A review of 93 cases of severe preeclampsia in Singapore: are there risk factors for complications?

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ABSTRACT

Introduction: This study aims to assess the epidemiology of severe preeclampsia in Singapore, the disease characteristics, maternal and perinatal outcome, and to identify risk factors for complications.

Methods: Data of 93 consecutive women with severe preeclampsia in KK Women's and Children's Hospital in Singapore was collected prospectively and analysed using the unpaired t-test for normally-distributed continuous variables and Fisher's exact chi-square test for discrete variables. Multivariate logistic regression analysis was performed for prediction of complicated cases.

Results: The incidence of severe pre-eclampsia was 29.3 per 10,000 deliveries, with an increased risk in women who were aged more than 35 years and who were nulliparous. The risk was also increased in women of the Malay race and they also had the tendency to book later, compared with the other races. 43 percent of women had maternal complications, including eclampsia, haemolysis/elevated liver enzymes/low platelets syndrome, oliguria, pulmonary oedema and placental abruption. Significantly raised levels of uric acid (439.5 +/- 114.1 µmol/L versus 395.4 +/- 96.7 µmol/L, p-value equals 0.047) and aspartate transaminase (80.1 +/- 107.41 U/L versus 38.8 +/- 16.1 IU/L, p-value equals 0.021) were found in those with complications, compared to those without complications. The average gestation at time of diagnosis was 33 weeks and the average gestation at delivery was 34 weeks. 89.3 percent of women required caesarean section and 59.1 percent of women were admitted to intensive care.

Conclusion: Age, parity and race are risk factors for severe preeclampsia with increased levels of uric acid and aspartate transaminase found in the complicated cases. The morbidity and cost of treatment of severe preeclampsia are high with a large percentage requiring caesarean section and intensive care admission.

Keywords: maternal morbidity, perinatal outcome, preeclampsia, pregnancy complications, severe preeclampsia

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INTRODUCTION

Preeclampsia and eclampsia are among the leading causes of maternal morbidity and mortality.[1] Eclampsia has previously been the focus of most studies. The reported incidence of eclampsia has however declined over the years to about 0.05% of all deliveries.[2-4] In Singapore, the incidence of eclampsia was found to be 6.7 per 10,000 deliveries between 1994 and 1999, falling to 4.4 per 10,000 deliveries between 1997 and 1999.[4] This has resulted in increasing attention on preeclampsia, in particular, severe preeclampsia (SPE), a major cause of maternal and perinatal morbidity. Although maternal mortality has traditionally been used as a measure of the success of obstetrical intervention, this outcome has fortunately become so rare in developed countries that it is now impractical for use as an outcome measure. As a better alternative measure,[5] efforts should therefore be aimed at minimising morbidity from SPE.

The objective of this study was to assess the incidence of SPE, its epidemiology, disease characteristics, and maternal and perinatal outcomes among patients with SPE in KK Women's and Children's Hospital (KK Hospital) in Singapore. A better understanding of the nature of SPE in our patient population will allow us to determine possible avenues for reducing morbidity from SPE among our obstetric patients. In particular, we were interested in looking at differences between the SPE cases which developed complications, compared to those that did not, and to identify particular risk factors associated with complicated SPE cases.

METHODS

KK Hospital is the largest tertiary hospital for obstetrics, gynaecology and neonatology in Singapore, with an annual

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delivery rate of about 15,000. Maternal and perinatal data of 93 consecutively-managed women with SPE and eclampsia were prospectively entered into a database over a period of two years from January 2000 to December 2001. The following variables were prospectively recorded: Demographical data, clinical and laboratory investigations, maternal outcome and complications, treatment with antihypertensives, magnesium sulphate, intensive care admission, perinatal outcome-gestational age at diagnosis, timing between diagnosis of SPE and delivery, indication and mode of delivery, foetal complications, birth weight, gender, and Apgar scores.

SPE was defined as systolic blood pressure of ≥ 170 mmHg and/or diastolic blood pressure of ≥ 110 mmHg, with proteinuria ≥ 0.3 g/day or ≥ two pluses on urine dipstick, and/or severe biochemical abnormalities. Cases with eclampsia were also included. Patients who met the above criteria were identified through daily screening of women admitted to the delivery suite, in the women's intensive care unit, women who had a lower segment caesarean section and women referred for high-risk consult. Weekly meetings were held for the discussion of optimal management of high-risk obstetrical cases. The labour ward protocol for the management of SPE or eclampsia includes guidelines for the use of antihypertensives, anticonvulsants and fluid therapy. The timing and mode of delivery are left to the obstetrician-in-charge of the case, following a referral made to the maternal-foetal medicine specialist.

An electronic database of all patients who delivered in KK Hospital between 2000 and 2001 was used to provide information on the background demographics of our obstetric patients. Results were analysed using the Statistical Package for the Social Sciences for Windows version 11.0 (SPSS Inc, Chicago, IL, USA). Comparisons between groups were made with the unpaired *t*-test for normally-distributed continuous variables and the Fisher's exact chi-square test for discrete variables. Values are reported as mean and standard deviation (SD), unless otherwise stated. A p-value of < 0.05 was considered to be significant. Multivariate logistic regression analysis was performed for prediction of complicated SPE cases.

RESULTS

In the two years from January 2000 to December 2001, there were 93 cases of SPE. During this time, the total number of deliveries in the hospital was 31,701. The incidence of SPE was therefore 29.3 per 10,000 deliveries. In our series, the patients' ages ranged from 19 to 45 years, with a mean of 31.2 and median of 31.0 years (Table I). The lowest incidence occurred among those aged 25–29 years. The incidence was highest in those older than 35 years, and this was statistically significant compared to those aged < 24 years ($p = 0.008$) and those aged 25–29 years ($p = 0.001$), but not significant when compared those aged 30–34 years ($p = 0.351$). The incidence of SPE in all women ≥ 35 years was calculated to be 48.3 per 10,000 deliveries, higher than the incidence in women < 35 years at 25.6 per 10,000 deliveries. This difference was statistically significant ($p = 0.011$).

When parity was considered, the incidence of SPE in nulliparous women was higher than the multiparous women, although this did not reach statistical significance ($p = 0.071$) (Table I). When age and parity were considered together, the incidence of SPE in elderly multiparous women was found to be significantly higher than the younger multiparous group ($p = 0.017$). Using binary logistic regression, both age and parity were found to have a significant impact on the risk of SPE with p-values of 0.017 and 0.021, respectively. Increased age of ≥ 35 years had an odds-ratio of 1.827 for SPE compared to < 35 years, while nulliparous women had an odds-ratio of 1.642 for SPE compared to multiparous women.

The incidence of SPE in the different racial groups was found to be highest in Malay women, and this difference was statistically significant compared to Chinese women ($p = 0.0001$) but not to Indian women ($p = 0.170$) or other races ($p = 0.086$). Ethnic differences were also found in the gestational age at booking (Table II). Nine out of 39 (23%) Malay women booked late at greater than 32 weeks gestation, compared to four out of 43 (9%) Chinese women. There were 22 (24%) in-utero transfer cases. These are women who received their antenatal care from an obstetrician or general practitioner based outside of KK Hospital and were referred to KK Hospital upon diagnosis of SPE. These cases were admitted between 24 and 36 weeks gestation, with a mean of 30.5 weeks and a median of 31.0 weeks.

22 (23.7%) women had a significant past medical history. Three had a history of hypertension, 18 had a history of preeclampsia in a preceding pregnancy of which 12 were severe. One woman had a cerebrovascular accident preceding the pregnancy. 33 (35.5%) women had antenatal complications preceding the diagnosis of SPE, including hypertension, preeclampsia, gestational diabetes and in-utero growth restriction. There was also one case of foetal hydrops with foetal supraventricular tachycardia, one case of foetal anomaly with pulmonary stenosis, one set of triplets and three sets of twins. 44 (47.3%) women had documented symptoms and signs of impending eclampsia. Among these cases, the most common symptom was headache (47%), followed by blurred vision (24%). Other symptoms and signs recorded included hyperreflexia (14%), epigastric pain (5%), nausea and vomiting (5%), ascites (2%), and shortness of breath (3%).

The highest recorded systolic blood pressure values during the antenatal period ranged from 149 to 225

Table I. Incidence of SPE according to age, parity and race.

	No. of SPE	No. of deliveries	Incidence per 10,000 deliveries
Age (years)			
< 24	13	5,958	21.8
25–29	19	11,046	17.2
30–34	36	9,516	37.8
> 35	25	5,174	48.3
Parity			
Nulliparous	47	12,965	36.3
Multiparous	46	18,736	24.6
Parity and age (years)			
Multiparous, ≥ 35	19	4,761	39.9
Multiparous, < 35	27	13,975	19.3
Nulliparous, ≥ 35	6	983	60
Nulliparous, < 35	41	12,010	30
Race			
Chinese	43	17,099	25.1
Malay	39	9,294	42.0
Indian	7	2,995	23.4
Others	4	2,313	17.3

Table II. Gestational age at booking for the different ethnic groups.

Gestation	Total (n)	Chinese (%)	Malay (%)	Indian (%)	Others (%)
≤ 14 weeks	45	24 (53)	17 (38)	3 (7)	1 (2)
> 22 weeks	38	15 (40)	17 (44)	3 (8)	3 (8)
> 32 weeks	13	4 (31)	9 (69)	0	0

mmHg, with a mean of 183 mmHg. The highest recorded diastolic ranged from 90 to 155 mmHg, with a mean of 115 mmHg. The mean arterial blood pressure ranged from 118 to 170 mmHg, with a mean of 137. The mean 24-hour urine total protein was 5.3g, with a median of 2.3g. The most abnormal laboratory values recorded before the onset of complications and delivery were also recorded. Uric acid levels ranged from 218 to 730 μmol/L, with a mean of 415 μmol/L and median of 409 μmol/L. AST ranged from 14 to 333 IU/L, with a mean of 52 IU/L and median of 33 IU/L. Creatinine levels ranged from 49 to 331 μmol/L, with a mean of 81 μmol/L and a median of 76 μmol/L. Platelet count ranged from 43 to 443 × 10^9/L, with a mean of 195 × 10^9/L and median of 196 × 10^9/L.

40 (43%) women had maternal complications, including eclampsia (16%), haemolysis/elevated liver enzymes/low platelets (HELLP) syndrome (16%), oliguria (50%), pulmonary oedema (14%) and placental abruption (4%). Eclampsia was defined as the occurrence of tonic-clonic convulsions between 20 weeks of gestation and the tenth postpartum day, together with at least two of the following features within 24 hours of the convulsions: hypertension, proteinuria, raised aspartate aminotransaminase (AST) or thrombocytopenia. HELLP was defined as haemolysis with an abnormal peripheral blood smear or raised total bilirubin (> 20.5 μmol/L), raised liver enzymes (AST ≥ 70 IU/L or raised gamma-glutamyltransaminase ≥ 70 IU/L) and low platelets (< 100 × 10^9/L). Oliguria was defined as urinary output of < 30 ml/hour over four hours. There were two cases of placental abruption. One of these cases resulted in an intrauterine death. We were unable to identify any demographical factor that was associated with the prediction of more complicated diseases (Table III). The only statistical difference found was for the laboratory values of uric acid and AST. For uric acid, the standard error difference was 21.9 (confidence interval [CI] 87.6–0.6). For AST, the standard error difference was 17.1 (CI 75.9–6.7).

With regard to acute anti-hypertensive treatment, labetalol was used in 46 (49.5%) of the cases, more frequently than hydralazine, which was used in 15 (16.1%) of the cases. Magnesium sulphate was used in 33 (35.5%) women. Of these, seven received only magnesium sulphate postnatally. An additional four women were recruited as part of the Magpie trial. Four (4.3%) women required intensive care monitoring antenatally. Altogether, 55

Table III. Differences between complicated and uncomplicated SPE cases.

Category	Complicated SPE cases (n = 40)	Uncomplicated SPE cases (n = 53)	Statistical significance
Age* (years)	30.9 ± 5.5	31.4 ± 5.4	NS
Race			
Chinese (%)	40	60	NS
Malays (%)	41	59	NS
Indians (%)	43	57	NS
Gestational age at booking* (weeks)	20.1 ± 11.2	17.8 ± 9.7	NS
24-hour UTP* (mg/24 hours)	6.1 ± 6.4	4.0 ± 5.4	NS
Highest systolic blood pressure* (mmHg)	183.7 ± 16.3	183.0 ± 15.8	NS
Highest diastolic blood pressure* (mmHg)	114.1 ± 12.5	114.8 ± 9.3	NS
Mean arterial pressure* (mmHg)	137.3 ± 11.5	137.6 ± 9.9	NS
Uric acid* (μmol/L)	439.5 ± 114.1	395.4 ± 96.7	p = 0.047
AST* (IU/L)	80.1 ± 107.4	38.8 ± 16.1	p = 0.021
Creatinine* (μmol/L)	88.8 ± 45.3	76.1 ± 14.5	NS
Platelets* (IU/L)	182.4 ± 97.7	203.7 ± 79.2	NS

NS: not significant
*Values are presented as mean and standard deviation

Table IV. List of indications for delivery.

Indication	No. (%)
Eclampsia	6 (6)
Impending eclampsia	19 (20)
HELLP	6 (6)
Impending HELLP	5 (5)
Pulmonary oedema	5 (5)
Olguria	13 (14)
SPE alone	17 (18)
Abruption	2 (2)
IUGR	1 (1)
NRFS	17 (18)
SPE + previous caesarian section	2 (2)
SPE + breech	2 (2)
SPE + PPROM	1 (1)

IUGR: intrauterine growth restriction; NRFS: non-reassuring foetal status; PPROM: preterm premature rupture of membranes

(59.1%) required intensive care admission. The gestational age at diagnosis of SPE ranged from 22 to 40 weeks gestation with a mean and median of 33 weeks. On average, the number of days by which the pregnancy was prolonged following diagnosis was three days with a median of one day. For cases diagnosed at less than 34 weeks gestation, the average number of days by which the pregnancy was prolonged was 5.8 days with a median of 2.5 days. A list of indications for delivery is shown in Table IV. The mode of delivery was caesarean section in 83 (89.3%) cases. There were seven (7.5%) normal vaginal deliveries and two (2.2%) forceps-assisted deliveries.

The gestational age at delivery ranged from 25 to 40 weeks, with a mean and median of 34 weeks. There were two intrauterine deaths. One case was associated with foetal anomaly with pulmonary stenosis, and the patient underwent a mid-trimester termination of pregnancy. The other case was associated with placental abruption. The birth weight of the singleton pregnancies ranged from 340 g to 3,965 g, with a mean of 2,023 g and a median of 1,892 g. There was an equal number of male and female infants. Only five infants had an Apgar score of ≤ 7 at five minutes.

DISCUSSION

The incidence of SPE in Singapore was calculated to be 29.3 per 10,000 deliveries. Although the exact incidence of SPE is unknown, this appears to be comparable with findings from a UK study where one-third of cases resulting in severe obstetrical morbidity were related to hypertensive disorders, with a calculated incidence of SPE being 39 per 10,000 deliveries.[5] Our study also supports previous data that the incidence of SPE is more likely in those at the extremes of age in particular women aged more than 35 years.[6] The incidence of SPE was higher in nulliparous women as expected, although this did not reach statistical significance. It was also higher in the elderly multiparous women compared to the younger multiparous women. This is important as more women are now delaying childbirth, and elderly multiparous women are forming an increasing proportion of our patients.

There appears to be differences in the incidences of

SPE among the different racial groups with a predilection for Malay women. This may be due to several factors. Apart from possible genetic or dietary factors, there were also differences in the antenatal care received. Our analysis showed that Malay women formed the majority of late bookers who first saw a doctor after 32 weeks gestation. Interestingly, while the incidence of SPE is highest in Malay women, a previous study on eclampsia in Singapore found the incidence of eclampsia to be highest in Indian women.[4] It may be postulated that different racial groups might have different predispositions for the various complications. The findings regarding treatment reflect our current practice. Since 1996, both labetalol and hydralazine have been available as first line acute anti-hypertensive agents. Labetalol has found favour as it tends to lower blood pressure more effectively and efficiently without tachycardia or other side effects associated with hydralazine.

A significant number of patients (43%) had complications with SPE. Attempts have been made to investigate the utility of an admission battery of findings and laboratory data in discriminating patients with SPE at high risk for development of significant maternal morbidity. Previously, it has been found that the degree of blood pressure elevation may not be predictive of systemic complications apart from cerebrovascular accidents.[7] The 24-hour urine total protein takes time to perform and has also not been found to be a useful predictor of maternal or foetal complications.[8,9] Our study supports data from a previous study by Martin et al, where significant differences between patients with complicated and uncomplicated SPE were found in the laboratory values, including uric acid and AST. Such information would be useful for management purposes, e.g. aid a decision regarding when to terminate a pregnancy and possibly grounds for transfer to intensive care.[10]

There remains some controversy over the need for early delivery in cases of early-onset preterm SPE to prevent the development of serious maternal complications, such as eclampsia and kidney failure. Others prefer a more expectant approach in an attempt to delay delivery and hopefully achieve a better neonatal outcome. Following a Cochrane review of two trials,[11] it was concluded that there was insufficient data for any reliable recommendation about which policy should be used for women with early onset SPE. In a retrospective study of SPE diagnosed between 24 weeks and 31 weeks and six days, it was found that despite an aggressive approach towards expectant management, most were delivered within 48 hours for maternal indications.[12] Our hospital also favours expectant management in cases < 34 weeks gestation, mainly to buy time for administration of intramuscular steroids. However, the vast majority of cases still delivered within 24–48 hours for maternal indications. In addition, 89.3% of the cases required caesarean section with the indication for 18% of cases being SPE alone. If the development of complications from SPE can be predicted, the timing and mode of delivery can be planned more effectively to prolong the pregnancy as far as possible, so long as the foetal status is reassuring. Furthermore, over half of our patients with SPE required admission for intensive care treatment. This reiterates the need to understand SPE well in order to fine-tune the criteria for admission to intensive care and reduce the cost of treatment of SPE.

REFERENCES

1. Royal College of Obstetrics and Gynaecology. Confidential Enquiries into Maternal Deaths in the United Kingdom. The 5th Report, 2001: 76-93.
2. Leitch CR, Cameron AD, Walker JJ. The changing pattern of eclampsia over a 60-year period. Br J Obstet Gynaecol 1997; 104:917-22.
3. Saftlas AF, Olson DR, Franks AL, Atrash HK, Pokras R. Epidemiology of preeclampsia and eclampsia in the United States, 1979-1986. Am J Obstet Gynecol 1990; 163:460-5.
4. Chen CY, Kwek K, Tan KH, Yeo GS. Our experience with eclampsia in Singapore. Singapore Med J 2003; 44:88-93.
5. Waterstone M, Bewley S, Wolfe C. Incidence and predictors of severe obstetric morbidity: case-control study. BMJ 2001; 322:1089-93.
6. Pridjian G, Puschett JB. Preeclampsia. Part 1: clinical and pathophysiologic considerations. Obstet Gynecol Surv 2002; 57:598-618.
7. Witlin AG, Saade GR, Mattar F, Sibai BM. Risk factors for abruptio placentae and eclampsia: analysis of 445 consecutively managed women with severe preeclampsia and eclampsia. Am J Obstet Gynecol 1999; 180:1322-9.
8. Walker JJ. Severe pre-eclampsia and eclampsia. Baillieres Best Pract Res Clin Obstet Gynaecol 2000; 14:57-71.
9. Newman MG, Robichaux AG, Stedman CM, et al. Perinatal outcomes in preeclampsia that is complicated by massive proteinuria. Am J Obstet Gynecol 2003; 188:264-8.
10. Martin JN, May WL, Magann EF, et al. Early risk assessment of severe preeclampsia: admission battery of symptoms and laboratory tests to predict likelihood of subsequent significant maternal morbidity. Am J Obstet Gynecol 1999; 180:1407-14.
11. Churchill D, Duley L. Interventionist versus expectant care for severe pre-eclampsia before term. Cochrane Database Syst Rev 2002; CD003106.
12. Blackwell SC, Redman ME, Tomlinson M, et al. Severe pre-eclampsia remote from term: what to expect of expectant management. J Matern Fetal Neonatal Med 2002; 11:321-4.