Thai Journal of Obstetrics and Gynaecology
January 2017, Vol. 25, pp. 26-34

OBSTETRICS

Prevalence, Risk Factors, and Pregnancy Outcomes of Early-onset Severe Preeclampsia among Severe Preeclamptic Women in Siriraj Hospital

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ABSTRACT

Objectives: To determine the prevalence, associated factors and outcomes of early-onset severe preeclampsia among severe preeclamptic women in Siriraj Hospital.

Materials and Methods: A total of 220 pregnant women diagnosed with severe preeclampsia were enrolled. Relevant data including obstetric data, diagnosis, treatment, route of delivery, maternal and neonatal outcomes were retrieved from medical records. Prevalence of early-onset severe preeclampsia (diagnosed before 34 weeks of gestation) was estimated. Various characteristics were compared between early and late-onset groups to determine associated risk factors.

Results: Mean age of pregnant women was 28.6 years, and 59.1% were nulliparous. Mean gestational age (GA) at first antenatal visit was 14.5 weeks and mean GA at delivery was 36.2 weeks. Prevalence of early-onset severe preeclampsia was 15.9%. Only 9.1% received expectant management and 32.7% delivered vaginally. Mean birth weight was 2514.1 g. Stillbirth, small for gestational age (SGA), birth asphyxia and neonatal intensive care unit (NICU) admission was found in 1.8%, 17.7%, 2.7%, and 6.8%, respectively. Mean GA at delivery was 30.6 weeks in early-onset group and 37.2 weeks among late-onset group. Early-onset group was more likely to receive expectant management than late-onset group (34.3% vs. 4.3%; $p<0.001$). Worse outcomes were more common among neonates of early-onset group and they were significantly more likely to require NICU admission (37.1% vs. 1.1%, $p<0.001$). Women with previous preeclampsia were significantly more likely to develop early-onset severe preeclampsia. (35.7% vs. 13.2%, $p=0.037$).

Conclusion: Prevalence of early-onset severe preeclampsia among preeclamptic women in Siriraj hospital was 15.9%. Worse neonatal outcomes were more commonly observed among early-onset cases. Previous preeclampsia was the only significant possible associated factors.

Keywords: Preeclampsia, early-onset, risk factors, pregnancy outcomes

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ความชุก ปัจจัยเสี่ยง และผลของการตั้งครรภ์ ของภาวะครรภ์เป็นพิษรุนแรงที่เกิดขึ้นก่อนอายุครรภ์ 34 สัปดาห์ ในโรงพยาบาลศิริราช

รัฐิญา เพียรพิเศษ, บูรยา พัฒนจินดากุล, ดิฐกานต์ บริบูรณ์หิรัญสาร

บทคัดย่อ

วัตถุประสงค์: *เพื่อศึกษาความชุก ผลของการตั้งครรภ์ และปัจจัยที่สัมพันธ์กับการเกิดภาวะครรภ์เป็นพิษรุนแรงก่อนอายุครรภ์ 34 สัปดาห์ ในสตรีตั้งครรภ์ที่มีภาวะครรภ์เป็นพิษรุนแรงในโรงพยาบาลศิริราช*

วัสดุและวิธีการ: *เป็นการศึกษาเชิงพรรณนา แบบย้อนหลัง โดยการทบทวนเวชระเบียน และประวัติการรักษาของสตรีตั้งครรภ์ที่ได้รับการวินิจฉัยว่ามีภาวะครรภ์เป็นพิษรุนแรงที่มาคลอดที่โรงพยาบาลศิริราช จำนวน 220 ราย ทำการเก็บข้อมูลต่างๆ ได้แก่ ข้อมูลพื้นฐาน, ข้อมูลทางสูติกรรม, ข้อมูลการวินิจฉัย และรักษาข้อมูลการคลอด และผลของการตั้งครรภ์ทั้งมารดาและทารก ทำการคำนวณหาความชุกของภาวะครรภ์เป็นพิษรุนแรงที่เกิดก่อนอายุครรภ์ 34 สัปดาห์ จากนั้น ทำการเปรียบเทียบข้อมูลต่างๆ ระหว่างกลุ่มที่มารดาเกิดภาวะครรภ์เป็นพิษก่อนและหลัง 34 สัปดาห์ เพื่อประเมินปัจจัยที่เกี่ยวข้อง*

ผลการศึกษา: *อายุเฉลี่ยของสตรีตั้งครรภ์เท่ากับ 28.6 ปี เป็นครรภ์แรก ร้อยละ 59.1 อายุครรภ์เฉลี่ยเมื่อมาฝากครรภ์คือ 14.5 สัปดาห์ และอายุครรภ์เฉลี่ยเมื่อคลอดคือ 32.6 สัปดาห์ ความชุกของภาวะครรภ์เป็นพิษรุนแรงที่เกิดตั้งแต่อายุครรภ์น้อยๆ คือ ร้อยละ 15.9 โดยที่มีเพียง ร้อยละ 9.1 เท่านั้น ที่ได้รับการรักษาแบบเฝ้าสังเกตอาการโดยไม่ยุติการตั้งครรภ์ทันทีหลังจากวินิจฉัย ร้อยละ 32.7 ของผู้ป่วยสามารถคลอดเองได้ทางช่องคลอด ในแง่ของทารกพบว่า น้ำหนักเฉลี่ยเมื่อแรกเกิดเท่ากับ 2,514.1 กรัม พบทารกตายคลอด ทารกน้ำหนักน้อยกว่าเกณฑ์ ทารกที่มีภาวะขาดออกซิเจน และทารกที่ต้องเข้ารักษาที่ไอซียู ร้อยละ 1.8, 17.7, 2.7, และ 6.8 ตามลำดับ เมื่อเปรียบเทียบข้อมูลระหว่างสองกลุ่มแล้วพบว่า อายุครรภ์เฉลี่ยเมื่อคลอดในกลุ่มที่ได้รับการวินิจฉัยก่อนอายุครรภ์ 34 สัปดาห์ คือ 30.6 สัปดาห์ ส่วนกลุ่มที่ได้รับการวินิจฉัยหลังอายุครรภ์ 34 สัปดาห์ คือ 37.2 สัปดาห์ หญิงที่มีประวัติเป็นครรภ์เป็นพิษในครรภ์ที่แล้วมีความเสี่ยงที่จะถูกวินิจฉัยครรภ์เป็นพิษชนิดรุนแรงก่อนอายุครรภ์ 34 สัปดาห์ (ร้อยละ 35.7 และ 13.2, p=0.037) โดยกลุ่มที่ได้รับการวินิจฉัยก่อนอายุครรภ์ 34 สัปดาห์ มีแนวโน้มที่จะได้รับการรักษาแบบเฝ้าสังเกตอาการมากกว่า (ร้อยละ 34.3 และ 4.3; p<0.001) พบภาวะแทรกซ้อนของทารกสูงกว่าในกลุ่มที่คลอดจากมารดาที่ถูกวินิจฉัยภาวะครรภ์เป็นพิษรุนแรงก่อนอายุครรภ์ 34 สัปดาห์*

สรุป: *ความชุกของภาวะครรภ์เป็นพิษรุนแรงที่เกิดก่อนอายุครรภ์ 34 สัปดาห์ ในสตรีตั้งครรภ์ที่มีภาวะครรภ์เป็นพิษรุนแรงในโรงพยาบาลศิริราช คือ ร้อยละ 15.9 โดยกลุ่มนี้มักจะสัมพันธ์กับภาวะแทรกซ้อนที่รุนแรงของทารก และประวัติครรภ์เป็นพิษในครรภ์ก่อน เป็นปัจจัยเดียวที่พบว่าสัมพันธ์ต่อการเกิดภาวะครรภ์เป็นพิษรุนแรงที่เกิดก่อนอายุครรภ์ 34 สัปดาห์*

คำสำคัญ: *ภาวะครรภ์เป็นพิษ, อายุครรภ์ก่อน 34 สัปดาห์, ปัจจัยเสี่ยง, ผลของการตั้งครรภ์*

Introduction

Severe preeclampsia is a pregnancy-specific disease characterized by new onset of hypertension plus proteinuria with the presence of severe features according to American College of Obstetricians and Gynecologists (ACOG) guideline[1]. The cause of this process is still unknown but it is believed that placental insufficiency and generalized endothelial dysfunction are probably be the basis of the clinical feature[2,3]. The progression of disease leads to maternal complications such as myocardial infarction, severe renal failure, retinal injury, and also fetal complications resulting from exposure to utero-placental insufficiency[1]. Therefore, the only definite treatment is delivery of fetus and placenta in order to avoid severe complications[2-5].

However, if severe preeclampsia occurs before 34 weeks gestation, also known as early-onset severe preeclampsia, termination of pregnancy may increase risk of adverse neonatal outcome from prematurity. Expectant management, although improves neonatal outcomes, may worsen maternal condition. Thus, risks and benefits for both mother and fetus must be balanced. So, it is important for physician to understand nature of the disease, risk factor and its outcomes[1,3-5].

Previous studies have reported incidence early-onset preeclampsia to be about 0.3% of all pregnancies and 10-30% among preeclamptic women. Variation in such prevalence might be from differences in population characteristics and risks for preeclampsia[1,3].

The primary objective of this study was to determine prevalence of early-onset severe preeclampsia among severe preeclamptic women. In addition, risk factors and perinatal outcomes were also evaluated.

Materials and Methods

After approval from Siriraj Institutional Review Board (SIRB), a cross-sectional study was conducted at the Department of Obstetrics and Gynecology, Faculty of Medicine Siriraj Hospital. A total of 220 pregnant women diagnosed with severe preeclampsia according to ACOG guideline who delivered at Siriraj hospital in 2011-2012 were enrolled. Pregnant women with multiple pregnancies, molar pregnancy, uncertain gestational age, those with medical problems that cause hypertension such as renal disease, thyroid disease or autoimmune disease and women with fetal abnormalities such as hydrops fetalis were excluded from this study. Data were retrieved from medical records, including baseline characteristic, obstetric data, diagnosis, management and outcome of both mother and fetus. Prevalence of early-onset severe preeclampsia was estimated. Various characteristics were compared between women with early and late-onset severe preeclampsia to determined associated risk factors and pregnancy outcomes.

Severe preeclampsia is defined as new onset of hypertension after 20 weeks of gestation plus proteinuria with the presence of severe features according to ACOG guideline, which are 1) Hypertension: systolic > 160 or diastolic >110 mmHg on two occasions at least 4 hours apart while the patient is on bed rest (unless antihypertensive therapy is initiated before this time); 2) Thrombocytopenia (platelet count < 100,000 / mm^3); 3) Impaired liver function (elevated blood levels of liver transaminases to twice the normal concentration), severe persistent right upper quadrant or epigastric pain unresponsive to medication and not accounted to alternative diagnoses, or both; 4) New development of renal insufficiency (elevated serum creatinine greater than 1.1 mg/dL, or doubling of serum creatinine in the absence of other renal disease); 5) Pulmonary edema; and 6) New-onset cerebral or visual disturbances. Early-onset severe preeclampsia is defined as severe preeclampsia that occurs before 34 weeks of gestation [1,6].

Sample size was estimated based on the prevalence of early-onset severe preeclampsia of 15% among severe preeclamptic women from pilot study. A sample size of 220 would be adequate to determine the incidence at 95% confidence level with 5% maximum allowable error.

Descriptive statistics including number, percentage, mean, and standard deviation were used to describe various characteristics as appropriate. The prevalence of early-onset severe preeclampsia was estimated and reported in percentage and 95%

confidence interval (CI). Various characteristics were compared between early and late-onset groups using Chi-square test and Student t-test. P-value of less than 0.05 was considered statistically significant.

Results

A total of 220 cases of pregnant women diagnosed with severe preeclampsia who delivered in Siriraj Hospital were enrolled in the study. Baseline characteristics of these cases are shown in Table 1. Mean age was 28 years, 59.1% were nulliparous. Mean pre-pregnancy body mass index (BMI) was 23.3 kg/m^2 and 30% of them were overweight. Mean GA at first antenatal care (ANC) was 14.5 weeks.

Table 1. Baseline characteristics of pregnant women in the study (N=220).

Characteristics	N (%)
Mean age ± SD (years)	28.6 ± 6.9
Age group	
< 20 years	26 (11.8)
20-34 years	145 (65.9)
≥ 35 years	49 (22.3)
Nulliparous	130 (59.1)
Mean GA at first ANC ± SD (weeks)	14.5 ± 7.0
Mean pre-pregnancy BMI ± SD (kg/m^2)	23.3 ± 5.5
BMI category	
Normal	122 (55.5)
Underweight	32 (14.5)
Overweight	66 (30.0)

Table 2 shows characteristics of diagnosis, management and maternal outcomes. Almost all women (95.9%) were diagnosed with severe preeclampsia and the rest had HELLP syndrome. Mean GA at diagnosis was 36.2 weeks. Of 220 severe preeclamptic women, 35 developed severe preeclampsia before 34 weeks, i.e., prevalence of early-onset preeclampsia was 15.9% (95%CI 11.7%-21.3%). Antihypertensive drugs were prescribed in 48.2% of patients. Hydralazine was more commonly prescribed than labetalol (29.1% vs. 19.1%). Expectant management was offered in 9.1% of cases. Mean GA at delivery was 36.2 weeks. Caesarean section was the most common route of delivery (67.2%), of which 58.6% were primary cesarean section. Majority of indications for cesarean delivery were failed labor induction, unfavorable cervical conditions, and non-reassuring fetal heart rate pattern.

Table 2. Diagnosis, management, and delivery of pregnant women in the study (N=220).

Characteristics	N (%)
Mean GA at diagnosis ± SD (weeks)	36.2 ± 3.0
Diagnosis	
Severe preeclampsia	211 (95.9)
HELLP	9 (4.1)

Table 2. Diagnosis, management, and delivery of pregnant women in the study (N=220). (Cont.)

Characteristics	N (%)
Early-onset preeclampsia	35 (15.9)
Intrapartum antihypertensive use	
No medication	114 (51.8)
Labetalol	42 (19.1)
Hydralazine	64 (29.1)
Management	
Expectant	20 (9.1)
Termination of pregnancy	200 (90.9)
Mean GA at delivery ± SD (weeks)	36.2 ± 3.0
Route of delivery	
Vaginal delivery	72 (32.7)
Repeat cesarean section	19 (8.6)
Primary cesarean section	129 (58.6)

Table 3 shows neonatal outcomes. Mean birth weight of the newborns was 2514.1 g and 17.7% were SGA. Birth asphyxia was observed in 2.7% and 6.8% required NICU admission. Stillbirth was found in 1.8%.

Table 3. Neonatal outcomes pregnant women in the study (N=220).

Neonatal outcomes	N (%)
Mean birth weight ± SD (g)	2514.1 ± 788.2
Stillbirth	4 (1.8)
Small for gestational age	39 (17.7)
Birth asphyxia	6 (2.7)
NICU admission	15 (6.8)

Comparison of various characteristics was made between early and late-onset group. Table 4 shows comparison of baseline characteristics between women with early and late-onset preeclampsia. There was no significant difference in terms of age, parity, GA at first ANC, and pre-pregnancy BMI. Among multiparous women, those with previous preeclampsia were significantly more likely to develop early-onset severe preeclampsia. (35.7% vs. 13.2%, p=0.037).

Table 4. Comparison of characteristics between women with early and late-onset severe preeclampsia.

Characteristics	Early-onset (N=35)	Late-onset (N=185)	P
Mean age ± SD (years)	28.6 ± 6.7	28.6 ± 7.0	0.990
Mean GA at 1st ANC ± SD (weeks)	13.25 ± 6.5	14.8 ± 7.0	0.239
Mean pre-pregnancy BMI ± SD (kg/m^2)	21.9 ± 4.0	23.6 ± 5.7	0.096

Table 4. Comparison of characteristics between women with early and late-onset severe preeclampsia. (Cont.)

Characteristics	Early-onset (N=35)	Late-onset (N=185)	p value
Nulliparous	21 (60.0%)	109 (58.9%)	0.905
BMI category			0.571
Normal	22 (62.9%)	100 (54.0%)	
Overweight	8 (22.8%)	58 (31.4%)	
Underweight	5 (14.3%)	27 (14.6%)	
Previous preeclampsia	5/14 (35.7%)	10/76 (13.2%)	0.037

Table 5 shows the comparison of diagnosis, management and maternal outcomes between the 2 groups. Mean GA at diagnosis and delivery in the early-onset group was 30.6 weeks while it was 37.2 weeks among late-onset group. Women in early-onset group were significantly more likely to received expectant management than late-onset group (34.3% vs. 4.3%, p<0.001). Diagnosis and mode of delivery were not significantly different between two groups.

Table 5. Comparison of diagnosis, management and delivery between women with early and late-onset severe preeclampsia.

Characteristics	Early-onset (N=35)	Late-onset (N=185)	p value
Mean GA at diagnosis ± SD (weeks)	30.6 ± 1.8	37.2 ± 1.8	< 0.001
Mean GA at delivery ± SD (weeks)	30.6 ± 1.8	37.2 ± 1.8	< 0.001
Management			< 0.001
Expectant	12 (34.3%)	8 (4.3%)	0.905
Termination	23 (65.7%)	177 (95.7%)	0.571
Diagnosis			0.144
Severe preeclampsia	32 (91.4%)	179 (96.8%)	
HELLP	3 (8.6%)	6 (3.2%)	
Mode of delivery			
Vaginal delivery	8 (22.9%)	54 (34.6%)	0.445
Repeat cesarean section	3 (8.6%)	16 (8.6%)	0.988
Primary cesarean section	24 (68.6%)	105 (56.8%)	0.193

Table 6 shows comparison of neonatal outcomes between the 2 groups. Mean birth weight was significantly higher in late-onset than early-onset group (2738.8 g vs. 1326.5 g, p<0.001). SGA, birth asphyxia, and stillbirth were more common among early-onset group, but without statistical significance. Infants of women in early-onset group were significantly more common to have NICU admission than late-onset group (37.1% vs. 1.1%, p<0.001).

Table 5. Comparison of neonatal outcomes between women with early and late-onset severe preeclampsia.

Characteristics	Early-onset (N=35)	Late-onset (N=185)	P
Mean birth weight ± SD (g)	1326.5 ± 455.1	2738.8 ± 618.2	< 0.001
Stillbirth	2 (5.7%)	2 (1.1%)	0.060
Small for gestational age	9 (25.7%)	30 (16.2%)	0.177
Birth asphyxia	2 (5.7%)	4 (2.2%)	0.237
NICU admission	13 (37.1%)	2 (1.1%)	< 0.001

Discussion

Early-onset severe preeclampsia (develops at < 34 weeks of gestation) is associated with highperinatal mortality and morbidity rates. Management with immediate delivery leads to highneonatal mortality and morbidity rates. Attempts to prolong pregnancy with expectant management may result in fetal death or asphyxial damage in utero and increased maternal morbidity[1].

The result of this study showed that the prevalence of early-onset severe preeclampsia among preeclamptic women in Siriraj Hospital was 15.9%. The prevalence was in between of those previously reported; 35% in a Chinese study and 12% in an American study[7-9]. The difference in prevalence could be due to differences in population and risk factors of preeclampsia. Previous preeclampsia was the only significant associated risk factor for early-onset severe preeclampsia in this study. Among multiparous women, those with previous preeclampsia were significantly more likely to develop early-onset severe preeclampsia. (35.7% vs. 13.2%, p=0.037). This was in consistent with other previous studies[1]. Previous Thai study reported that, as compared to normal pregnant women, history of chronic hypertension, family history of diabetes, BMI > 25 kg/m^2, and weight gain of > 0.5 kg/week were significant risks of early-onset preeclampsia[10].

Early identification of these at-risk women could help in providing appropriate counseling and preventive measures could also be initiated in a timely manner. Among at-risk women, low-dose aspirin have been demonstrated to significantly reduce the risk of severe preeclampsia, fetal growth restriction, and gestational hypertension in the subgroup in which treatment was initiated before 16 weeks[11,12]. Other reported risks from previous studies included advanced maternal age, chronic hypertension, high mean arterial pressure, uterine artery PI from Doppler study of > 95th percentile. Biomarkers such as PAPP-A and PIGF were also previously discussed that low serum markers were associated with early-onset severe preeclampsia[13-15]. However, these tests had relatively low predictive values and currently are not recommended[16]. According to ACOG, taking a detailed medical history to evaluate for risk factors is currently the best and only recommended screening approach for preeclampsia[17].

As expected, women with early-onset preeclampsia generally had worse neonatal outcomes than those with late onset. However, the adverse outcomes in this study were less severe than previous study in China, of which, perinatal death was approximately 22% and NICU admission rate was approximately 60% among early-onset severe preeclampsia[7]. In another Thai study, birth asphyxia was reported to be 11.2% and 1% among early and late-onset severe preeclampsia[10]. These adverse outcomes were mainly related to indicated-preterm delivery. Only 34% of women with early-onset severe preeclampsia were stable enough to receive expectant management but only a few days can be delayed. Most of them were terminated after a 2-day course of corticosteroid injection to promote infant's lung maturity. Traditional management of severe preeclampsia has focused on maternal safety with expedited delivery. However, for early-onset preeclampsia, some have suggested some form of expectant management in an

attempt to prolong gestation and improve perinatal outcome including time for antenatal corticosteroid administration[1,18]. Previous studies have shown that median latency with expectant management ranges from 7–14 days[19]. It is recommended that expectant management of severe preeclampsia remote from term should be individualized and is appropriate in selected cases which could help in pregnancy prolongation and improving newborn outcomes[1].

The limitations of this study included the retrospective nature of data collection that some data might be inaccurate or incomplete. Some previously reported associated factors were not available, especially Doppler study and other biomarkers. The prevalence of early-onset preeclampsia in this study might be higher than other settings in Thailand due to the nature of tertiary care hospital. In addition, the study might not have enough power to detect significant associated factors. Further study with larger samples might be needed to understand more about the nature of the condition as well as associated factors. Effective preventive measures should also be determined to minimize adverse pregnancy outcomes.

In conclusion, prevalence of early-onset severe preeclampsia was 15.9% among preeclamptic women in Siriraj hospital. It is associated with worse neonatal outcomes. Previous preeclampsia was the only significant possible associated factor among multiparous women. According to the results, attention should be paid in the women with previous preeclampsia.

Potential conflicts of interest

The authors declare no conflict of interest.

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