergoing dialysis. In the study by Drakeleyet al,[31] renal dialysis was done for 10% of their patients who had eclampsia. The low rate of renal dialysis shown in our study may also represent a practice that is a little more tolerant of the threshold of renal compromise deemed necessary for dialysis. This decision is often tinted by the perceived socio-economic status of the patient against the background clinical need for such an intervention. Moreover, many of these patients with mild to moderate renal failure are expected to recover fully.[31]

Almost 90% of our patients presented after 33 weeks gestation and this probably accounted for the low frequency of birth asphyxia in this series. It is also likely that the use of MgSO4 contributed to the improved APGAR scores, and in effect to the overall favorable perinatal outcome.[8,32,33] During the period studied by Onuh and Aisien[6] in this department, diazepam was still being used to treat and prevent eclampsia, and they reported a perinatal mortality rate of 214 per 1000 births, a higher figure than the 149 per 1000 births found in the present study. Perinatal deaths in this study resulted mainly from a combination of prematurity, birth asphyxia and neonatal sepsis, and this agrees with previous findings.[5,6,21]

The retrospective design of this study can affect the validity of the results mainly because of inadequate documentation in case notes. This limitation, therefore, prevented the exploration of factors such as place where seizure started, number of seizures encountered, prior exposure to herbal/native medicament, onset of seizure to treatment interval, as well as onset of seizure to delivery interval, obviously compounded by the emergency nature of these patients at admission, which is often attended by distorted or misrepresented history from relatives and/or neighbors. However, the information retrieval in this study was made relatively easy and reliable because the computer-coded departmental obstetric data sheets captured details of management of most of our patients.

Many studies are currently highlighting the tendency to overlook the role of hospital-based delays in accessing care, as well as deficiency of health care services, because of the common practice of emphasizing mainly patient-side delays. Therefore, the future direction of research in this area of interest will be a prospective evaluation of factors which may contribute to mortality in eclampsia in our locale, such as availability of haematological, renal, and intensive care, cardiological, ophthalmological and neurological supports, as well as determine postpartum performance following the use of MgSO4 vis-à-vis blood pressure control and time of return of biochemical and hematological parameters to normal values.

In conclusion, the incidence of eclampsia remains high and adverse outcome persists in our environment. Anaemia and kidney injury increase the rate of maternal mortality, but the roles of sociocultural factors and hospital-based delays require a much closer attention.

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Author Contribution

NO Enaruna: Project development, Data collection, Data analysis, Manuscript writing
JA Osaikhuwuomwan: Data analysis, Manuscript writing
Both authors read and approved the final manuscript.

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Legends

Table 1: Patient-specific characteristics			
Characteristic	**Frequency**		**P value**
	Near miss (n=90)	**Mortality (n=11)**	
Age (year)			
< 20	4	1	0.702
20−34	72	9	
≥ 35	14	1	
Parity			
0	2	0	0.173
1−4	77	8	
≥ 5	11	3	
Social class			
Low	65	9	0.497
middle	22	2	
High	3	0	
Booking status			
Booked	12	1	1.000
Unbooked	78	10	
Distance to hospital			
< 5	14	2	0.685
≥ 5	76	9	
Presence of proteinuria			
Proteinuric	71	11	0.119
Non-proteinuric	19	0	
Packed cell volume			
PCV <30	4	2	0.018
PCV 30−40	74	5	
PCV >40	12	4	

Abbreviation: PCV packed cell volume

Table 2: Hospital-related events			
Event/intervention	**Frequency**		**P value**
	Near miss (n=90)	**Mortality (n=11)**	
Time of day to arrive hospital			
Before 6pm	54	6	0.754
After 6pm	36	5	
Time to initiate MgSO4 therapy (min)			
< 10	87	11	0.378
10−30	1	0	
>30	2	0	
Time of consultant review (h)			
< 4	57	4	0.107
≥ 4	33	7	
Duration on MgSO4 before delivery (h)			
< 6	43	5	1.000
6−12	47	6	
Route of delivery			
Vaginal	29	7	0.051
Caesarean	61	4	

Abbreviation: MgSO4 magnesium sulphate

Table 3: Clinical markers of severity			
Characteristic	**Frequency**		**P value**
	Near miss (n=90)	**Mortality (n=11)**	
MABP ≥ 140mmHg	21	4	0.017
Severe proteinuria	18	7	0.001
Organ-system dysfunctions	8	11	0.001
Length of hospital stay > 14 days	25	1	0.002
ICU admission	7	4	0.018
Dialysis	0	1	0.109
Stillbirth	5	5	0.001
SCBU admission	50	8	0.346
ENND	2	3	0.002

Abbreviation: MABP mean arterial blood pressure, ICU intensive care unit, SCBU special care baby unit, ENND early neonatal death.

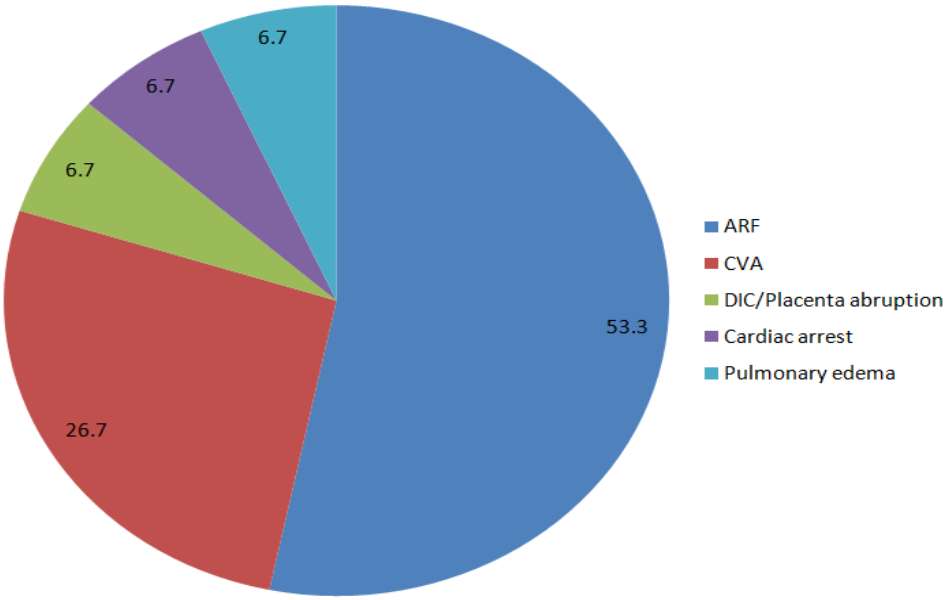

Figure I: Causes of maternal death

Abbreviation: ARF acute renal failure, CVA cerebrovascular accident, DIC, disseminated intravascular coagulopathy

Table 4: Logistic regression analyses to predict maternal mortality

Variable	P value
Age	0.799
Parity	0.177
Booking status	0.999
Distance to hospital	0.093
Social class	1.000
PCV	0.132
Proteinuria	0.819
Time of day to arrive hospital	0.998
Time to initiate MgSO4 therapy	0.994
Time of consultant review	0.999
Duration on MgSO4 before delivery	0.999
Route of delivery	0.999

Abbreviation: PCV packed cell volume, MgSO4 magnesium sulphate