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Maternal and Neonatal Outcomes in Pre-eclampsia and Normotensive Pregnancies

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ABSTRACT

Objective: To compare the maternal and neonatal outcomes of pregnancies with pre-eclampsia to those with normotensive.

Materials and Methods: Cases were defined as pregnancies with pre-eclampsia who delivered between January 1st, 2009 and December 31st, 2009 at Khon Kaen Hospital and were compared with normal blood pressure with a ratio of 1:1 match for age and date of delivery. The information of maternal and neonatal outcomes were reviewed from the medical and delivery records. Adjusted odds ratio with 95% confidence intervals were used to evaluate the effect of pre-eclampsia.

Results: There were 302 cases in the study which half of them were pre-eclampsia and the others were normotensive pregnancies. Maternal and neonatal morbidities were significantly higher in pre-eclampsia pregnancies. Pre-eclampsia increases the risk of vaginal operative delivery (adjusted OR 2.6, 95% CI 1.1- 5.9), cesarean section (adjusted OR 1.8, 95% CI 1.1- 3.0), low birth weight (< 2,500 g) (adjusted OR 2.9, 95% CI 1.4- 5.8), and birth asphyxia (adjusted OR 5.3, 95% CI 1.1- 25.1). The most common indication for cesarean section was fetal distress. There were eight neonatal deaths. The causes of death were respiratory distress syndrome, sepsis and very low birthweight.

Conclusion: Pre-eclampsia significantly increased the risk of adverse maternal and neonatal outcomes.

Keywords: pre-eclampsia, maternal outcomes, neonatal outcomes, Khon Kaen Hospital

Introduction

Pre-eclampsia is a multi-system syndrome unique to pregnancy characterized by the new onset of hypertension and proteinuria during the second half of pregnancy[1,2]. This disorder complicates between 2- 8% of all pregnancies[3]. Seventy-five percent are experienced in a mild form, and 25% in a severe form [4]. In the past three years, pre-eclampsia has shown

an increasing trend of 2.2%, 2.8%, and 3.0% at Khon Kaen Hospital.

Pre-eclampsia is more common in women who have pre-existing hypertension, autoimmune disease, diabetes and renal disease. It increases risk of maternal and infant mortalities and morbidities such as abruptio placentae, disseminated intravascular coagulation, thrombocytopenia, pulmonary edema, intrauterine growth restriction and preterm birth by 3 - 25 folds[5, 6]. In women with severe pre-eclampsia, there will be more maternal and neonatal complications, leading to early termination of pregnancy[7].

Since there have been few studies that reported maternal and neonatal outcomes of pre-eclampsia in Thailand, this study was conducted to analyze the effects of pre-eclampsia on maternal and neonatal outcomes compared to those of normotensive pregnancies.

Materials and Methods

This was a retrospective cohort study that was approved by the Research Ethics Committee of Khon Kaen Hospital. The medical and delivery records of all pregnant women who were diagnosed as pre-eclampsia (study group) and the normotension (control group) at Khon Kaen Hospital between January 1st, 2009 and December 31st, 2009 were reviewed. The exclusion criteria included incomplete medical records and pre-eclamptic women who had a hydatidiform mole.

Data about maternal age, parity, gestational age, systolic and diastolic blood pressures, underlying diseases, previous pre-eclampsia, mode of delivery, indications of obstetric procedures and cesarean section, referral status, birth weight, Apgar score, and maternal and neonatal complications were collected.
The definition of pre-eclampsia according to the National High Blood Pressure Education Program (NHBPEP) Working Group was used[8]. Pre-eclampsia was defined as systolic pressure[3] 140 mmHg and/or diastolic pressure[3] 90 mmHg on 2 occasions, at least 6 hours apart, and proteinuria with a urinary total protein of[3]300 mg/24 hours in a single specimen occurring for the first time in the second half of pregnancy. The severity is classified into two forms, mild and severe pre-eclampsia.

Mild pre-eclampsia was diagnosed as the presence of hypertension (BP[3]140/90 mm Hg) and proteinuria with protein in urine[3] 300 mg/24 hours in a single specimen. Severe pre-eclampsia was diagnosed on the basis of pre-eclampsia plus at least one of the followings:

1 the presence of systolic BP[3] 160 mmHg and/or diastolic BP[3] 110mmHg;
2 proteinuria with protein in urine[3] 5 g in 24-hour;
3 pulmonary edema;
4 oliguria (urine < 400 mL in 24 hours);
5 persistent headaches;
6 epigastric pain and/or impaired liver function;
7 eclampsia;
8 thrombocytopenia;
9 hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome;
10 intrauterine growth restriction[9] which was defined as fetal weight below the tenth percentile of weight distribution at a specified gestational age.

Preterm birth was defined as birth before 37 weeks' gestation[10]. Low birthweight (LBW) was defined as birth weight < 2,500 g[10] and very low birth weight (VLBW) was defined as birthweight < 1,500 g[10].

The controls were age-matched pregnant women with normal blood pressure who delivered next to the study one, on the same day. The ratio of study to control was 1:1.

All patients were admitted to the labor ward. They were carefully evaluated and treated follow by Khon Kaen Hospital's protocol. For all of severe pre-eclampsia cases, initial drug therapy consisted primarily of intravenous magnesium sulfate to prevent convulsions and intravenous nicardipine or hydralazine to maintain diastolic blood pressure (DBP) between 90- 110 mmHg. The decision of whether to use aggressive or expectant management was based on the physician's preference.

Data were presented as mean ± SD, number (%). The Chi-square test, 2-sample t-test, one-way analysis of variance (ANOVA) test, Kruskal-Wallis test, and multiple logistic regression analysis were used as

appropriate. A p-value of less than 0.05 was considered statistically significant. Bartlett's test was used to test the equality of variances. Bonferroni test was used to compare between subgroups if there was any difference with the one-way ANOVA test. If the Kruskal-Wallis and Chi-square tests showed a difference between three subgroups, Mann-Whitney-U and Chi-square tests were used to compare between each pair of subgroups with a p-value of 0.0167 as statistically significant[11].

Results

From 1st January to 31st December 2009, 5,549 pregnant women were delivered at this hospital. Of these, 151 were pre-eclampsia without exclusion. We compared these 151 pregnant women with 151 age-matched normotensive pregnant women. Among these 151 pre-eclampsia patients, 57 (37.7%) had mild, 91 (60.3%) had severe pre-eclampsia and 3 (2%) had eclampsia. There were two multifetal pregnancies in the study group and one case in the control group. Pregnant women with pre-eclampsia had more underlying diseases than those with normotensive blood pressure such as gestational diabetes mellitus (9% vs 3%), chronic hypertension (5% vs 0), and systemic lupus erythematosus (2% vs 0).

The characteristics of all participants are shown in Table 1. The mean age was 26.7 ± 6.9 years. The proportion of nulliparity and history of previous pre-eclampsia were higher in pregnant women with pre-eclampsia than those without pre-eclampsia. One hundred pre-eclamptic pregnancies (66.2%) were referred cases, but only 44 (28.7%) of the controls were referred cases (p<0.001).

Comparison of the maternal characteristics between mild, severe pre-eclampsia, and the controls are shown in Table 2. Induction of labor was higher in severe pre-eclampsia than in normotensive pregnancies (p=0.016). Of the pre-eclamptic women, 112 patients (74.2%) underwent induction of labor. The common reasons for labor induction were the severity of preeclampsia 92 cases (82.1%), post-term pregnancy 11 cases (9.8%), premature rupture of the membranes 7 cases (6.3%), and intrauterine fetal death 2 cases (1.8%). Referred patients with severe pre-eclampsia were more prevalent than those with mild pre-eclampsia (p<0.01). The proportion of vaginal operative delivery and cesarean section were significantly higher in severe pre-eclampsia than in normotensive pregnancies (p=0.001). Different indications of cesarean section between the two groups are shown in Table 3. The most frequent indication of cesarean section in the pre-eclamptic group was fetal distress (38.9 % vs. 7.3%; p= 0.02), whereas in normotensive women, it was cephalopelvic disproportion (32.7 % vs 29.2%; p= 0.68).

Although the number of intrauterine growth restriction (IUGR) cases in pre-eclampsia was higher than in normotensive women (6 cases vs. 3 cases), the difference was not statistically significant (p=0.47). Two pre-eclamptic pregnancies developed total placental abruption and intrauterine fetal death. Four patients had hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome. All of them had been moved to intensive care unit and required a nitroprusside infusion. They recovered without sequelae. Three women with eclampsia had no permanent sequel of seizure up to six weeks post-delivery. There was no maternal death.

The prevalence of preterm birth, LBW and birth asphyxia were significantly higher in women with pre-eclampsia (31.1% vs.11.3%, p< 0.001; 34.4% vs. 10.6%, p< 0.001; and 11.3% vs. 1.3%, p= 0.0004, respectively). Eight neonates died from respiratory distress syndrome (RDS) (5 cases), sepsis (2 cases) and very low birthweight (VLBW) (1 case). Other neonatal morbidities were only found in the pre-eclamptic group such as jaundice (8 cases), sepsis (2 cases), and meconium aspiration syndrome (1 case).

By multivariate logistic regression analysis pregnancies with pre-eclampsia had a significant increased risk of vaginal operative delivery (adjusted OR 2.6, 95% CI of 1.1- 5.9), caesarean section (adjusted OR 1.8, 95% CI of 1.1- 3.0), LBW (adjusted OR 2.9, 95% CI of 1.4- 5.8), and birth asphyxia (adjusted OR 5.3, 95% CI of 1.1- 25.1) compared with normotensive pregnancies (Table 4).

There were only three patients with eclampsia. All patients were referred from nearby provinces and underwent labor induction. Two patients had cesarean

delivery and one had a normal delivery. The indications for cesarean delivery were fetal distress and failed induction. Two of the neonates were prematurity, the other one was term. There was no birth asphyxia, IUGR, stillbirth, maternal or neonatal death among the eclamptic patients.

Table 1. Characteristics of preeclamptic and normotensive pregnant women

Characteristics	Pre-eclampsia (n=151)	Normotensive (n=151)	p-value
Mean age (years)	26.7 ± 6.9	26.7 ± 6.8	0.94
Parity (%)			0.14
0	94 (62.2)	81 (53.3)	
≥ 1	57 (37.7)	70 (46.7)	
Gestational age (weeks)	37.0 ± 3.1	38.2 ± 1.9	<0.001*
Systolic blood pressure (mmHg)	159.4 ± 19.3	112.8 ± 8.5	<0.001*
Diastolic blood pressure (mmHg)	101.4 ± 10.1	72.3 ± 7.2	<0.001*
Anticonvulsant usage ($MgSO_4$)	94 (62.2)	0	-
Number of antenatal care (%)			0.54
< 4	47 (31.1)	52 (34.4)	
≥ 4	104 (68.9)	99 (65.6)	
Refer (%)			<0.001*
No	51 (33.8)	107 (70.9)	
Yes	100 (66.2)	44 (29.1)	
Previous pre-eclampsia (%)	7 (4.7)	0	-

*statistically significant.

Table 2. Comparison of maternal characteristics between three groups

	Severe pre-eclampsia (n=94)	Mild pre-eclampsia (n=57)	Normotensive pregnancies (n=151)	p-value
Maternal age (years)	26.5 ± 6.5	27.1 ± 7.5	26.7 ± 6.9	0.8
Parity				0.2
0	62 (66.0)	32 (56.1)	81 (53.3)	
≥ 1	32 (34.0)	25 (43.9)	70 (46.7)	
Gestational age (weeks)	36.3 ± 3.5	38.1 ± 1.7[a]	38.2 ± 1.9[b]	0.0002*
Systolic pressure (mmHg)	168.9 ± 17.8	143.8 ± 8.6[b]	112.8 ± 8.5 [b,c]	0.0001*
Diastolic blood pressure (mmHg)	106.6 ± 8.6	92.9 ± 5.6[b]	72.3 ± 7.2 [b,c]	0.0001*
Antenatal care				0.2

Table 2. Comparison of maternal characteristics between three groups (cont.)

	Severe pre-eclampsia (n=94)	Mild pre-eclampsia (n=57)	Normotensive pregnancies (n=151)	p-value
< 4	34 (36.2)	13(22.8)	52 (34.4)	
≥ 4	60 (63.8)	44 (77.2)	99 (65.6)	
Refer				<0.0001*
No	24 (25.5)	27 (47.4)	107 (70.9)	
Yes	70 (74.5)	30 (52.6)[e]	44 (29.1) [b,d]	
Labor induction	76 (80.9)	36 (63.2)	98 (64.9)	0.016
Type of delivery				0.004
Normal delivery	32 (34.0)	22 (38.6)	85 (56.3)[h]	
Vaginal operative delivery	17 (18.1)	8 (14.0)	11 (7.3)	
Cesarean section	45 (47.9)	27 (47.4)	55 (36.4)	

a: p<0.001 compared with severe pre-eclampsia; b: p<0.001 compared with severe pre-eclampsia; c: p<0.001 compared with mild pre-eclampsia; d; p < 0.01 compared with severe pre-eclampsia; e: p < 0.01 compared with mild pre-eclampsia; h: p=0.001 compared with severe pre-eclampsia.

Table 3. Indications of cesarean section in pre-eclamptic and normotensive pregnant women

Indication	Pre-eclampsia (n=72) (%)	Normotensive (n=55) (%)	p-value
Fetal distress	28 (38.9)	4 (7.3)	0.02*
Cephalopelvic disproportion	21 (29.2)	18 (32.7)	0.68
Previous cesarean section	9 (12.5)	12 (21.8)	0.54
Malpresentation	4 (5.6)	9 (16.4)	0.23
Induction failure	7 (9.7)	4 (7.3)	0.17
Placenta previa	1 (1.4)	5 (9.1)	0.37
Eldery pregnancy	2 (2.8)	3 (5.5)	0.80

*statistically significant.

Table 4. Multivariate logistic regression analysis of variables associated with pre-eclampsia*

Outcomes	Pre-eclampsia (n=151) (%)	Normotensive pregnancies (n=151) (%)	Adjusted OR (95% CI)	p-value
Maternal outcomes				
Normal delivery	54 (35.8)	85 (56.3)	0.4 (0.2-0.6)	<0.001*
Vaginal operative delivery	25 (16.6)	11 (7.3)	2.6 (1.1-5.9)	0.004*
Cesarean section	72 (47.6)	55 (36.4)	1.8 (1.1-3.0)	0.004*
Neonatal outcomes				
Preterm birth	47 (31.1)	17 (11.3)	1.9 (0.6-5.9)	0.54
Low birthweight	52 (34.4)	16 (10.6)	2.9 (1.4-5.8)	<0.001*
IUGR	5 (3.3)	3 (1.9)	1.7 (0.4-7.0)	0.86
Apgar score at 5 min < 7	17 (11.3)	2 (1.3)	5.3 (1.1-25.1)	0.004*

OR= odds ratio. * Adjusted for gestational age, referral status, and parity.
IUGR = Intrauterine growth restriction

Discussion

The incidence of pre-eclampsia in this study (3.1%) was similar to that of previous reports (1.2-7.1%) [12-15]. Moreover, this rate representing the medical school hospital based data in the north-eastern area was quite similar to that of the report from Ramathibodi Hospital, medical school in Bangkok (4.9%)[14]. However, it was slightly higher than that reported from the southern general hospital (1.2%)[15]. The discrepancy could be explained by the fact that our study as well as the other[14] in Thailand was performed in the tertiary referral centers.

In this study, pre-eclampsia was associated with no maternal mortality, but higher frequencies of maternal morbidity and neonatal morbidity and mortality were encountered. The maternal morbidity rate of 29% in the present study is consistent with those previously reported[16]. However, it was lower than those reported in the Netherlands (1993 -2002) (65%) [17], which can partially be explained by early referral, active management and the use of an adequate intensive care unit.

In this study, frequency of cesarean section and vaginal operative delivery were significantly higher in pre-eclamptic pregnancies. Our finding was consistent with Al-Mulhim et al's and Saadat et al's reports[7, 18]. The reasons for cesarean section in pregnancies with pre-eclampsia were aimed to reduce further serious complications of the fetuses as well as the mothers, with the evidence that the most frequent indication of cesarean section in pre-eclampsia was fetal distress. As for vaginal operative delivery, the most common indication was severe pre-eclampsia that could reduce the fetal hazard. The hypothesis of compromised utero-placental circulations especially in severe pre-eclampsia that play a role in acute fetal distress[19] substantially supports the need of these procedures. These facts were also found in Witlin et al's work[20].

The neonatal morbidity was more common in pre-eclampsia with the higher rate compared with that of the controls. This finding was consistent with a previous one[21]. The authors noted that pre-eclampsia was associated with a 2.9 times (95% CI of 1.4- 5.8) increased risk of low birthweight (LBW) that was similar to the report of Hiett et al[22]. One major causative factor of LBW might be prematurity that was more prevalent in our study as well as the other[23]. However, there was a contradicting result in this issue. A study from the USA showed that pre-eclampsia was associated with a 3.8 fold increased risk of LBW[24]. An interesting study with

a larger population showed that birth weight seemed to be lower in women with preeclampsia than the controls, but did not reach statistical significance[25].

The authors found that pre-eclampsia was also linked to a significantly increased risk of Apgar score < 7 at 5 min with OR of 5.3 (95% CI of 1.1- 25.1). This was consistent with a previous study[26]. Evidence showed that the neonatal morbidity and mortality, especially in the pre-eclamptic group would be predicted by low Apgar scores at 1 and 5 min[27]. Factors that may influence a low Apgar score included fetal hypoxia and preterm birth. Fetal hypoxia in preeclampsia could be explained by a decrease in the uteroplacental blood flow resulting from severe hypertension[28]. As for the preterm infant, respiratory efforts including muscle tone and reflex irritability have not developed completely because of immaturity leading to inevitably low Apgar scores[29].

Different incidences of the neonatal death in severe pre-eclampsia and eclampsia have been reported[26,30-31]. The neonatal mortality of 5% in the current study was similar to that of the work of Tuffnell and team[30]. By contrast, the study from Saudi Arabia reported the higher perinatal mortality rate of 30.7% in pre-eclampsia with severe status[31]. The main reason responding to this neonatal mortality was prematurity. It could cause respiratory distress syndrome. Furthermore, preterm infants were at risk of sepsis with the fact that there was placental insufficiency in severe preeclampsia resulting in intrauterine starvation and immune deficiency[32].

The limitation of this study was that it was a retrospective design that could not completely record all variables such as renal function test, duration of labor and other obstetric complications. These variables may have affected the maternal and neonatal outcomes between the study and the control groups.

In conclusion, pre-eclampsia was significantly associated with maternal and neonatal morbidities as well as increasing vaginal operative delivery, cesarean section, LBW, and birth asphyxia. This information may be useful for counseling and also for early identification of pregnant women who have a high-risk for severe pre-eclampsia, subsequent monitoring and treatment of pregnancies with pre-eclampsia.

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ผลกระทบต่อมารดาและทารกในความดันโลหิตสูงเนื่องจากการตั้งครรภ์เปรียบเทียบกับความดันโลหิตปกติ

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วัตถุประสงค์ *: เพื่อศึกษาผลของความดันโลหิตสูงเนื่องจากการตั้งครรภ์ต่อมารดาและทารกจากเปรียบเทียบกับสตรีตั้งครรภ์ที่มีความดันโลหิตปกติ*

วัสดุและวิธีการ *: ศึกษาสตรีตั้งครรภ์ที่มีความดันโลหิตสูงเนื่องจากการตั้งครรภ์เปรียบเทียบกับสตรีตั้งครรภ์ที่มีความดันโลหิตปกติที่โรงพยาบาลขอนแก่นในช่วงเวลาตั้งแต่ 1 มกราคม 2552 ถึง 31 ธันวาคม 2552 ในอัตรา1:1 โดยมีอายุและวันที่คลอดเดียวกัน ข้อมูลได้จากบันทึกของเวชระเบียนและทะเบียนคลอด วิเคราะห์ข้อมูลคำนวณอัตราเสี่ยง (Adjusted odd ratio) มีช่วงเชื่อมั่นที่ระดับนัยสำคัญร้อยละ 95*

ผลการศึกษา *: สตรีตั้งครรภ์ที่มีความดันโลหิตสูงเนื่องจากการตั้งครรภ์ 151 รายและสตรีตั้งครรภ์ความดันโลหิตปกติ151ราย พบว่าภาวะความดันโลหิตสูงเนื่องจากการตั้งครรภ์มีผลต่อมารดาและทารกอย่างมีนัยสำคัญทางสถิติ ได้แก่ เพิ่มหัตถการช่วยคลอดทางช่องคลอด (adjusted OR 2.6, 95% CI 1.1- 5.9), การผ่าท้องทำคลอด (adjusted OR 1.8, 95% CI 1.1- 3.0), ทารกน้ำหนักน้อยกว่า 2,500 กรัม (adjusted OR 2.9, 95% CI 1.4- 5.8) และทารกแรกเกิดขาดออกซิเจนหลังคลอด (adjusted OR 5.3, 95% CI 1.1- 25.1) ข้อบ่งชี้หลักในการผ่าตัดคลอดคือ ทารกขาดออกซิเจน สาเหตุของทารกเสียชีวิตหลังคลอดคือ ภาวะการหายใจล้มเหลว การติดเชื้อและทารกมีน้ำหนักแรกเกิดน้อยมาก*

สรุป *: ภาวะความดันโลหิตสูงเนื่องจากการตั้งครรภ์เพิ่มความเสี่ยงต่อมารดาและทารก*