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Liver enzyme patterns in maternal deaths due to eclampsia: A South African cohort

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ABSTRACT

Eclampsia is an obstetric emergency and a major cause of maternal mortality in low and middle-income countries such as South Africa. Despite years of research, there is no single test for the prediction of eclampsia, however liver function tests have been effective in monitoring the prognosis of this disorder.

This was a retrospective study of patients in whom the final cause of death was eclampsia in South Africa between the years 2014–2016.

Of 109 cases who died from eclampsia, the highest prevalence was found among primigravidae (42.1%: n = 45) of whom 26.6% (n = 29) were between 20 and 24 years of age. Twenty-six (23.9%) eclamptics did not receive antenatal care and of these 80.7% (n = 21) had the first eclamptic seizure at home. The first level of health care was used by 63.3% (n = 69) of patients; liver function test results were documented in 56.9% (n = 57). An association was found between eclampsia and elevated aspartate aminotransferase levels.

Primigravidae especially teenagers are at risk of eclampsia. These women in particular must be informed of the warning signs of preeclampsia and requested to attend for antenatal care frequently especially in the third trimester so that early signs of preeclampsia are detected and timeous delivery is carried out to prevent eclampsia. Furthermore, liver function tests and platelet counts should be done in all women with the pre-eclampsia-eclampsia syndrome during antenatal and in the immediate postpartum period to prognosticate progression of the disorder and or timing of discharge from hospital.

1. Introduction

Eclampsia, a pregnancy specific condition associated with seizures, hypertension and proteinuria is a major cause of maternal and fetal morbidity and mortality in low and middle income countries [1]. The Saving Mother's Report 2014–2016 indicates that eclampsia accounts for approximately 50% of all maternal deaths due to hypertensive disorders of pregnancy (HDP) in South Africa [2].

The International Society for the Study of Hypertension in Pregnancy (ISSHP) has recently classified HDP broadly into the following groups: white coat hypertension, masked hypertension, chronic hypertension (high blood pressure prior to pregnancy or that presenting for the first time before the 20th week of gestation), gestational hypertension, preeclampsia (de novo hypertension and proteinuria) without features of severe disease, preeclampsia with features of severe disease such as persistent headache, visual disturbances, nausea and vomiting, epigastric pain and eclampsia. The HELLP (hemolysis, elevated liver enzymes and low platelets) syndrome is a variant of the preeclampsia syndrome which carries with it additional significant morbidity and mortality [3].

Despite a progressive decline in maternal deaths due to HDP in high-income countries (HICs), the risk of morbidity and mortality still remains high in low and middle-income countries (LMICs) [4]. This is due to lack of access to antenatal care/emergency obstetric care, socio-cultural factors resulting in poor attendance of antenatal clinic or "booking" for care at a late gestational age and poor quality of antenatal care given the shortage of experienced health professionals particularly at primary health care facilities (clinics and district hospitals) [5]. While epilepsy is the more frequent cause of convulsions in pregnancy in HICs, eclampsia remains the commonest cause in LMIC [1,6]. Intracranial pathology, including haemorrhage and global cerebral oedema are the commonest final causes of death associated with eclampsia [6].

Although the pathophysiology of eclampsia is unclear, deposition of

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fibrin, coagulopathy and hypertensive encephalopathy are distinct hallmarks [7]. Due to its high maternal and fetal morbidity and mortality rates, it is important to identify preeclampsia and institute clinical interventions timeously. Also, since the only real treatment presently is delivery of the placenta, there is need to ensure use of antihypertensive drugs and delivery by the end of the 37th week if not before, dependent on the individual biochemical and clinical indices of the individual patient.

Preeclampsia is the most frequent cause of liver function test abnormalities in pregnancy in LMIC. Liver enzymes could have useful prognostic value in predicting the sequel of preeclampsia-eclampsia syndrome which is associated with increased rate of cell death. Gifford et al., [7] suggested that pre-eclamptics with normal liver enzymes have a reduced risk of progressing to eclampsia. Asides other 'red-flags', the ISSPH recommends immediate delivery in pre-eclamptic women with progressively abnormal liver enzyme tests. Other researchers have also suggested that determination of liver function tests have proved useful in monitoring the sequel of pre-eclampsia eclampsia syndrome [8].

In order to reduce maternal mortality from eclampsia, there is need for continuous search for predictors of this pregnancy disorder; hence this study examined the patterns of liver enzymes in women who died from eclampsia.

2. Materials and methods

Following institutional regulatory permissions, a retrospective chart review of maternal deaths due to eclampsia in South Africa between 2014 and 2016 was performed. Eclampsia was defined as seizures associated with hypertension (> 140/90 mmHg) and proteinuria (at least +1 detected dipstick). Maternal death due to eclampsia is the death of a woman during pregnancy or within 42 days of termination of pregnancy, irrespective of the duration and site of the pregnancy, from eclampsia. This was analysed with reference to age, parity, antenatal care, final cause of death, timing of emergency/death, place of onset and clinical presentation of eclampsia.

We also assessed the Glasgow coma scale (GCS), haemoglobin, platelet counts, liver function tests including liver enzymes and obstetric outcomes. The liver enzymes were classified as high, normal or low based on the standard reference vales: Alkaline phosphatase (ALP) (42–98 U/L), Gamma-glutamyl transferase (GGT) (< 30 U/L), Aspartate aminotransferase (AST) (13–35 U/L), Alanine aminotransferase (ALT) (7–35 U/L), Total protein (60–78 g/L, Total bilirubin (5–21 μmol/L), Conjugated bilirubin (0–3 μmol/L), Lactate dehydrogenase (LDH) (208–378 U/L) and Albumin (35–52).

Timing of emergency included: early pregnancy (< 20 weeks), antenatal period (≥20 weeks), intrapartum and postpartum. The referral system in South Africa involves levels of health care including level 1 (Community health care centre and district hospitals), level 2 (regional hospital), level 3 (provincial tertiary hospitals), level 4 (central hospitals) and private hospitals.

Women with eclampsia are usually managed at regional and tertiary hospitals. The Glasgow coma scale (GCS) was used to determine the level of consciousness at the time of emergency. This was defined as fully conscious (14–15), semi-conscious (6–13) and unconscious (≤5). Pregnancy was grouped into 3 trimesters according to weeks: 1st trimester (week 1–12), 2nd trimester (week 13–28) and 3rd trimester (week 29–40).

Analysis of the data was done with the IBM SPSS software version 25 (Cary, USA). Shapiro Wilk's test for normality was used to determine if continuous data followed a normal distribution. Normally distributed data was summarized as mean ± standard deviation, while non-normal data was summarized as median (interquartile range) and compared using Student's *t*-test and Wilcoxon-Mann-Whitney test as appropriate. Chi-square test or Fisher's exact test was used to determine if there was an association between variables. A $p < 0.05$ was considered significant.

Table 1
Clinical characteristics of 109 maternal deaths due to eclampsia, 2014–2016.

Age (years)	*N* (%)
≤14	3 (2.8)
15–19	23 (21.0)
20–24	29 (26.6)
25–29	18 (16.6)
30–34	20 (18.4)
≥35	16 (14.6)
Parity (mean 1, range 0–5)	
0	45 (42.1)
1	28 (26.2)
2	19 (17.8)
3	11 (10.3)
≥4	4 (3.7)
Gestational Age	
2nd Trimester	18 (16.5)
3rd Trimester	87 (79.8)
Unknown	4 (3.7)
Antenatal care	
Booked for antenatal care	83 (76.1)
Unbooked	26 (23.9)
HIV status	
Positive	30 (27.5)
Negative	59 (54.1)
Unknown	20 (18.4)
Obstetric problem	
Eclampsia	84 (77.1)
Eclampsia + HELLP	25 (22.9)
History of chronic hypertension	11 (10.1)
Obesity	9 (8.2)
Glasgow coma scale (GCS) on arrival at final facility	
Fully conscious (14–15/15)	5 (4.6)
Semi-conscious (6–13/15)	37 (34)
Unconscious (≥5/15)	36 (33)
Place of onset of seizure(s)	
Home	78 (71.6)
Hospital	31 (28.4)
Stroke involvement	
Yes	11 (10.1)
No	97 (88.9)
Dialysis	
Yes	7 (6.4)
No	93.6
Timing of emergency	*N* (%)
Early pregnancy	1 (0.9)
Antenatal	77 (70.6)
Intrapartum	16 (14.7)
Postpartum	15 (13.8)
Timing of death	
Antenatal	32 (29.4)
Intrapartum	8 (7.3)
Postpartum	69 (63.3)
Pregnancy outcome	
Live birth	43 (39.5)
Early neonatal death	3 (2.7)
Stillbirth	27 (24.8)
Undelivered	36 (33)

Hemolysis, Elevated liver enzymes, Low platelets (HELLP).

3. Results

Data from 109 maternal deaths due to eclampsia were analysed. As seen in Table 1, the mean age (standard deviation) was 26.0 (6.9) years, (range 14–41); the majority (42.1%) were primigravidae.

3.1. Antenatal care

Despite the fact that 83 (76.1%) had booked for antenatal care; 8 (9.6%) were not referred from level 1 and 2 health facilities despite

presentation with borderline/high blood pressure levels, these borderline blood pressures were not recognised in 2 (2.4%) patients and there was no documentation of blood pressure in 2 (2.4%) cases. While 5 (6%) of patients with high blood pressure at level 1 and 2 health facilities were untreated, there was delayed referral in 5 (6%) patients and 8 (9.6%) had booked late. Twenty-six (23.9%) patients did not book for antenatal care; of these 2 (7.7%) were immunocompromised due to HIV, 21 (80.7%) developed eclamptic fits at home while 5 (19.3%) had seizures in the hospital (Table 1).

3.2. Occurrence of seizures/deaths

As shown in table 1, seizure events occurred in all patients. The timing of the emergency was during early pregnancy (prior to 20 weeks gestation) in 1 (0.9%) patient, antenatal period in 77 (70.6%), intrapartum period in 16 (14.7%) and postpartum period in 15 (13.8) patients. Maternal death occurred during the antenatal period, intrapartum period and postpartum period in 32 (29.4%), 8 (7.3%) and 69 (63.3%) patients respectively.

3.3. Level of health care

As shown in Table 2, 69 (63.3%) were referred from CHC/district health facility to regional/tertiary hospitals, 8 (11.5%) however died in transit while 1 (1.4%) patient was discharged from ICU to the maternity ward and died therein. Among 4 (3.7%) patients who received care at private health facilities, 3 (75%) were not referred while 1 (25%) patient was referred to a higher level of care. Of the 35 (32.1%) that received treatment at CHCs and district hospitals without referral; 5 (14.2%) were discharged and subsequently died at home.

3.4. Clinical and laboratory investigations

Sixty-nine (63.3%) were referred from CHCs and district hospitals. Seventy-four (67.9%) had urine dipstick ≥1+. Among the 35 (32.1%) that did not have proteinuria documented, 6 (17.1%) had no urine output. Liver function tests were performed in 62 (56.9%) patients (Table 3). Of the 47 (43.1%) that did not have any liver function test, the equipment for liver function tests were not functioning in a level 4 hospital where 1 (2.1%) was admitted while there was no equipment for liver function tests in the district hospitals in 3 (6.4%) cases. Table 4 shows the pattern of liver enzymes in the study population. There was elevation ALP, AST, ALT, Conjugated bilirubin, LDH, Albumin and GGT in majority of the patients.

In Table 5, there is a significant association between the eclampsia and ALT, total protein, LDH and GGT ($p < 0.05$). Also, a significant association was found between platelet counts and ALT, total and conjugated bilirubin ($p < 0.05$) (Table 6).

Table 2
Levels of health care.

Referral	
Yes	69 (63.3)
No	35 (32.1)
Initial level of care	
CHC	79 (72.5)
District	20 (18.3)
Regional	4 (3.7)
Tertiary/National Centre	2 (1.8)
Private	4 (3.7)
Facility where death occurred	
CHC	17 (15.6)
District	29 (26.6)
Regional	39 (35.8)
Tertiary/National Centre	12 (11)
Private	3 (2.8)
Transit	5 (3.6)
Home	5 (4.6)

Community Health Centre (CHC).

Table 3
Clinical and laboratory investigations.

Blood pressure levels (mmHg), mean (SD); range	
Systolic	198 (17); 186–210
Diastolic	112.5 (16.2); 101–124
Proteinuria	2.2 (1.1); 0–4
Haematocrit (L/L)	0.392 (0.12); 0.304–0.480
Haemoglobin (g/dL)	9.15 (3.3); 6.8–11.5
Platelets ($\times 10^9$/L)	181 (164); 65–297
Serum urea (mmol/L)	5.6 (0.14); 5.5–5.7
Serum creatinine (μmol/L)	123.5 (27.6); 104–143
Liver enzymes	
	Referring facility
ALP (U/L)	169.5 (30.4); 148–191
AST (U/L)	760 (1022.5); 37–1483
ALT (U/L)	402 (560); 6–798
Total protein	54.5 (11.8); 32–75
Total bilirubin (μmol/L)	33.5 (43.1); 3–64
Conjugated bilirubin (μmol/L)	11.5 (14.8); 1–22
Lactate Dehydrogenase (U/L)	2824.5 (3154.4); 594–5055
Albumin	24.1 (7.8); 10–44
GGT	57.5 (59.5); 2–275

Alkaline phosphatase (ALP), Gamma-glutamyl transferase (GGT), Aspartate aminotransferase (AST), Alanine aminotransferase (ALT).

Table 4
Pattern of liver enzymes.

	n (%)		
	High	Low	Normal
ALP (U/L)	40 (90.9)	4 (9.1)	
AST (U/L)	49 (86)	4 (7)	4 (7)
ALT (U/L)	44 (77.2)	3 (5.3)	10 (17.5)
Total protein	2 (4.6)	27 (62.8)	14 (32.6)
Total bilirubin (μmol/L)	19 (43.2)	11 (25)	14 (31.8)
Conjugated bilirubin (μmol/L)	28 (75.7)	9 (24.3)	
Lactate Dehydrogenase (U/L)	22 (91.7)	2 (8.3)	
Albumin	34 (91.9)	3 (8.1)	
GGT	25 (67.6)	12 (32.4)	

Alkaline phosphatase (ALP), Gamma-glutamyl transferase (GGT), Aspartate aminotransferase (AST), Alanine aminotransferase (ALT).

Table 5
Association of liver enzymes with Eclampsia.

	p-value ($^*p < 0.05$)
ALP (U/L)	0.051
AST (U/L)	0.038*
ALT (U/L)	0.061
Total Protein	0.034*
Total bilirubin (μmol/L)	0.080
Conjugated bilirubin (μmol/L)	0.064
Lactate Dehydrogenase (U/L)	0.032*
Albumin	0.078
GGT	0.049*

Alkaline phosphatase (ALP), Gamma-glutamyl transferase (GGT), Aspartate aminotransferase (AST), Alanine aminotransferase (ALT).

4. Discussion

One of the main findings in the current study was that 15% of patients developed eclampsia in the postpartum period; 25% of these occurred within 48 h to 4 weeks postpartum. As against earlier belief that eclampsia occurs only up to 48 h postpartum, our findings support the existence of late postpartum eclampsia similar to that of other reports [9,10]. Hence, there is need for proper follow up of patients with

Table 6
Association of platelet count with liver enzymes.

	p-value ($^{*}p < 0.05$)
ALP (U/L)	0.435
AST (U/L)	0.146
ALT (U/L)	0.000*
Total Protein	0.069
Total bilirubin (μmol/L)Highlights	0.004*
Conjugated bilirubin (μmol/L)	0.003*
Lactate Dehydrogenase (U/L)	0.601
Albumin	0.259
GGT	0.150

Alkaline phosphatase (ALP), Gamma-glutamyl transferase (GGT), Aspartate aminotransferase (AST), Alanine aminotransferase (ALT).

eclampsia and preeclampsia with severe features. Also, the Saving Mothers Report, 2016 suggests that antihypertensive agents are not stopped abruptly on discharge from hospital, that all such women be kept in hospital for at least three days for "close "monitoring of blood pressure levels and laboratory tests of organ dysfunction and that follow up of such patients continues at an appropriate level of care for at least 4 weeks postpartum [1].

It is noteworthy that both pre-eclampsia and eclampsia can develop in the absence of either hypertension or proteinuria. Of the four patients that had so called "atypical eclampsia", one had a blood pressure lower than 140/90 mmHg with proteinuria while 3 had high blood pressure levels with no proteinuria. Atypical eclampsia has been reported by various authors [1,9,11] and includes patients who develop preeclampsia with severe features or rapid onset eclampsia. Hence, clinicians should treat all cases of eclamptic seizures in the absence of neurological signs as for eclampsia. In our study, there was no treatment/timely referral to a higher level of health care in about 10% of the patients despite borderline elevations of BP. Although there is a debate on the risk of exposure of the foetus to antihypertensive agents in the event of mild-to moderate BP elevations [12], advocacy still continues for the use of antihypertensive drugs at BP levels of 130/80 mmHg in the event of a 10-year risk of a cardiovascular event > 10%. [13].

In the current study, 10% of the patients developed haemorrhagic stroke subsequent to eclamptic seizures. Consistent BP control reduces the risks of stroke and other associated complications [13] hence the need for proper control of management of high-risk patients with HDP. The use of rapid acting antihypertensive agents such as quick acting nifedipine and labetalol to lower high blood pressure levels to less than 150 mmHg systolic and 110 mm Hg diastolic is strongly recommended [1].

In the current study, 32% of patients did not have urine dipstick results documented. Although, the degree of proteinuria has been shown to be of little or no value in considering the risk of eclampsia [14]; high degree of proteinuria is linked with poor prognosis for the foetus, hence it is the authors opinion that there is need for measurement of proteinuria to both detect preeclampsia eclampsia syndrome and assist in predicting morbidity and mortality.

The findings of the current study demonstrate that eclampsia is a condition which occurs mostly in primigravidae between 20 and 24 years followed by teenagers. It is most likely that in the teenagers these were "hidden pregnancies"; in 3 teenage patients, the family members were not aware of the pregnancy until they developed seizures at home. This trend has also been observed in similar studies in South Africa [1,15] and worldwide [10]. It suggests the need to increase knowledge and adherence to contraceptive use amongst teenagers and women of reproductive age in South Africa, especially in rural areas. Moreover, because teenage pregnancies are prone to result in preeclampsia, contraceptive services must be strengthened in this age group. Previous studies have indicated that there is an increased use of contraceptives in urban communities in comparison to rural areas in South Africa [16]. Hence, we recommend a more pro-active approach to the accessibility of high quality contraception for nulliparous women in rural areas in order reduce deaths from eclampsia.

Regular routine antenatal visits and assessments are essential for all pregnant women. About 26% of our patients did not attend antenatal care. One of these was immunocompromised with HIV. Early detection of women at risk of preeclampsia and progression to eclampsia is a challenge in low resourced settings hence women in such environments are more affected than those in well-resourced settings [17]. This calls for continuous sensitization, especially at the grassroot level on the need for pregnant women to seek antenatal services. The involvement of family members is also crucial.

Approximately, 87% of patients in the current study had seizures in the third trimester of pregnancy. The WHO recommends four antenatal visits for women without HDP, this results in reduced visits in the last trimester of pregnancy especially in low resourced settings [18]. Asides from the risk of atypical eclampsia and onset of preeclampsia in the third trimester, fewer antenatal visits have been linked with high risk of perinatal mortality as reported in the WHO antenatal care trial [19]. In addition, in low resourced settings, the choice of investment in antenatal care could be difficult for pregnant women especially when they feel healthy. The current study shows that 78% of seizures occurred at home. Consequent to these findings, South Africa has introduced "basic antenatal care plus" which means that all women have at least 8 antenatal visits, with two weekly visits from the 34th week of gestation in the hope that this will detect preeclampsia early and also prevent stillbirths.

Apart from haemoglobin and platelet count levels, the monitoring of liver function tests is essential in order to track the progression of preeclampsia to eclampsia. A study by Munazza et al. [20] demonstrated an upregulation in the levels of ALT and AST with hyperbilirubinemia and these are more significant in the presence of hemolysis. A major cause for the increased liver enzymes in preeclampsia-eclampsia syndrome is the presence of lesions arising from haemorrhagic necrosis in the periphery of the liver lobule. Similarly, Mol et al., suggested that liver transaminases are good indicators for the prognosis of eclampsia and suggested that estimation of liver enzymes is probably better than platelet counts, serum creatinine and albumin levels [8]. In the present study, with the exception of GGT, elevation of liver transaminases ranked higher among the other liver function tests that are routinely assessed in the management of patients with preeclampsia-eclampsia syndrome.

Although, endothelial damage is known to cause depletion in platelets, there has been controversies over the use of platelet count as a marker for prediction of preeclampsia/eclampsia [21]. The present study demonstrated a significant correlation between elevated levels of ALT, total and conjugated bilirubin on one hand, and low platelet count. This shows that despite the affordability of low platelet count testing in pregnant women especially in LMIC, it cannot be used as a single prediction test for the prediction/prognosis of preeclampsia.

Several researchers have suggested an upregulation in the levels of serum bilirubin, LDH and liver enzymes in preeclampsia/ eclampsia [22]. As an intracellular enzyme, LDH levels are increased in response to increased cellular death observed in preeclampsia. Elevation of LDH levels was observed in the current study, this is in accordance with the work of Jaiswar et al. [23] who observed an association between LDH levels and adverse maternal and fetal outcomes in women with the preeclampsia-eclampsia syndrome. Sibai and Stella also demonstrated that AST or ALT and LDH levels twice the upper limit of normal are laboratory test results consistent with preeclampsia-eclampsia in addition to persistent proteinuria, low platelet count and increased serum creatinine level [9]. Malvino et al., reported that serum AST levels was about four times higher in eclampsia when compared with preeclampsia [24]. Although liver function tests have limited singular accuracy in prediction of the sequalae of preeclampsia-eclampsia, AST levels have been incorporated into the full preeclampsia integrated

estimate of risk (PIERS) multivariate model [22]. This predicts adverse maternal outcome in women on admission for preeclampsia within 48 h.

In the present study population, on the average, the liver function test results were available in 38% of patients; of these AST and ALT results ranked the highest with results in 52.3% of patients respectively. We suggest advocacy for the incorporation of liver transaminases in the blood investigations required for the management protocol of the pre-eclampsia-eclampsia syndrome. Bearing in mind the cost effectiveness of these investigations, there may be need for government subsidies especially in low resourced settings. In the present study, the equipment for determination of liver function tests was faulty in the health facilities attended by two patients. These patients were also not referred on time. About 73% of our patients initially received care at the first level of health care (level 1). Hence, if patients with eclampsia are going to be managed at district hospitals, these health facilities must have fully functioning laboratories. However, it is probably best to manage all patients with preeclampsia with severe features and eclampsia at regional or tertiary hospitals. Health workers must also be enlightened on the inclusion of liver transaminases investigations/proper monitoring in the clinical protocols for the management of eclampsia.

A limitation of our study is that there was no documentation of 'repeat' liver function tests. Also, we do have not the record of liver function tests in eclamptic patients who survived. These would have further substantiated our findings. Future research will be in this direction.

In conclusion, in order to reduce maternal and perinatal morbidity and mortality due to eclampsia especially in low and middle-income countries, there is need for a more proactive approach to improved investment in health care, equal accessibility and affordability of health care services and training and retraining of health workers especially at the lower levels of heath care to be better equipped with skills for the detection of preeclampsia with emphasis on the incorporation of liver function tests as part of routine investigations during the management of preeclampsia; albeit, in combination with platelet count.

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Declaration of Competing Interest

The authors declare no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.preghy.2019.05.002.

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