Our Experience with Eclampsia in Singapore

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ABSTRACT

Aim: To assess the incidence, epidemiological factors, preceding symptoms and signs, management regimens and obstetric outcomes of eclampsia in a tertiary care hospital in Singapore.

Method: A retrospective study of all obstetric patients who suffered one or more eclamptic seizures in our hospital between January 1994 and December 1999.

Result: There were 62 cases of eclampsia among 92,305 deliveries (6.7 per 10,000 deliveries). The incidence was highest among Indians. Those aged between 25 and 34 had the lowest incidence, while women younger than 25 or older than 34 had a significantly higher incidence. Forty (64.5%) patients had symptom or sign of impending eclampsia of which headache was the most common. Most of the patients (81.6%) who received antenatal care with us suffered their first eclamptic seizure in hospital, compared to 50% of the unbooked patients. There was one maternal death (mortality rate 1.6%), and 15 (24.2%) women had significant morbidity. There were 61 singleton pregnancies and one twin pregnancy. There were six intrauterine deaths and 57 livebirths. The perinatal mortality rate was 95.2 per 1,000 births.

Conclusion: Eclampsia is still a major cause of maternal and foetal mortality and morbidity in Singapore. Race and age appear to be risk factors for eclampsia with Indian women and those at the extremes of reproductive age at greater risk. Antenatal care is important in reducing perinatal mortality and possibly maternal complications.

Keywords: eclampsia, incidence, symptom, mortality, Singapore

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INTRODUCTION

Eclampsia remains an important obstetric condition that causes significant maternal and perinatal mortality and morbidity worldwide. This study reviewed all the eclampsia cases that were treated in KK Women's & Children's Hospital, the largest referral maternity hospital in Singapore between January 1994 and December 1999.

The reported incidence of eclampsia ranges from 0.05% to 0.2% of all deliveries. Maternal mortality from eclampsia ranges from less than 1% to nearly 20%, but in recent years figures of less than 5% have prevailed[1]. Similarly, the perinatal mortality rate has decreased to between 10-28%[2].

Differences in the figures quoted are often attributed to differences in population demographics and in the availability and standard of obstetric care in the study population. This survey was undertaken to assess the incidence of eclampsia, the epidemiological factors, symptoms and signs preceding eclampsia, management regimens, maternal and perinatal morbidity and mortality among the obstetric patients in Singapore.

MATERIALS AND METHOD

KK Women's & Children's Hospital is a tertiary hospital for obstetrics, gynaecology and neonatology with about 15,000 deliveries annually and a perinatal mortality rate of 5.3 per 1,000 births for the period between 1994 and 1999.

Eclampsia is defined as the occurrence of tonic-clonic convulsions between the 20th week of gestation and the 10th postpartum day, together with at least two of the following features within 24 hours of the convulsions: hypertension, proteinuria, thrombocytopenia, or raised plasma aspartate transaminases.

Hypertension is defined as systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg. Proteinuria is the presence of at least 1+ protein in a random urine sample or ≥ 0.3 g in a 24 hours urine collection. Thrombocytopenia is platelet count of less than 100×10^9/L. Plasma aspartate transaminases are considered as elevated if they are ≥ 42 U/L[3].

The case records of all the patients who had eclampsia or unexplained convulsion occurring during the antenatal, intrapartum or postpartum periods were reviewed together with the case records

of their babies. An electronic database of all patients delivered in our hospital is used to provide information on patient demographics. The results were analysed using the Statistical Package for the Social Sciences programme and the statistical significance calculated using Pearson Chi-square test or Fisher's Exact test when the numbers are small.

RESULTS

In the six years from January 1994 to December 1999, there were 62 cases of eclampsia among a total of 92,305 deliveries (6.7 per 10,000 deliveries) at KK Women's & Children's Hospital. The incidence was 6.1 per 10,000 deliveries in 1994, rising to 10.1 in 1995 and increasing further to 11.2 in 1996. After 1996, it decreased to an average incidence of 4.4 per 10,000 deliveries from 1997 to 1999 (Table I).

In our series of 62 eclampsia cases, there were 24 (38.7%) Chinese, 21 (33.9%) Malays, 13 (21.0%) Indians and 4 (6.4%) of other races. The incidence was highest in the Indians (14.2 per 10,000 deliveries). It was significantly more than that in the Chinese (6.2 per 10,000 deliveries, $p<0.05$) and the Malays (6.8 per 10,000 deliveries, $p<0.05$). There was no statistical difference between the incidences of Chinese, Malays and other minority groups (Table II).

The patients' ages ranged from 16 to 45 years, with a mean of 29.4 years and median of 29.5 years. The lowest incidence occurred among those aged 25 to 34 years (4.3 per 10,000 deliveries). The incidence was significantly higher in those younger than 25 (11.2 per 10,000 deliveries, $p=0.001$) and those older than 34 (11.8 per 10,000 deliveries, $p<0.001$). There was no statistical difference between the incidences of eclampsia among patients younger than 25 and those older than 34.

Forty (64.5%) patients were primiparous. For one patient, it was the first pregnancy in her second marriage.

Most of the patients had no significant medical history predisposing to pre-eclampsia. Six patients had pre-existing medical diseases. Three (4.8%) patients had a history of childhood epilepsy. Of these, two of them had been seizure-free for several years and had been discontinued from their anti-epileptic medication for at least five years prior to the eclamptic seizure. The third patient was compliant with her anti-epileptic medication, Carbamazepine, up to the time of her eclamptic seizure.

One patient had systemic lupus erythematosus. She had defaulted on her appointments with her rheumatologist and had not sought antenatal care. One patient was diagnosed as suffering from nephrotic syndrome after investigation for proteinuria in the first trimester, and one patient had hypothyroidism and was on thyroxine replacement.

Table I. Annual incidence of eclampsia in KKWCH.

Year	1994	1995	1996	1997	1998	1999
No. of cases	9	15	17	9	3	9
No. of Deliveries	14,809	14,812	15,155	15,962	15,686	15,881
Incidence *	6.1	10.1	11.2	5.6	1.9	5.7

* Incidence per 10,000 deliveries

Table II. Incidence of eclampsia among the different ethnic and age groups.

		No. of eclampsia	No. of deliveries	Incidence *
Race	Chinese	24	38,667	6.2
	Malay	21	30,814	6.8
	Indian	13	9,148	14.2
	Others	4	5,097	7.8
Age	<20	4	2,446	16.4
	20-24	14	13,603	10.3
	25-29	13	32,233	4.0
	30-34	13	28,475	4.6
	35-39	15	12,701	11.8
	>40	3	2,492	12.0

* Incidence per 10,000 deliveries

Table III. Frequency of symptoms and signs of impending eclampsia.

Symptom/Sign	Number (%)
Headache	31 (50.0%)
Hyper-reflexia	16 (25.8%)
Nausea	15 (24.2%)
Visual disturbance	13 (21.0%)
Epigastric pain	4 (6.5%)
None	15 (24.2%)
Not documented	7 (11.3%)

Forty (64.5%) patients had documented symptom or sign prior to the first convulsion. The most common symptom was headache, experienced by 31 (50.0%) patients. Sixteen (25.8%) patients had hyper-reflexia, and 15 (24.2%) patients complained of nausea. Visual disturbance was present in 13 (21%) patients, of whom six experienced blurring of vision and seven experienced complete blindness. All seven patients who had blindness recovered full vision within 48 hours. The frequencies of symptoms and signs of impending eclampsia are listed in Table III.

The last recorded systolic blood pressure immediately preceding the first eclamptic seizure ranged from 110 to 253 mmHg with a mean of 173 mmHg, and the diastolic blood pressure ranged from 70 to 173 mmHg with a mean of 103 mmHg. There were 12 (19.4%) patients who had systolic blood pressure less than 160 mmHg, and 40 (64.5%) patients with diastolic blood pressure less than 110 mmHg. Six (9.7%) patients had blood pressure equal to or less than 140/90 mmHg prior to the first seizure. One patient suffered an eclamptic seizure at

Table IV. Severity of Proteinuria.

Proteinuria	Nil	1+	2+	3+	4+	Unknown
Number	5	9	12	11	19	6
Percentage (%)	8.1	14.5	19.4	17.7	30.6	9.7

Table V. Comparison of eclampsia in different populations.

	KKH (1994 – 1999)	United Kingdom (1992)	Melbourne Hospitals # (1978 – 1992)
Antepartum (%)	61.30	38.0	58.0
Intrapartum (%)	19.35	18.0	10.0
Postpartum (%)	19.35	44.0	32.0
Incidence *	6.7	4.9	3.9
Maternal mortality (%)	1.6	1.8	5.6
Perinatal mortality ^	95.2	54.2	181.0

* Incidence per 10,000 deliveries
^ Perinatal mortality rate per 1,000 births
# Mercy Maternity Hospital. Queen Victoria Hospital & The Royal Women's hospital

home, and subsequently presented to our emergency room in hypovolemic shock secondary to abruptio placentae. Her first recordable blood pressure was 112/60 mmHg.

Fifty-one (82.2%) patients had significant proteinuria. There were 5 (8.1%) patients with no proteinuria, and urine analysis for proteinuria was not documented in 6 (9.7%) patients (Table IV).

Thirty-eight (61.3%) patients received antenatal care at KKH with at least two antenatal visits. Twelve (19.4%) of them had their booking visit in the first trimester, 20 (32.3%) in the second trimester and 6 (9.7%) in the third trimester. Ten patients received antenatal care outside our hospital: nine with private obstetricians and one with a general practitioner. One patient on antenatal follow-ups had elevated blood pressure and complained of headache, but refused admission into hospital against her doctor's advice. She subsequently suffered an eclamptic convulsion prior to admission. Another patient defaulted on her appointments after 39 weeks amenorrhoea due to financial and family problems and was admitted in labour at 45 weeks amenorrhoea.

The patient with systemic lupus erythematosus had no antenatal care. During her admission to a general hospital for management of her SLE, she developed eclampsia and was referred to our hospital. All three patients with a history of epilepsy received antenatal care and the patient who was on medication was jointly managed with her neurologist. They were all free from seizure during pregnancy prior to the onset of eclampsia.

Forty-three (69.4%) patients experienced their first convulsion in hospital, of which two occurred immediately upon admission before clinical review. Most (81.6%) of the patients who received antenatal care with us suffered their first eclamptic seizure in hospital, compared to the unbooked patients where only 50% of them had their first seizure in the hospital.

Thirty-eight (61.3%) patients had their first eclamptic seizure in the antepartum period, the earliest occurred at 24 weeks amenorrhoea. There were 12 (19.35%) patients each in the intrapartum and postpartum periods. Ten cases of postpartum eclampsia occurred within 24 hours of delivery while the remaining two were late postpartum eclampsia[4] occurring more than 72 hours after delivery (7 and 9 postpartum day respectively).

Most of the antepartum eclampsia (76.3%) occurred among patients who were less than 37 completed weeks of amenorrhoea, while most of postpartum eclampsia (66.7%) occurred in term patients. All three cases of preterm postpartum eclampsia had symptoms and signs of impending eclampsia before delivery. Two of these patients underwent emergency Caesarean section for impending eclampsia and one had an assisted vaginal delivery. All the intrapartum eclampsia occurred in term patients.

The majority (67.7%) of the patients experienced only one seizure, and only 1 (1.6%) patient suffered more than three seizures.

Thirty-seven (97.4%) of the 38 patients with antepartum eclampsia were delivered by emergency Caesarean section. All the Caesarean sections were performed within 24 hours of the first convulsion except for one patient who was transferred from another hospital where she was being treated for acute exacerbation of systemic lupus erythematosus. Her Caesarean section was performed 33 hours after her first convulsion. Only one patient with antepartum eclampsia was delivered vaginally after prostaglandin pessary induction.

Of the 12 patients who suffered an intrapartum eclamptic seizure, six had a fully dilated cervix at the time and vaginal delivery was achieved in five of them, the remaining one had a failed vacuum attempt and was delivered by Caesarean section. The other six who did not have a fully dilated cervix at the time of eclampsia were delivered by Caesarean section. Of the 12 patients with post-partum eclampsia, five were delivered by Caesarean section and in four of these cases the indication for Caesarean section was impending eclampsia.

Overall, 49 (79.0%) patients underwent a Caesarean section. Five (8.1%) patients had assisted vaginal deliveries and 8 (12.9%) had normal vaginal deliveries.

There was one maternal death (mortality rate 1.6%) resulting from multi-organ failure complicating eclampsia. This patient was a 45-year-old Malay woman in her 7th pregnancy. Her first five pregnancies had been uneventful. She developed severe pre-eclampsia during her 6th pregnancy and suffered an eclamptic seizure at 26 weeks gestation, with an intra-uterine foetal demise. She defaulted on her postnatal appointment. For her 7th pregnancy, she did not seek antenatal care and presented to our hospital after suffering a tonic-clonic seizure at home. Upon admission, she was unresponsive, her blood pressure was 229/152 mmHg and she had proteinuria of 4+ on labstix. An ultrasound examination confirmed intra-uterine foetal demise with foetal parameters corresponding to 26 weeks gestation. Her blood pressure was controlled with hydralazine infusion, and she received diazepam infusion to prevent further seizures. However her condition deteriorated rapidly and she developed disseminated intravascular coagulopathy, renal failure and liver failure. The foetus was delivered vaginally 48 hours later following vaginal prostaglandin induction. She died four days after admission from multi-organ failure.

Fifteen other patients had significant morbidity (24.2%). The HELLP syndrome was the most common maternal complication (four patients), followed by abruptio placentae (3); cerebral infarct (3) and pulmonary oedema (3). All three patients with abruptio placentae suffered intrauterine foetal demise, one had associated thrombocytopenia and one developed disseminated intravascular coagulopathy. Seventeen (27.4%) patients had persistent hypertension in the postnatal period, of which eight of them defaulted on their follow-up appointment after discharge. One patient suffered chronic renal impairment following acute renal failure during the puerperium and required follow-up with a renal physician. All three patients who suffered cerebral infarct confirmed on computed tomography recovered completely with no neurological deficit.

The patients who were booked had a lower rate of maternal complications (26.3%) compared to the unbooked cases (45.8%), but this was not statistically significant (p>0.05).

The gestation at the time of eclampsia ranged from 24.0 to 45.4 weeks with a mean of 35.0 weeks. The birth-weight of the babies ranged from 550 g to 3,985 g with a mean weight of 2,211 g and a median weight of 2,295 g.

Of the 62 pregnancies complicated by eclampsia, 61 were singleton pregnancies and one was a twin pregnancy. There were six intrauterine deaths and 57 livebirths. There was no neonatal death. The perinatal mortality rate was 95.2 per 1,000 births. The perinatal mortality rate was significantly higher in the patients who did not receive antenatal care compared to those that did (20.8% versus 2.6%, Fisher's Exact Test p< 0.05).

At one minute after birth, 13 of the livebirths (22.8%) had Apgar score of 3 or less and another 20 (35.1%) had Apgar score between 4 and 7. At five minutes after birth, almost all the babies had Apgar score above 3 (98.2%).

DISCUSSION

The incidence of eclampsia has decreased significantly from the early part of the century, but has remained relatively constant over the last 15 to 30 years in many countries. The maternal and perinatal mortality from this serious condition on the other hand has continued their decreasing trend. In the United Kingdom, the incidence has declined from 80 per 10,000 deliveries in 1922 to 4.9 per 10,000 deliveries in 1992[3]. In New Zealand, the incidence declined from 32 per 10,000 deliveries (1928-1933) to 8 per 10,000 deliveries (1956-1958)[5]. In Singapore, the incidence has also declined significantly from 28.7 per 10,000 deliveries in 1957 to 14 per 10,000 deliveries in 1968[2] and even further to 6.7 per 10,000 deliveries in our series (1994-1999).

An Eclampsia Registry was established by our hospital in the latter part of 1994. The low rate prior to this might have been due to an under-ascertainment of the cases. The increase in incidence from 1994 to 1996 might be contributed in part by an actual increase in the incidence locally, more accurate diagnosis and reporting of cases and a higher number of tertiary referrals of high-risk patients. The subsequent decrease might be due to a trend towards earlier delivery of patients with severe pre-eclampsia or impending eclampsia, as a result of increased awareness among obstetricians of the seriousness of severe hypertensive disorders in pregnancy. Antenatal care and education of obstetricians are important in reducing both maternal and perinatal morbidity and mortality.

The observed difference in the incidences among the races might be due to a genetic predisposition or differences with regards to socio-economic status, diet and antenatal care received. Our study supports previous data that suggested the incidence of eclampsia is higher among teenagers and those above the age of 34. This correlates with findings in the United Kingdom and the United States where there was a three- to five-fold increase in eclampsia among teenage patients[3,6].

The proportion of antenatal eclampsia in our study was relatively higher than that reported in the United Kingdom of 38%[3]. It is however similar to that in three teaching hospitals in Melbourne where antenatal eclampsia accounted for 58% of their eclampsia

cases[7]. Our proportion of postpartum eclampsia was however the lowest at 19.35%, compared to 44% in the United Kingdom and 32% in Melbourne (Table V).

The high incidence of antenatal eclampsia in our hospital is important as they contribute significantly to maternal and perinatal mortality[8]. Five of the six intrauterine foetal deaths occurred in those patients with antenatal eclampsia. Our perinatal mortality rate of 95.2 per 1,000 births (consisting entirely of stillbirths) is higher than that of the United Kingdom where the perinatal mortality rate was 54.2 per 1,000 births (stillbirth and neonatal mortality rates of 22.2 and 32.0 per 1,000 births respectively)[3]. It is however lower than that in the Melbourne study where the perinatal mortality rate was 181.0 per 1,000 births (stillbirth and neonatal mortality rates of 127.7 and 53.3 per 1,000 births respectively)[7].

The maternal mortality rate in our eclampsia study was 1.6% (one out of 62 cases), while it was 1.8% in the United Kingdom (seven out of 383 cases)[3] and 5.6% in the Melbourne hospitals (five out of 90 cases)[7]. The majority of patients had some preceding symptom or sign of impending eclampsia, therefore it is important to educate the patients to report these to their doctors, and for the doctors to treat these complaints seriously.

In our hospital, there is a management protocol for eclampsia. This includes guidelines for fluid therapy, anticonvulsant therapy and antihypertensive medications as well as the necessary investigations for monitoring the progress of the disease.

From 1994 to October 1996, intravenous hydralazine was the first line anti-hypertensive agent recommended for acute management of elevated blood pressure in severe pre-eclampsia. Intravenous labetolol was added if the blood pressure remained elevated or the patient developed tachycardia. The anticonvulsant agent for seizure prophylaxis and control was intravenous diazepam. After October 1996, both intravenous hydralazine and labetalol were available as first line anti-hypertensive agents. The anticonvulsant of choice for recurrent seizure prophylaxis was also changed from diazepam to magnesium sulphate following the results from the Collaborative Eclampsia Trial[9].

Intravenous hydralazine was used to control the blood pressure in 29 patients. The concomitant use of intravenous labetalol was necessary in 10 patients to achieve satisfactory control. Intravenous labetalol was used alone in 13 patients, mostly in cases occurring after October 1996 following the change in our protocol. One patient continued to have elevated blood pressure in spite of intravenous hydralazine, labetalol and esmolol, and required the addition of intravenous sodium nitroprusside to achieve control.

Controlling the blood pressure in these patients does not stop the progression of the disease but it prevents complications directly related to maternal hypertension. We had no patient who suffered cerebral haemorrhage as compared to other studies, which may be due to our management protocol regarding anti-hypertensive therapy achieving good blood pressure control in most patients.

The main anti-hypertensive agents used in our hospital include hydralazine, labetalol, nifedipine and sodium nitroprusside (in one case of very resistant hypertension). Hydralazine dilates the capacitance vessels followed by subsequent dilatation of the resistance vessels[10], thus causing severe headache, anxiety, restlessness and hyper-reflexia in up to 50% of patients in some studies due to prolonged release of noradrenaline which may mimic the symptoms of impending eclampsia[11]. Labetalol has recently found favour as it lowers blood pressure smoothly, rapidly and without tachycardia or the other side effects associated with hydralazine[11].

Experience with the use of nifedipine in pre-eclampsia and eclampsia cases is increasing and in an observational study by Redman, it appeared to be as safe and effective as hydralazine and its effect on the foetal or uteroplacental circulation as assessed by Doppler flow study has been reassuring[11]. Caution is necessary when starting magnesium sulphate in a patient treated with calcium channel blockers as there may be a synergistic effect causing a precipitous fall in blood pressure.

Sodium nitroprusside is potentially toxic to the foetus[11] and is rarely used in obstetric patients. It was used in one of our patient who already had an intrauterine death when the blood pressure remained dangerously high in spite of high doses of intravenous hydralazine, labetalol and esmolol.

Result from the Collaborative Trial showed that magnesium sulphate was superior to either diazepam or phenytoin in preventing recurrent eclamptic seizures[9]. In the earlier years, diazepam was our drug of choice for terminating seizures as well as prophylaxis against recurrent seizure. After 1996, when magnesium sulphate became the anti-convulsant of choice in our protocol for the management of eclampsia, it was used in 19 (79.2%) of the 24 eclampsia cases. In spite of this, familiarity with diazepam and the ease of administration has continued to make diazepam a popular drug for seizure termination with our doctors. It was used in 45 (72.6%) patients in our series.

CONCLUSION
Eclampsia is still a major cause of maternal and foetal mortality and morbidity in Singapore. The incidence

of eclampsia in our hospital over the last six years has been 6.7 per 10,000 deliveries.

Race and age appear to be risk factors for eclampsia with Indians, teenagers and patients older than 34 years old at greater risk. Majority of the patients had some preceding symptom or sign and due attention must be given to them.

Our current screening methods do not identify all the patients at risk of developing eclampsia. Monitoring of high-risk patients may reduce the complication rate but does not prevent eclampsia. A search for screening markers outside the traditional clinical indicators of elevated blood pressure and proteinuria is needed to decrease the incidence of eclampsia further.

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