Outcomes of Early-onset Preeclampsia With Severe Features at the University Hospital in Southern Thailand: a 15-year Experience

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Research Article

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Abstract

Purpose: To evaluate outcomes and factors associated with adverse outcomes among patients with early-onset preeclampsia with severe features at Songklanagarind Hospital.

Methods: A retrospective study of 326 singleton women with early-onset preeclampsia with severe features treated at Songklanagarind Hospital between 2004-2019 was conducted. Baseline characteristics, management and outcomes were reviewed. Multivariate logistic regression was used to evaluate predictors of adverse outcomes. Statistical significance was set at $p < 0.05$.

Results: There were no maternal mortalities, with 3.1% stillbirths and 6.7% neonatal deaths. High maternal serum creatinine (OR 3.26, 95% CI 1.27-8.36, p = 0.01) was significantly associated with adverse maternal outcomes. Early gestational age at delivery [< 28 weeks (OR 16.63, 95% CI 6.95-39.80, p <0.01), 28-32 weeks (OR 3.24, 95% CI 1.54-6.85, p <0.01)], maternal diabetes mellitus (OR 5.62, 95% CI 1.43-22.06, p = 0.01), high maternal serum creatinine (OR 2.66, 95%CI 1.20-5.93, p = 0.02) and elevated serum aminotransferases (OR 2.26, 95% CI 1.19-4.29, p = 0.01) were associated with serious adverse perinatal outcomes.

Conclusions: Early-onset preeclampsia with severe features had favorable outcomes. Maternal diabetes mellitus, high serum creatinine, elevated serum aminotransferases and early gestational age at delivery were factors associated with poor outcomes.

Introduction

Preeclampsia is a pregnancy-specific multiple-organ disorder associated with high rates of maternal and neonatal morbidity and mortality. Recent studies reported incidence ranges from 2.7–8.2% globally and 2.2% in Thailand [1, 2]. Appropriate diagnosis and timely management are crucial as more than half of these morbidities and mortalities are preventable [3].

The diagnosis of preeclampsia is made by recognizing new onset hypertension plus proteinuria and/or other signs and symptoms of organ dysfunction during pregnancy [4]. Preeclampsia is classified into early- and late-onset, defined as those requiring delivery before or after 34 weeks of gestation [5]. The pathophysiology of early-onset preeclampsia is abnormal placental development leading to deficient uterine spiral artery remodeling, while late-onset preeclampsia mainly arises from degenerative placenta accompanied by maternal predisposition to cardiovascular or metabolic disease. Both types of preeclampsia lead to dysfunctional maternal peripheral endothelial cells and systemic inflammatory responses, which lead to organ dysfunction and death in some women [6–9]. The fetuses are also affected from utero-placental insufficiencies. They have higher risk of growth restriction, hypoxia and death [8, 9].

Since the cause of preeclampsia is principally from the placenta, termination of pregnancy is the definitive treatment for the affected women. However, when preeclampsia is diagnosed early in gestation,

physicians have to take into account the high neonatal mortality and morbidity related to preterm birth. [10] Attempts to prolong pregnancy at risk of preeclampsia using expectant management practices may improve neonatal outcomes. On the other hand, pregnancy prolongation may increase morbidity and mortality in some women [4, 11].

Songklanagarind Hospital is the university hospital and tertiary care center in Southern Thailand, and thus receives a large number of referral preeclampsia women from all of the southern provinces. In 2018, the incidence of preeclampsia with severe features in our hospital was 4.2% of the total births (140/3299), of which about 11% (15/140) were early-onset. Early-onset preeclampsia with severe features is a condition which needs suitable guidelines, meticulous evaluation, and good physician judgment. To date, there have been no studies evaluating maternal and neonatal outcomes among cases of early-onset preeclampsia with severe features in Southern Thailand. Therefore, we aimed to evaluate maternal and neonatal outcomes among women with early-onset preeclampsia with severe features and also possible predictive factors for poor maternal and neonatal outcomes.

Material And Methods

A retrospective analytical study was conducted after approval by the Institutional Review Board of the Faculty of Medicine, Prince of Songkla University (REC 63-126-12-4). The medical records of women who delivered at Songklanagarind Hospital during a 15-year study period (November 1, 2004 to October 31, 2019) were reviewed. The inclusion criteria were: 1) singleton pregnant woman; and 2) early-onset preeclampsia with severe features according to the diagnostic criteria used in the period of diagnosis.

The exclusion criteria were women with severe medical problems including heart disease, severe anemia (Hb < 7 mg/dl), cirrhosis, thrombocytopenia diagnosed prior preeclampsia, severe systemic infection, and serious antepartum complications, including placenta previa, placenta accreta spectrum disorder, intraamniotic infection and having fetal anomalies.

The diagnosis and management clinical practice guidelines of Songklanagarind Hospital were according to the American College of Obstetricians and Gynecologists (ACOG) guidelines. The 15-year period of data collection included two ACOG diagnostic guidelines, the 2002 version and the 2013 versions [4, 12].

Sample size was calculated based on the prevalence of adverse maternal outcomes with proportion (p) = 0.105 (retrieved from a pilot study of Songklanagarind Hospital between 2018 and 2019), alpha = 0.05, and error (d) = 0.05; at least 145 cases were needed.

Demographic characteristics, treatment details until delivery along with maternal and neonatal outcomes were retrieved from the Medical Statistics Unit of the Department of Obstetrics and Gynecology and the Hospital Information System of Songklanagarind Hospital.

Women were identified as having adverse outcomes if they had at least one of the following: 1) death; 2) abruptio placentae; 3) pulmonary edema; 4) posterior reversible encephalopathy syndrome (PRES); and

5) postpartum hemorrhage. Serious adverse perinatal outcome was defined as at least one of the following; 1) stillbirth; 2) neonatal death; and 3) low 5-minutes Apgar score (< 7).

Data were recorded using EpiData Version 3.1. Statistical analysis was done using Stata 14.2.

Mean (SD), median (IQR) or number (%) were used as appropriate regarding the type of variables and data distribution. Multivariate logistic regression was used to estimate odds ratios for the association between variables and adverse maternal and perinatal outcomes. Statistical significance was set at $p < 0.05$.

Results

There were a total of 41,884 singleton deliveries during the 15-year period (from November 1, 2004 to October 31, 2019) at Songklanagarind Hospital, of whom 2087 were diagnosed with preeclampsia and 392 women were diagnosed with early-onset preeclampsia with severe features. Sixty-six women were excluded (23 due to severe medical problems and 43 due to serious antepartum complications). Finally, 326 early-onset preeclampsia with severe features women were analyzed. (Fig. 1)

The demographic data are shown in Table 1. Most of the diagnoses were based on elevated blood pressure defined as systolic blood pressure ≥ 160 mm Hg and/or diastolic blood pressure ≥ 110 mm Hg (314/326 women, 96.3%) and significant proteinuria defined as urine protein ≥ 300 mg/24 hours or spot urine protein to creatinine ratio ≥ 0.3 or urine protein dipstick ≥ 2+ (301/326 women, 92.3%), with 178/326 women (54.6%) reporting the symptoms of headache, blurred vision or epigastrium pain. The pre-delivery management followed the ACOG recommendations [4, 14] in nearly all cases. Only 5/326 (1.5%) women did not receive magnesium sulfate for maternal neurostabilization.

Table 1
Demographic data (N = 326)

Characteristics	N (%) or Median (IQR)
Maternal age (years)	32 (28,36)
Advanced maternal age (≥ 35 years)	109 (33.4)
Nulliparity	127 (39.0)
Gestational age at diagnosis (weeks)	31.1 (28.6,32.7)
Body mass index (kg/$m^{2)}$	23.3 (20.9,27.0)
Obesity (body mass index ≥ 30 kg/m^2)	50 (14.7)
Obstetric complications	
Previous pregnancy-induced hypertension	58 (17.8)
Gestational hypertension	4 (6.9)
Preeclampsia without severe features	9 (15.5)
Preeclampsia with severe features	46 (79.3)
History of indicated preterm delivery from pregnancy-induced hypertension	44 (13.5)
Medical diseases	
Chronic hypertension	85 (26.1)
Renal disease	11 (3.4)
Diabetes mellitus	10 (3.1)
Systemic lupus erythematosus	10 (3.1)
Thyroid disease	5 (1.5)
ASA usage	22 (6.7)
Gestational age at start (weeks)	14.5 (12,17)
Duration of ASA usage (weeks)	14 (11,16)

Most deliveries were induced (301/326, 92%), with uncontrolled blood pressure being the most frequent indication. Cesarean section was performed in the majority of cases. Hydralazine was the most frequently used anti-hypertensive drug followed by nifedipine and labetalol. Nicardipine was used only in women whose blood pressure failed to be controlled by the above-mentioned drugs. Expectant management was offered in less than half of the women, with time from diagnosis to delivery ranging from 2 hours to 29 days. (Table 2)

Table 2
Management of early-onset preeclampsia with severe features (N = 326)

Management	N (%) or Median (IQR)
MgSO4	321 (98.5)
Antihypertensive drugs	271 (83.1)
Hydralazine	224 (82.7)
Nifedipine	38 (14.0)
Labetalol	31 (11.4)
Nicardipine	21 (7.7)
Expectant management	141 (43.3)
Duration from diagnosis to delivery (hours)	43 (21,72)
Types of preterm delivery	
Spontaneous preterm labor	26 (8.0)
Indicated preterm labor	300 (92.0)
Uncontrolled blood pressure	186 (62.0)
Persistent symptoms	163 (54.3)
HELLP syndrome	93 (31.0)
Fetal distress	81 (27.0)
Renal dysfunction	25 (8.3)
Pulmonary edema	13 (4.3)
Abruptio placentae	5 (1.5)
Eclampsia	2 (0.6)
Route of delivery	
Vaginal delivery	43 (13.2)
Cesarean section	283 (86.8)

The maternal and neonatal outcomes are shown in Table 3. There was no maternal death. High percentages of uncontrolled blood pressure and persistent symptoms were observed. HELLP syndrome was noted in approximately one-third of cases. There were no eclamptic women during expectancy. Rates of other complications including pulmonary edema, abruptio placentae, postpartum hemorrhage and

posterior reversible encephalopathy syndrome (PRES) were low. Three out of five women with abruptio placentae were detected during expectant management (within 48 hours after diagnosis), with the first sign being non-reassuring fetal heart rate; and two out of three had difficulties in blood pressure control. The other two women with abruptio placentae were detected at the time of diagnosis and received immediate termination of pregnancy. Regarding nine cases of postpartum hemorrhage, all had successful conservative management.

Table 3

Maternal and perinatal outcomes (N = 326)

Outcomes	N (%) or Median (IQR)
Maternal outcomes	
Uncontrolled hypertension	186 (61.8)
Persistent symptoms	228 (70.0)
HELLP syndrome	91 (27.9)
Hemolysis	6 (1.8)
Elevated serum aminotransferases	76 (23.3)
Low platelet	45 (13.9)
Pulmonary edema	13 (4.0)
Abruptio placentae	5 (1.5)
Postpartum hemorrhage	9 (2.8)
Intracranial hemorrhage/ posterior reversible encephalopathy syndrome (PRES)	3 (0.9)
Perinatal outcomes	
Birth weight	1285 (965,1645)
Apgar scores	
Apgar score at 1 min	7 (5,8)
Apgar score at 5 min	9 (7,9)
Low 5-minutes Apgar score	66 (20.3)
Stillbirth	10 (3.1)
Neonatal death	22 (6.7)
Neonatal intensive care unit admission	289 (88.7)
Respiratory distress syndrome	87 (26.7)
Necrotizing enterocolitis	59 (18.1)
Bronchopulmonary dysplasia	40 (12.3)
Septicemia	33 (10.1)
Intraventricular hemorrhage	7 (2.1)
Convulsions	3 (0.9)

Regarding perinatal outcomes, about 90% of cases were alive with high rate of neonatal intensive care unit admission. Other complications were related to preterm delivery.

Univariate analysis showed that high maternal serum creatinine (> 1.1 mg/dL) was the only factor associated with adverse maternal outcomes (OR 3.26, 95% CI 1.27–8.36, p = 0.01). Multivariate analysis showed that early delivery at gestational age (GA) < 32 weeks, maternal diabetes mellitus, high maternal serum creatinine and elevated serum aminotransferases (AST or ALT > 70 IU/L) were risk factors for serious adverse perinatal outcomes adjusted by gestational age at diagnosis and maternal low platelet count. (Table 4)

Table 4

Multivariate analysis of factors associated with serious adverse perinatal outcomes[a]

Maternal characteristic	Serious adverse perinatal outcomes aOR (95% CI)	P-value
Gestational age at diagnosis		
GA < 28 weeks	13.13 (0.14-68.17)	0.47
GA 28-32 weeks	1.10 (0.14-8.54)	0.93
GA 32-34 weeks		
Gestational age at delivery		
GA < 28 weeks	16.63 (6.95-39.80)	<0.01
GA 28-32 weeks	3.24 (1.54-6.85)	<0.01
GA 32-34 weeks		
Diabetes mellitus	5.62 (1.43-22.06)	0.01
Serum Creatinine > 1.1 mg/dL	2.66 (1.20-5.93)	0.02
Elevated serum aminotransferases (AST or ALT > 70 IU/L)	2.26 (1.19-4.29)	0.01
Low platelet count (< 100000 cells/dL)	1.83 (0.78-4.31)	0.17

[a]stillbirth, low 5-minutes Apgar score and neonatal death

Discussion

In this study, women with early-onset preeclampsia with severe features had favorable outcomes. High maternal serum creatinine was associated with adverse maternal outcomes, while delivery before 32 weeks of gestation, maternal diabetes mellitus, high serum creatinine and elevated serum aminotransferases increased the risk of adverse perinatal outcomes.

Similar to other studies, there was very low rate of maternal death among women with early-onset preeclampsia with severe features [13–18]. The incidence of HELLP syndrome was similar to that in a previous report in Thailand, about 28% [13], but was more than those reported in other countries, which ranged from 12–15% [14–17], which might be explained by the differences in gene expression in placenta, concentrations of anti-angiogenic factors or degrees of inflammatory responses in different ethnicities [19]. The rates of abruptio placentae and eclampsia reported in our study were low. Since two out of three women with abruptio placentae during expectant management had uncontrolled blood pressure, and all had non-reassuring fetal heart monitoring, we suggest that physicians should emphasize on blood pressure control and close observation of fetal health status. Poorly controlled blood pressure needs expedited delivery. In regard to perinatal outcomes, the perinatal mortalities were not different among various parts of the world [13–17].

We found that high maternal serum creatinine was the only factor associated with adverse maternal outcomes. It is understandable as kidney is one of the most frequently affected organs from inflammatory response and/or vasoconstriction in preeclampsia [6, 20]. Once kidney dysfunction is evident, it indicates that other organs might be deteriorated. It is generally accepted that preterm delivery and maternal diabetes mellitus are related to adverse neonatal outcomes [10, 21]. They were also associated with poor perinatal outcomes in our study. Apart from gestational age at delivery and maternal diabetes mellitus, we found that high maternal serum creatinine and elevated serum aminotransferases, which reflect the severity of preeclampsia, were also associated with serious adverse neonatal outcomes. Ganzevoort et al. reported that early gestational age at admission was the only significant factor influencing adverse neonatal outcomes. However, they did not evaluate the associations between maternal diabetes mellitus or maternal serum creatinine level and adverse outcomes [22].

The strengths of this study were; 1) large sample size; 2) complete and reliable database; 3) diagnoses and managements adherent to ACOG guidelines; and 4) determination of factors associated with adverse maternal and perinatal outcomes.

The limitation of our study was that it was a retrospective study. There were a few incomplete data such as laboratory results from referring hospitals, and patient histories and physical examination findings depended on the level of completion of medical records at the time of diagnosis. As aspirin prescription was just recently added to the preeclampsia prevention guideline in 2016 [23], there was only a small percentage (6.7%) of aspirin prescription in our data. Because of this small percentage, the effects of aspirin prescription on the severity of preeclampsia might not be apparent.

According to the favorable outcomes of the management of early-onset preeclampsia with severe features in our study, we encourage the use of the ACOG practice guideline. In addition, knowing factors associated with adverse maternal and perinatal outcomes can guide physicians in patient counselling and providing optimal neonatal care planning.

Conclusion

Women with early-onset preeclampsia with severe features had favorable outcomes. High maternal serum creatinine was associated with adverse maternal outcomes, while early gestational age at delivery, maternal diabetes, high serum creatinine and elevated serum aminotransferases increased the risk of adverse perinatal outcomes.

Declarations

Declarations of Conflicts of Interest

None

Author contributions

N Khwankaew: Protocol development, data collection or management, data analysis and manuscript writing/editing

R Sawaddisan: Protocol development, data collection or management, data analysis and manuscript writing/editing

C Suwanrath: Protocol development, data analysis and manuscript writing/editing

A Geater: Data analysis and manuscript writing/editing

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Figures

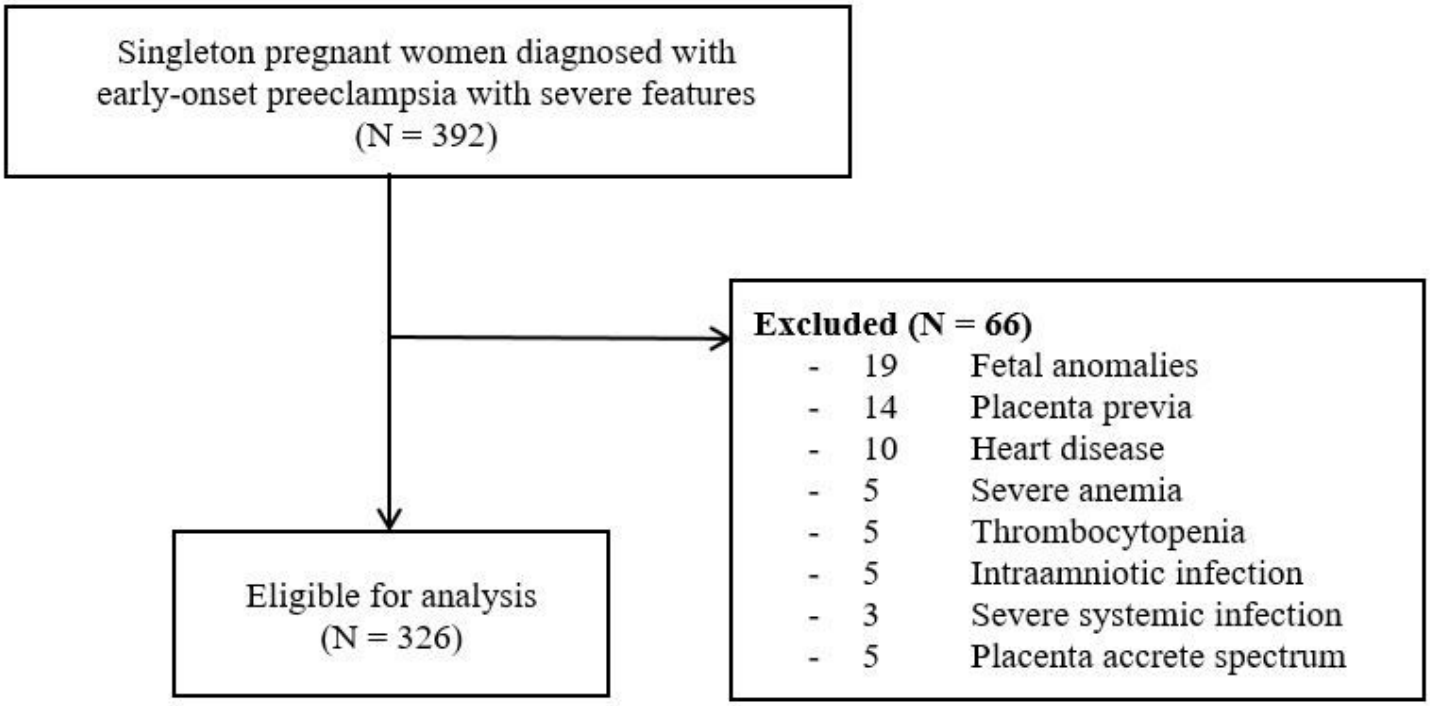

Figure 1

The study flow chart