Title: Eclampsia in Australia and New Zealand: a prospective population-based study.

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Conflict of interest

The authors have no conflicts of interest to declare.

Keywords: eclampsia; preeclampsia; maternal morbidity; pregnancy; seizure

Abstract

Background: Eclampsia is a serious consequence of preeclampsia. There are limited data from Australia and New Zealand (ANZ) on eclampsia.

Aim: To determine the incidence, management and perinatal outcomes of women with eclampsia in ANZ.

Materials and methods: A two year population-based descriptive study, using the Australasian Maternity Outcomes Surveillance System (AMOSS), carried out in 263 sites in Australia, and all 24 New Zealand maternity units, during a staggered implementation over 2010- 2011. Eclampsia was defined as one or more seizures during pregnancy or postpartum (up to 14 days) in any woman with clinical evidence of preeclampsia.

Results: Of 136 women with eclampsia, 111 (83%) were in Australia and 25 (17%) in New Zealand. The estimated incidence of eclampsia was 2.2 (95% confidence interval (CI) 1.9 – 2.7) per 10,000 women giving birth. Aboriginal and Torres Strait Islander women were over-represented in Australia (n=9; 8.1%). Women with antepartum eclampsia (n=58, 42.6%) were more likely to have a preterm birth (p=.04). Sixty-three (47.4%) women had preeclampsia diagnosed prior to their first eclamptic seizure of whom 19 (30.2%) received magnesium sulphate prior to the first seizure. Nearly all women (n=128; 95.5%) received magnesium sulphate post-seizure. No woman received prophylactic aspirin during pregnancy. Five women had a cerebrovascular haemorrhage and there were five known perinatal deaths.

Conclusions: Eclampsia is an uncommon consequence of preeclampsia in ANZ. There is scope to reduce the incidence of this condition, associated with often-catastrophic morbidity, through the use of low-dose aspirin and magnesium sulphate in women at higher risk.

Introduction

Eclampsia can be defined as a generalised seizure in the setting of preeclampsia, in the absence of another more likely cause. It is a serious consequence of preeclampsia and remains a significant cause of maternal mortality and morbidity worldwide. Since the MAGPIE trial showed a 50% reduction in eclampsia with the use of magnesium sulphate ($MgSO_4$),[1] there has been universal recommendation to use $MgSO_4$ as the drug of choice to prevent and treat eclampsia in women deemed to be at higher risk of this complication. Eclampsia rates vary across geographic regions with the highest incidences observed in low and middle income countries.[2] However, the incidence also varies among high income countries, with higher quality care associated with lower incidences.[3] Population-based data on eclampsia in Australia and New Zealand (ANZ) are scarce.

The aim of this study was to examine the incidence, management and perinatal outcomes of eclampsia in ANZ.

Materials and Methods

Study design

A bi-national population-based case cohort study was undertaken using the Australasian Maternity Outcomes Surveillance System (AMOSS): a research platform that enables population-based audit of rare, severe disorders of pregnancy. The AMOSS surveillance process has been described in detail in previous studies.[4-6] In brief, all hospital-based maternity units across Australia with more than 50 births per annum, and all New Zealand maternity units are asked to respond to a monthly email to report the presence or absence of a case.

A staggered implementation of the AMOSS occurred as ethics, governance and site approvals were received between 2008 and 2011.[7] At the commencement of bi-national surveillance, in

January 2010, 107 (35.5%) of 301 eligible sites were active, covering 59% of births across ANZ. This rose to 260 sites, covering over 90% of births by December 2010, and to 291 eligible sites (96% of births) by December 2011. Estimates were calculated using denominator data based on the number of births for each hospital according to the number of days active as an AMOSS participating site. There was proportionate representation of public and private hospital sites.

Case definition

Eclampsia was defined as seizure/s during pregnancy or in the first 14 days postpartum not caused by any concurrent neurological disease such as epilepsy, together with at least two of the features listed in Box 1 within 24 hours of seizure/s, indicative of a diagnosis of preeclampsia.

Surveillance and data collection

Women experiencing eclampsia were identified prospectively by maternity unit based AMOSS data collectors, through active surveillance between January 1, 2010 and December 31, 2011. The average monthly response rate was 88% during the study period. Data were submitted by AMOSS data collectors with two secure web-based clinical surveys completed. The general survey provided information on demographic and pregnancy factors, obstetric interventions and perinatal outcomes. The second condition-specific survey collected information particular to eclampsia and its management. Data were compiled and logic validation checked by AMOSS staff.

Statistical analyses

Women were categorised into three groups: antepartum, intrapartum or postpartum according to when the first seizure occurred. Demographics, eclampsia treatment and management, pregnancy and birth outcomes were compared between the three groups using Chi-square

test. Changes of high systolic and diastolic blood pressure during/after first seizure were tested using Paired T-test. A p-value less than 0.05 was considered statistically significant. Data were analysed using the Statistical Package for the Social Sciences software, version 24.0 (IBM Corporation, Somers, NY, USA).

Ethical considerations

Ethics approval was obtained from all participating sites.[7] All data provided to AMOSS were de-identified, with AMOSS data collectors in hospitals maintaining a log of cases to enable data query follow-up. Individual consent was not required at any site.

Results

Over the staged two-year period, 170 women with eclampsia were reported with 136 women meeting inclusion criteria: 111 (83%) from Australia and 25 (17%) from New Zealand (Supplementary Figure 1). The estimated incidence of eclampsia was 2.2 (95% CI 1.9 – 2.7) per 10,000 women giving birth: 2.3 (95% CI 1.9 – 2.8) in Australia and 2.0 (95% CI 1.3 – 2.9) in New Zealand. Of the 136 cases, nine women identified as being Aboriginal and/or Torres Strait Islander (6 antepartum, 1 intrapartum and 2 postpartum) and five as Maori (2 antepartum, 1 intrapartum and 2 postpartum). Fifty-eight cases (42.6%) occurred antenatally, 33 (24.3%) intrapartum and 45 (33.1%) postpartum. Of the 45 postpartum cases, 23 (51.1%) occurred in the first 24 hours post-birth; three women experienced their first seizure on day 10 postpartum, the most remote day of first seizure. There were no maternal deaths.

There was no difference in maternal demographic characteristics related to the timing of the first seizure, apart from a significantly higher incidence of antenatal eclampsia in the public sector compared to the private sector (p=0.04) (Table 1). Whilst the majority of cases were in women having their first birth, 43 (31.6%) cases of eclampsia were in multiparous women. For the 42 multiparous women with available data, the median time since the last birth was

29.5 months (IQR 24.0 – 52.3); the maximum time was 12.5 years. Twelve multiparous women had a history of preeclampsia, including three with a history of eclampsia. None of these women were on aspirin during pregnancy. Eight of the twelve women experienced antenatal eclampsia. Two primiparous and three multiparous women had a history of chronic hypertension, and one primiparous and one multiparous woman had a history of chronic renal failure: again, none of these women received aspirin during pregnancy. Women who experienced an antenatal episode of eclampsia were more likely to have a preterm birth ($p<.001$) (Supplementary Figure 2).

Of the 120 women with documented blood pressure (BP) in the week prior to the first seizure, 33 (27.5%) had a normal systolic pressure and 30 (25.0%) had a normal diastolic pressure. Premonitory symptoms were noted to be present in 87 (64.0%) women in the week prior to the first eclamptic fit (Table 2). During or following the first seizure, systolic and diastolic BP increased in most women ($p<.001$), with 93 (69.9%) women receiving antihypertensive medication following the seizure; labetalol was the most common drug prescribed (n=45), followed by hydralazine (n=31). Most women received one anti-hypertensive agent (n=73; 78.5%), with 12 (12.9%) receiving two and eight (8.6%) receiving three or more. Laboratory results showed less than half of the women had abnormal liver function (Table 2). Haemolysis was present in 20 of the 108 (18.5%) cases where recorded, and 26 (20.3%) women were given a diagnosis of haemolysis elevated liver enzymes and low platelets (HELLP) syndrome.

Most women experienced a single seizure (n=88, 64.7%) with those who experienced their first seizure intrapartum less likely to have a second seizure ($p= 04$). Thirty (22.7%) women experienced two seizures, 11 (8.3%) three seizures, two (1.5%) six seizures and one woman experienced 20. Overall, 36 (26.5%) women experienced their first seizure at home; 10 of whom had a diagnosis of preeclampsia in the index pregnancy prior to the seizure. Of the

remaining cases, 49 (36%) occurred on a birth suite and 33 (24.3%) on a maternity ward. There was no difference according to parity on whether preeclampsia was diagnosed prior to eclampsia (p= 0.89), or on the number of seizures (p= 0.79).

Nearly half of the women (n=63; 47.4%) had a diagnosis of preeclampsia in the index pregnancy before their first seizure; of these, 19 (30.2%) women received prophylactic $MgSO_4$ (Table 3). To treat an eclamptic seizure, 47 (34.6%) women received $MgSO_4$ and 15 (11%) diazepam. Most women (n=128; 95.5%) received a continuous $MgSO_4$ infusion following the first seizure and nine (6.9%) women received diazepam following the first seizure. Three women received no magnesium and no other anti-convulsant following the seizure. Monitoring related to the provision of intravenous $MgSO_4$ varied. Of the 128 women who received a continuous $MgSO_4$ infusion, 92 (71.9%) had serum monitoring; 23 had no serum monitoring and serum monitoring status was not known for 13 women. The most common frequencies of serum monitoring was twice (n= 21), three times (n=24) and four times (n= 22) in the first 24 hours. Respiratory rate was mostly recorded hourly with a median of 24.0 times in 24 hours (IQR 17.5-24.0), as was urine output (n=115; 89.8%). In contrast, deep tendon reflexes were recorded much less frequently, with a median of 7.0 times in 24 hours (IQR 3.0-23.5). At discharge, 81/121 (66.9%) women were prescribed antihypertensive medication, 86/116 (74.1%) women were referred to a physician for follow-up and staff had concerns noted for 22 women at discharge, including for five women who discharged themselves against medical advice.

Women experienced substantial morbidity with nearly half admitted to ICU and five (3.9%) women experienced a cerebrovascular haemorrhage (Table 3). The highest systolic BP (mmHg) for the five women who experienced a cerebrovascular haemorrhage was 150, 185, 210, 222 and 250mm Hg respectively. All acute blindness episodes occurred in women who had their first seizure postpartum and major obstetric haemorrhage was more common in

women who experienced their first seizure intrapartum. Most women (n=89; 66.9%) gave birth by caesarean section, with the main indication being 'maternal illness' (Table 3). General anaesthesia was common, particularly among women who experienced antenatal eclampsia (n=32; 55.2%).

The 136 women gave birth to 142 babies. A number of neonates were born in poor condition with 19 (14.3%) neonates having a 5 minute Apgar score less than 7 (Table 4). Over half of the neonates required admission to a neonatal intensive care unit and 52 (38.7%) received breathing support. The perinatal mortality rate was 43.5 per 1000 births, consisting of four stillbirths and one neonatal death for 116 neonates with a known outcome. Neonates born to women who experienced antenatal eclampsia were more likely to be born preterm (Table 4).

Discussion

Eclampsia was a very uncommon event in ANZ being diagnosed in about one in every 4,500 women who gave birth. Eclampsia rates are highly variable and may be related to the quality of antenatal and intrapartum care.[3] Although the eclampsia rate is significantly lower in high resource countries than low resource countries, there is marked variation, with the United Kingdom reporting a rate of 2.7/10,000 compared with the Netherlands rate of 5.4/10,000,[3] and New York City (New York, United States of America) 4.3/10,000[8] compared with Memphis (Tennessee, United States of America) 15.0/10,000.[9]

Four percent of women giving birth in Australia are Aboriginal and/or Torres Strait Islander women, yet they constituted eight percent of eclampsia cases in Australia.[10] There is a higher risk of pregnancy-induced hypertensive disorders in Aboriginal and/or Torres Strait Islander women, related to high rates of chronic high blood pressure, kidney disease, diabetes and other risk factors, and which culminated in a six-fold increase in deaths due to hypertensive disorders in the latest report into maternal mortality in Australia.[11] Additionally, access to

care may have been an issue. In contrast, Maori women accounted for 20% of NZ cases which was similar to the NZ childbearing population (22.8%).[12] Further examination of the cases in Aboriginal and/or Torres Strait Islander women is warranted to examine the quality of maternity care and antenatal engagement.

Overall, the clinical picture and management were not dissimilar to other like-countries, with a little over a quarter of women experiencing their first seizure at home.[3] In keeping with clinical practice guidelines, almost all women received an intravenous $MgSO_4$ infusion to prevent recurrent eclampsia. Whilst only about one-third of women with a diagnosis of preeclampsia received prophylactic $MgSO_4$ prior to first seizure, this was three times more common than in the United Kingdom and the Netherlands.[3] Hourly urine output and respiratory rate recordings were mainly adhered to, however deep tendon reflexes were recorded less than expected. Neither the Society of Obstetric Medicine of ANZ 2008 guidelines (active at the time of the study), or the updated 2014 guidelines, recommend serum magnesium monitoring unless there is oliguria or renal impairment.[13,14] Whilst deep tendon reflex checks are recommended, the frequency is not stated. The MAGPIE trial protocol directed 30 minutely deep tendon reflex checks (or usual practice).[1] The ideal frequency of deep tendon reflex checks warrants further examination as it is a time consuming task and one on which junior medical staff are often relied. Alternatively, midwives must be skilled to conduct this important observation.

The low rate of eclampsia in our study suggests that there was a good level of antenatal care in ANZ overall. One quarter of women were normotensive in the week prior to first seizure, highlighting the unpredictable nature of eclampsia. A similar number of women received antihypertensive medication compared to the United Kingdom Obstetric Surveillance System study, which was substantially higher than the Netherlands eclampsia study. However, there was room for further improvement in the management of hypertension with a number of

women sub-optimally managed. Four of the five women who had a cerebral haemorrhage had very high systolic BP confirming that judicious control of systolic BP is warranted.

There has been increasing focus and recommendations made to use low-dose aspirin to prevent preeclampsia in women with moderate to high risk. None of the multiparous women in our study with a history of preeclampsia (of which three had experienced eclampsia) received preventative aspirin during the index pregnancy. This represents a missed opportunity to potentially prevent preeclampsia and thus prevent eclampsia. Only one in five eligible women were prescribed low dose aspirin in a Melbourne study with recruitment in 2010, a similar time as this eclampsia cohort.[15] Current Australian first trimester screening and preventative aspirin prescription rates are unknown though it is probably higher than the 20% in 2010. However with studies consistently showing a strong benefit of preventative aspirin, especially for the prevention of pre-term preeclampsia, the clear message is that low-dose aspirin is a treatment that should be offered to women with risk factors, such as, a history of preeclampsia.[16-18]

There is no doubt that eclampsia results in substantial morbidity for both mother and neonate. Whilst there were no reported maternal deaths, some women experienced very serious complications with life-long consequences, including cerebral haemorrhage. Additionally, there is a high level of reported cognitive failure, depression and anxiety in women following eclampsia,[19] with follow-up an area that warrants more attention both clinically and in the research arena. Antenatal eclampsia in particular was associated with poor fetal outcomes with nearly one in four infants born with a five minute Apgar less than seven, indicative of an increased likelihood of neonatal and infant death, neurologic disability and poor educational outcomes.[20-22]

Our study has a number of strengths and limitations. This was a bi-national population-based study. We were unable to ascertain any missed cases and although the rate of eclampsia in our study was close to our expected rate, it is lower than that reported in a New South Wales hospital and perinatal data linkage study.[23] However, the accuracy of eclampsia recorded in both hospital and perinatal data is rated as poor.[24] A population-based validation study on eclampsia in Victoria reported 4 confirmed cases per 10,000 confinements in 1995[25] – a rate more in line with ours given the reduction in eclampsia cases seen following the MAGPIE trial.[9,26] Like many population-based studies on eclampsia, we did not have data on the preeclampsia population from which the eclampsia cases arose. Furthermore, due to a number of reasons, including server upgrade and movement of AMOSS to a new host university, there has been a delay in reporting the results of this study and the reported results may not reflect the current clinical situation.

Eclampsia is an uncommon event in Australia and New Zealand and there were missed opportunities to potentially prevent preeclampsia, and thus eclampsia, with low dose aspirin. Addressing possible contributory factors, for instance, barriers to engagement with antenatal care, is paramount, particularly in high-risk populations such as Aboriginal and/or Torres Strait Islander women. Neonates were adversely affected by their mother's eclampsia, further emphasising the need to prevent eclampsia.

Box 1: Eclampsia case definition and inclusion criteria

Table 1: Maternal characteristics

Table 2: Markers of clinical condition

Table 3: Eclampsia management and outcomes

Table 4: Neonatal outcomes and timing of first eclamptic fit

Supplementary Figure 1: Recruitment summary

Supplementary Figure 2: Gestational age by the timing of first eclamptic fit

References

1. Altman D, Carroli G, Duley L, et al. Do women with preeclampsia, and their babies, benefit from magnesium sulphate? The Magpie Trial: a randomised placebo-controlled trial. Lancet. 2002;**359**:1877-90.

2. Abalos E, Cuesta C, Grosso AL, et al. Global and regional estimates of preeclampsia and eclampsia: a systematic review. European Journal of Obstetrics & Gynecology and Reproductive Biology. 2013;**170(1)**:1-7.

3. Schaap TP, Knight M, Zwart JJ, et al. Eclampsia, a comparison within the International Network of Obstetric Survey Systems. BJOG: An International Journal of Obstetrics & Gynaecology. 2014;**121**:1521-8.

4. Sullivan E, Dickinson J, Vaughan G, et al. Maternal super-obesity and perinatal outcomes in Australia: a national population-based cohort study. BMC Pregnancy and Childbirth. 2015;**15(1)**:322.

5. McDonnell N, Knight M, Peek MJ, et al. Amniotic fluid embolism: an Australian-New Zealand population-based study. BMC Pregnancy and Childbirth. 2015;**15(12)**:1-7.

6. Halliday LE, Peek MJ, Ellwood DA, et al. The Australasian Maternity Outcomes Surveillance System: An evaluation of stakeholder engagement, usefulness, simplicity, acceptability, data quality and stability. Australian and New Zealand Journal of Obstetrics and Gynaecology. 2013;**53**:152-7.

7. Vaughan G, Pollock W, Peek MJ, et al. Ethical issues: The multi-centre low-risk ethics/governance review process and AMOSS. Aust N Z J Obstet Gynaecol. 2012;**52**:195-203.

8. New York City Department of Health and Mental Hygiene. Severe Maternal Morbidity in New York City, 2008-2012. New York. NY; 2016.

9. Schenone MH, Miller D, Samson JE, Mari G. Eclampsia characteristics and outcomes: a comparison of two eras. Journal of Pregnancy. 2013; http://dx.doi.org/10.1155/2013/826045.

10. Li Z, Zeki R, Hilder L, Sullivan E. Australia's mothers and babies 2011. Perinatal statistics series no. 28. Cat. no. PER 59. Canberra: AIHW National Perinatal Epidemiology and Statistics Unit.; 2013.

11. Australian Institute of Health and Welfare 2017. Maternal deaths in Australia 2012–2014. Cat. no. PER 92. Canberra: AIHW.

12. PMMRC. Seventh Annual Report of the Perinatal and Maternal Mortality Review Committee: Reporting mortality 2011. Wellington: Health Quality and Saftey Commission. 2013.

13. Lowe SA, Bowyer L, Lust K, et al. SOMANZ guidelines for the management of hypertensive disorders of pregnancy 2014. Australian and New Zealand Journal of Obstetrics and Gynaecology. 2015;**55**:e1-e29.

14. Lowe S, Brown M, Dekker G, et al. SOMANZ Guidelines for the management of hypertensive disorders of pregnancy 2008. Society of Obstetric Medicine of Australia and New Zealand, Sydney, 2008.

15. Helou A, Walker S, Stewart K, George J. Management of pregnancies complicated by hypertensive disorders of pregnancy: Could we do better? Australian and New Zealand Journal of Obstetrics and Gynaecology. 2017;**57**:253-9.

16. Tolcher MC, Chu DM, Hollier LM, et al. Impact of USPSTF recommendations for aspirin for prevention of recurrent preeclampsia. American Journal of Obstetrics and Gynecology. 2017;**217**:365.e1-.e8.

17. Poon LC, Wright D, Rolnik DL, et al. Aspirin for Evidence-Based Preeclampsia Prevention trial: effect of aspirin in prevention of preterm preeclampsia in subgroups of women according to their characteristics and medical and obstetrical history. American Journal of Obstetrics & Gynecology. 2017;**217**:585. e1-. e5.

18. Rolnik DL, Wright D, Poon LC, et al. Aspirin versus Placebo in Pregnancies at High Risk for Preterm Preeclampsia. New England Journal of Medicine. 2017;**377**:613-22.

19. Postma IR, Bouma A, Ankersmit IF, Zeeman GG. Neurocognitive functioning following preeclampsia and eclampsia: a long-term follow-up study. American Journal of Obstetrics and Gynecology. 2014;**211**:37.e1-.e9.

20. Iliodromiti S, Mackay DF, Smith GCS, et al. Apgar score and the risk of cause-specific infant mortality: a population-based cohort study. The Lancet. 2014;**384**:1749-55.

21. Ehrenstein V, Pedersen L, Grijota M, et al. Association of Apgar score at five minutes with long-term neurologic disability and cognitive function in a prevalence study of Danish conscripts. BMC Pregnancy and Childbirth. 2009;**9**:14.

22. Stuart A, Otterblad Olausson P, Källen K. Apgar Scores at 5 Minutes After Birth in Relation to School Performance at 16 Years of Age. Obstetrics & Gynecology. 2011;**118**:201-8.

23. Thornton C, Dahlen H, Korda A, Hennessy A. The incidence of preeclampsia and eclampsia and associated maternal mortality in Australia from population-linked datasets: 2000-2008. American Journal of Obstetrics & Gynecology. 2013;**208(6)**:476.e1-.e5.

24. Lain SJ, Hadfield RM, Raynes-Greenow CH, et al. Quality of data in perinatal population health databases: a systematic review. Medical care. 2012;**50(4)**:e7-e20.

25. Riley M, Halliday J. The accuracy of eclampsia cases reported to the Victorian Inpatient Minimum Database and the Perinatal Data Collection Unit. Health Information Management. 1998;**28**:13-5.

26. Knight M. Eclampsia in the United Kingdom 2005. BJOG: An International Journal of Obstetrics and Gynaecology. 2007;**114**:1072-8.

Box 1: Eclampsia case definition and inclusion criteria

Case definition: Eclampsia was defined as seizure/s in a woman during pregnancy or in the first 14 days postpartum not caused by any concurrent neurological disease such as epilepsy, together with at least two of the following features within 24 hours of the seizure/s:

- Hypertension (BP >=140 systolic or >=90 diastolic)
- Renal involvement
    - Proteinuria (at least 2+ protein in a random urine sample or ≥ 30mg/mmol in a spot urine protein/creatinine ratio or ≥ 0.3g in a 24 hour collection)
    - serum creatinine > 90µmol/L
- Haematological involvement
    - Thrombocytopenia (platelet count of less than 100 $x10^9$/L)
    - Haemolysis
    - Disseminated Intravascular Coagulopathy
- Liver involvement
    - Raised plasma alanine aminotransferase concentration (>42iu/l), or an increased plasma aspartate aminotransferase concentration (>42iu/l)
    - Severe epigastric pain or right upper quadrant pain
- Pulmonary oedema
- Placental involvement
    - Fetal growth restriction
    - Placental abruption

Table 1: Maternal characteristics

Maternal characteristic	n data available on	Cases (%) or Median (IQR)
Woman born outside Australia/New Zealand	136	30 (22.1%)
Indigenous status	136	
Aboriginal &/or Torres Strait Islander	111	9 (8.1%)
Maori	25	5 (20%)
Age	136	
<20 years		23 (16.9%)
20-24 years		23 (16.9%)
25-29 years		30 (22.1%)
30-34 years		33 (24.3%)
35+		27 (19.9%)
BMI (kg/m^2)	122	
< 18.5		5 (4.1%)
18.5-24.9		57 (46.7%)
25-29.9		28 (22.9%)
30 – 34.9		13 (10.7%)
35^+		19 (15.6%)
Hospital sector*	135	
Public		115 (85.2%)
Private		20 (14.7%)
Smoking status	126	
Never smoked during pregnancy		88 (69.8%)
Smoked in pregnancy		38 (30.2%)
ART conception	130	6 (4.4%)
Parity	136	
Nulliparous/primiparous		93 (68.4%)
Multiparous		43 (31.6%)
Multiple gestation	136	6 (4.4%)
Chronic hypertension	133	5 (3.7%)
Chronic renal failure	132	2 (1.5%)
Preeclampsia in a prior pregnancy (multiparous only)	42	12 (28.6%)
Eclampsia in a prior pregnancy (multiparous only)	43	3 (7.0%)

BMI Body Mass Index; * $p < .05$ – however private patients who experienced early-onset preterm preeclampsia or eclampsia at home may not have gone to a private hospital

Table 2: Markers of clinical condition

Evident in week prior to first eclamptic seizure	Data available on n	Cases (%) or Median (IQR)
Systolic BP ≥ 140 mmHg	120	87 (72.5%)
Systolic BP ≥ 160 mmHg		48 (40.0%)
Systolic BP ≥ 170 mmHg		32 (26.7%)
Diastolic BP ≥ 90 mmHg	120	90 (75.0%)
Diastolic BP ≥ 110 mmHg		31 (25.8%)
Proteinuria		
24hr urine collection	33	310 (165-605)
24hr ≥ 300mg		21 (63.6%)
Spot protein/creatinine ratio	63	130 (39-589)
Spot protein/creatinine ratio ≥ 30mg/mmol		51 (80.9%)
Premonitory symptoms		
Headache	126	86 (63.2%)
Hyper-reflexia	117	62 (45.6%)
Visual disturbance	121	50 (36.8%)
Epigastric/RUQ pain	117	30 (22.1%)
Nausea/vomiting	126	30 (22.1%)
Worst recorded result during/after first eclamptic seizure		
Systolic BP ≥ 140 mmHg	136	133 (97.8%)
Systolic BP ≥ 160 mmHg		105 (77.2%)
Systolic BP ≥ 170 mmHg		77 (56.6%)
Diastolic BP ≥ 90 mmHg	135	128 (94.8%)
Diastolic BP ≥ 110 mmHg		60 (44.4%)
Proteinuria		
24hr urine collection	37	400 (202-872)
24hr ≥ 300mg		25 (67.6%)

Spot protein/creatinine ratio	82	117 (41-552)
Spot protein/creatinine ratio ≥ 30mg/mmol		68 (82.9%)
Haemolysis on FBE	108	20 (18.52%)
Serum AST (IU/L)	113	49.0 (31.0-130.5)
Maximum reported		2447
AST > 42		62 (45.6%)
Serum ALT (IU/L)	125	34.0 (18.0-80.5)
Maximum reported		3000
ALT > 42		54 (39.7%)
Platelet count (x 10^9/L)	131	159 (98-230)
Minimum reported		27
< 50,000		8 (5.9%)
50,000-99,999		27 (19.9%)
100,000-149,999		25 (18.4%)
≥ 150,000		71 (52.2%)

AST aspartate transaminase；ALT alanine transaminase

Table 3: Eclampsia management and outcomes

	Antenatal n=58 Cases(%) or Median(IQR)	**Intrapartum n=33** Cases(%) or Median(IQR)	**Postpartum n=45** Cases(%) or Median(IQR)	**All (n=136)**
Diagnosis of preeclampsia prior to eclampsia	25/56 (44.6%)	16/33 (48.5%)	22/44 (50.0%)	63/133 (47.4%)
Magnesium sulphate prophylaxis (in women with a diagnosis of preeclampsia before eclampsia)	3/25(12.0%)	4/16(25.0%)	12/22(54.5%)	19/63 (30.2%)
Recurrent seizure	21 (36.2%)	5 (15.2%)	18 (40.0%)	44 (32.4%)
Received antihypertensive after first seizure	40 (69.0%)	20 (60.6%)	35 (77.8%)	95 (69.9%)
Preterm birth <37 weeks	35/56 (62.5%)	7/33 (21.2%)	9/45 (20.0%)	51/134 (38.1%)
Any labour	12/56 (21.4%)	28/33 (84.8%)	32/45 (71.1%)	72/134 (53.7%)
Induction of labour	11/12 (91.7%)	14/28 (50.0%)	15/32 (46.9%)	40/72 (55.6%)
Analgesia/anaesthesia				
None	1/55 (1.8%)	0/33	6/44 (13.6%)	7/132 (5.3%)
N_2O/opiods/pudendal or caudal block	2/55 (3.6%)	8/33 (24.2%)	8/44 (18.2%)	18/132 (13.6%)
Epidural	3/55 (5.5%)	9/33 (27.3%)	11/44 (25.0%)	23/132 (17.4%)
Spinal	11/55 (20.0%)	4/33 (12.1%)	11/44 (25.0%)	26/132 (19.7%)
Combined epidural/spinal	6/55 (10.9%)	1/33 (3.0%)	3/44 (6.8%)	10/132 (7.6%)
General anaesthesia	32/55 (58.2%)	11/33 (33.3%)	5/44 (11.4%)	48/132 (36.4%)
Caesarean birth	48/56 (85.7%)	19/33 (57.6%)	22/44 (50.0%)	89/133 (66.9%)
Admitted to ICU	29/55 (52.7%)	10/33 (30.3%)	17/43 (39.5%)	56/131 (42.7%)
Admitted to HDU	20/54 (37.0%)	15/33 (45.5%)	18/44 (18.2%)	53/131 (40.5%)
Transferred to another hospital	18/58 (25.9%)	5/33 (15.2%)	11/45 (24.4%)	34/136 (25.0%)
Acute blindness	0/54	0/32	2/41 (4.9%)	2/127 (1.6%)
Acute pulmonary oedema	4/55 (7.3%)	1/32 (3.1%)	2/40 (5.0%)	7/127 (5.5%)

Acute kidney injury	4/55 (7.3%)	1/32 (3.1%)	1/41 (2.4%)	6/128 (4.7%)
Cerebrovascular haemorrhage	1/54 (1.9%)	1/32 (3.1%)	3/43 (7.0%)	5/129 (3.9%)
DIC	1/54 (1.9%)	0/31	0/41	1/126 (0.8%)
HELLP syndrome	11/55 (20.0%)	5/32 (15.6%)	10/41 (24.4%)	26/128 (20.3%)
Obstetric haemorrhage ≥ 1000mL	3/53 (5.7%)	6/33 (18.2%)	2/43 (4.7%)	11/129 (8.5%)
Other complications*	8/53 (15.1%)	2/32 (6.3%)	2/39 (5.1%)	12/124 (9.7%)

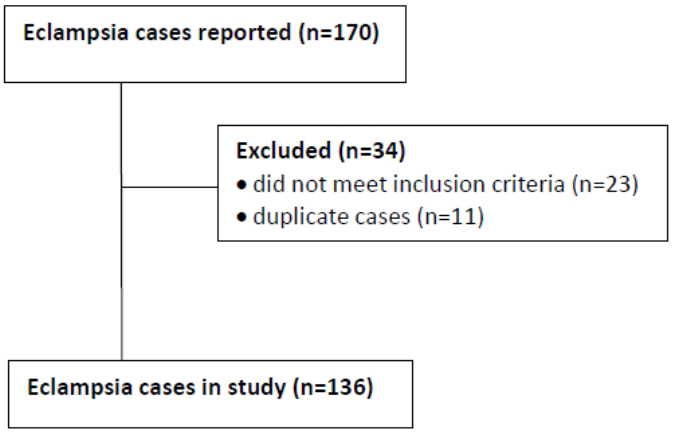
ICU Intensive Care Unit; HDU High Dependency Unit; DIC Disseminated Intravascular Coagulopathy; HELLP Haemolysis, Elevated Liver enzymes, Low Platelets; *includes one liver laceration

Table 4: Neonatal outcomes and timing of first eclamptic fit

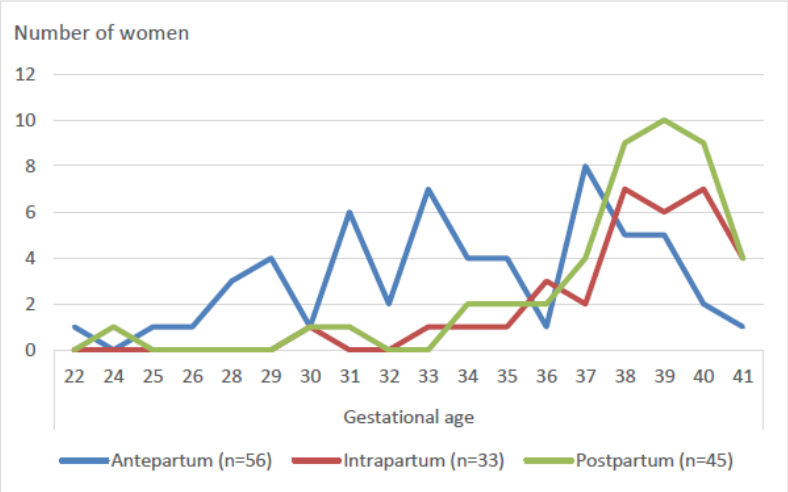
	Antenatal n=60 Cases(%) or Median(IQR)	**Intrapartum n=34** Cases(%) or Median(IQR)	**Postpartum n=48** Cases(%) or Median(IQR)	**All n=142*** Cases(%) or Median(IQR)
Birth gestation	(n=56)			
≤ 27 weeks	3 (5.4%)	0 (0.0%)	1 (2.2%)	4 (3.0%)
28-31 weeks	14 (25.0%)	1 (3.0%)	2 (4.4%)	17 (12.7%)
32-33 weeks	9 (16.1%)	1 (3.0%)	0 (0.0%)	10 (7.5%)
34-36 weeks	9 (16.1%)	5 (15.2%)	6 (13.3%)	20 (14.9%)
≥ 37 weeks	21 (37.5%)	26 (78.8%)	36 (80.0%)	83 (61.9%)
Birthweight				
< 1500g	19/57 (33.3%)	1/34 (2.9%)	3/48 (6.3%)	23/139 (16.5%)
1500-2499g	18/57 (31.6%)	5/34 (14.7%)	4/48 (8.3%)	27/139 (19.4%)
≥ 2500g	20/57 (35.1%)	28/34 (82.4%)	41/48 (85.4%)	89/139 (64.0%)
5 min Apgar < 7	13/55 (23.6%)	4/31 (12.9%)	2/47 (4.3%)	19/133 (14.3%)
Admitted to NICU	49/56 (87.5%)	14/32 (43.8%)	11/46 (23.4%)	74/134 (55.2%)
Breathing support				
Nil				
CPAP (mask only)	22/54 (40.7%)	20/30 (66.7%)	37/44 (84.1%)	79/128 (61.7%)
Intubated (CPAP	14/54 (25.9%)	7/30 (23.3%)	5/44 (11.4%)	26/128 (20.3%)
only)	3/54 (5.6%)	1/30 (3.3%)	1/44 (2.3%)	5/128 (3.9%)
Intubated and				
ventilated	15/54 (27.8%)	2/30 (6.7%)	1/44 (2.3%)	18/128 (14.1%)
Not known	4	3	3	10
Transferred out & lost to follow-up	16/60 (25.0%)	3/34 (9.1%)	7/48 (14.9%)	26/142 (18.3%)
Perinatal death				
Fetal death	2/58 (3.4%)	1/34 (2.9%)	1/48 (2.1%)	4/140 (2.9%)
Neonatal death	1/42 (2.4%)	0/30 (0.0%)	0/40 (0.0%)	1/112 (0.9%)

* Multiple gestation [antepartum x 2 (31 & 33 weeks); intrapartum x 1 (38 weeks); postpartum x3 (36, 37 & 38 weeks)];

NICU Neonatal Intensive Care Unit; CPAP Continuous Positive Airway Pressure



Supplementary Figure 1: Recruitment summary



Supplementary Figure 2: Gestational age by the timing of first eclamptic seizure