Risk Factors of Preeclampsia in Thai Women

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Objective: *To determine the risk factors of preeclampsia in a university hospital.*
Material and Method: *The authors conducted a case control study involving 309 Thai pregnant women with preeclampsia and 309 controls who delivered at King Chulalongkorn Memorial Hospital, Bangkok, Thailand between June 2008 and May 2009. Information was taken from maternal inquiry, delivery records and antenatal care records.*
Results: *The risk factors that were significantly associated with increased risk of preeclampsia were maternal age ≥ 35 years (ORs 1.7; 95% CI 1.1-2.9), nulliparity (ORs 3.8; 95% CI 2.5-5.7), prepregnancy body mass index ≥ 30 kg/m^2 (ORs 3.0; 95% CI 1.4-6.3), multifetal pregnancy (ORs 2.8; 95% CI 1.2-7.1), history of preeclampsia in a previous pregnancy (ORs 17.0; 95% CI 3.3-87.6) and chronic hypertension (ORs 19.5; 95% CI 2.4-155.7). Maternal age < 20 years (ORs 0.4; 95% CI 0.2-0.9) and prepregnancy body mass index < 20 kg/m^2 (ORs 0.4; 95% CI 0.2-0.6) were significant protective factors against the development of preeclampsia.*
Conclusion: *Risk factors of preeclampsia were maternal age ≥ 35 years, nulliparity, prepregnancy body mass index ≥ 30 kg/m^2, multifetal pregnancy, history of preeclampsia in previous pregnancy and chronic hypertension. On the other hand, maternal age < 20 years and prepregnancy body mass index < 20 kg/m^2 were significant protective factors against the development of preeclampsia. These risk factors should be of value to obstetricians counseling women regarding preeclampsia.*

Keywords: *Risk factor, Preeclampsia, Age, Parity, Body mass index*

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Preeclampsia, which affects 5-10% of pregnancies, is a common obstetric complication that leads to maternal and perinatal morbidity and mortality in both developed and developing countries. Preeclampsia is also associated with high rates of pre-term delivery, small for gestational age infant and perinatal death worldwide[1]. The exact etiology of preeclampsia is still unknown, however, many studies have demonstrated that preeclampsia is associated with failure of trophoblastic invasion of the maternal spiral arteries, leading to increased vascular resistance of the uterine arteries and decreased uteroplacental blood flow[2,3].

Although risk factors for preeclampsia have been studied in many settings, results are conflicting. Most studies were retrospective. A few studies were performed to find the risk factors for preeclampsia in an Asian population[4,5]. There have been significant differences in the prevalence of the risk factors in Asians compared to other ethnic groups, involving blood pressure, obesity, and maternal age adjusted for parity[6]. The authors aimed to identify risk factors associated with development of preeclampsia in Thai population.

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Material and Method

Subjects

This was a case control study at the Department of Obstetrics and Gynecology, King Chulalongkorn Memorial Hospital, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand between June 2008 and May 2009. The present study was approved by the Research Ethics Committee of the Faculty of Medicine.

Pregnant women with gestational age of at least 22 weeks who delivered at the Department of Obstetrics and Gynecology during the study period were included. Subjects were divided into two groups. Cases were those diagnosed with preeclampsia. Controls were normotensive pregnant women who delivered consecutively after preeclamptic pregnant women. Pregnancies complicated with chromosomal or structural anomalies were excluded.

Every subject received a detailed inquiry about her pregnancy, medical history and antenatal care. Pregnancy outcome information was taken from labor and delivery records.

Preeclampsia was defined as a blood pressure of at least 140/90 mmHg measured on two occasions 6 hours apart, accompanied by proteinuria of at least 300 mg per 24 hours, or at least 1+ on dipstick testing after 20 weeks. Severe preeclampsia was defined as having one or more of the following criteria: blood pressure of at least 160/110 mmHg measured on two occasions 6 hours apart, proteinuria of at least 5 g per 24 hours, or at least 3+ on dipstick testing, oliguria of less than 500 ml per 24 hours, cerebral or visual disturbances, pulmonary edema or cyanosis, epigastric or right upper quadrant pain, impaired liver function, thrombocytopenia, or fetal growth restriction[7].

The sample size calculation was based on risk factors of preeclampsia at King Chulalongkorn Memorial Hospital obtained from the presented pilot study. The authors found that nulliparity was the risk factor that gave the largest sample size. Thus, 189 women in each group were needed to detect a statistical difference ($\alpha = 0.05$, $\beta = 0.1$).

The following maternal risk factors were evaluated: age, parity, prepregnancy weight, height, body mass index (BMI) (categorized as underweight (BMI < 20 kg/m^2, normal weight (BMI 20-24.9 kg/m^2), overweight (25-29.9 kg/m^2), obesity (BMI $\geq$ 30 kg/m^2), history of spontaneous abortion, history of chronic hypertension, previous preeclampsia, mother's Rh status, cigarette smoking, multifetal gestation, diabetic mellitus (overt or gestational), and infant's gender.

Statistical analysis

Student's t-test and Mann-Whitney U test were used for continuous variables. Chi-square test and Fisher's exact test were used for categorical variables. Multivariate regression analysis was used to evaluate the association between preeclampsia and the various risk factors. The risk factors that produced a point estimate at a p-value of < 0.1 on the univariate analysis were entered into a multivariate regression analysis. Adjusted odds ratio (ORs) with 95% confidence interval (CI) was calculated. A p-value < 0.05 was considered statistically significant.

Results

During the present period, there were 309 women with preeclampsia. Thus, a total of 309 women with preeclampsia and 309 controls were included in the present study. Demographic and perinatal characteristics of the study population are shown in Table 1 and 2, respectively. The mean maternal age was significantly higher in the preeclampsia group than in controls. The proportion of nulliparity was significantly higher in women with preeclampsia than in controls. Furthermore, the total antenatal care visit, total weight gain and pregestational body weight, preterm delivery, birth weight, the frequencies of low birth weight (birth weight < 2,500 g), cesarean delivery, Apgar scores < 7 at 1 and 5 min were also statistically higher in women with preeclampsia.

Table 3 provides the information regarding the risk factors in women with preeclampsia and controls through univariate analysis. Age, parity, gestational age at first ANC, prepregnancy BMI, multiplicity, history of preeclampsia in previous pregnancy and history of chronic hypertension were significantly associated with increased risk of preeclampsia.

Table 4 shows the results of multivariate logistic regression analysis. The risk factors that were significantly associated with increased risk of preeclampsia were: maternal age $\geq$ 35 years (odds ratio (ORs) 1.7; 95% CI 1.1-2.9), nulliparity (ORs 3.8; 95% CI 2.5-5.7), prepregnancy body mass index $\geq$ 30 kg/m^2 (ORs 3.0; 95% CI 1.4-6.3), multifetal pregnancy (ORs 2.8; 95% CI 1.2-7.1), history of preeclampsia in previous pregnancy (ORs 17.0; 95% CI 3.3-87.6) and history of chronic hypertension (ORs 19.5; 95% CI 2.4-155.7). On the other hand, maternal age < 20 years (ORs 0.4; 95% CI 0.2-0.9) and prepregnancy body mass index < 20 kg/m^2 (ORs 0.4; 95% CI 0.2-0.6) were significant protective factors against the development of pre-eclampsia.

Discussion

The results of this present study demonstrate that maternal age $\geq$ 35 years, nulliparity, prepregnancy body mass index $\geq$ 30 kg/m^2, multifetal pregnancy, history of preeclampsia in a previous pregnancy and chronic hypertension are associated with a significantly increased risk of preeclampsia, whereas maternal age < 20 years and prepregnancy body mass index < 20 kg/m^2 are significant protective factors against the development of preeclampsia.

The authors found that maternal age $\geq$ 35 years carried an increased risk of developing pre-eclampsia. This was consistent with previous studies[4,5,8]. This may be related to the progressive vascular endothelial damage that occurs with maternal aging[9] and obstruction of maternal spiral arteriolar

Table 1. Demographic characteristic of study population

Characteristic	Preeclampsia (n = 309)	Control (n = 309)	p-value
Age (years)	29.3 ± 6.3	27.9 ± 6.2	0.008
Parit			
Nulliparity	198 (64.1%)	149 (48.2%)	
Multiparity	111 (35.9%)	160 (51.8%)	<0.001
Previous abortion			
No	243 (78.6%)	244 (79%)	
Yes	66 (21.4%)	65 (21%)	<0.001
Total antenatal care visit (times)	7.8 ± 3.4	8.9 ± 2.7	<0.001
Total weight gain (kg)	16.3 ± 9.9	13.9 ± 5.1	<0.001
Pregestational BW (kg)	59.4 ± 13.2	53.1 ± 10.9	<0.001

Table 2. Perinatal characteristic

Characteristic	Preeclampsia (n = 309)	Control (n = 309)	p-value
Gestational age at delivery (weeks)	36.5 ± 3.1	38.2 ± 1.7	<0.001
Preterm delivery			
Yes	111 (35.9%)	34 (11%)	
No	198 (64.1%)	275 (89%)	<0.001
Birth weight(gm) (median)	2,750	3,115	<0.001
Birth weight < 2500 gm			
Yes	118 (38.2%)	25 (8.1%)	
No	191 (61.8%)	284 (91.9%)	<0.001
Cesarean delivery			
Yes	189 (61.2%)	130 (42.1%)	
No	120 (38.8%)	179 (57.9%)	<0.001
Apgar scores at 1 min < 7	38 (12.3%)	4 (1.3%)	<0.001
Apgar scores at 5 min < 7	18 (5.8%)	2 (0.6%)	<0.001

lumina by atherosis[10]. Previous studies[11,12] did not find maternal age ≥ 35 years as an increased risk of developing preeclampsia. This may reflect confounding factors due to the association of advanced maternal age with increased prevalence of essential hypertension[13].

The authors did not find maternal age < 20 years itself to be a risk factor for preeclampsia. This may be due to a confounding factor from the association of young maternal age and nulliparity as in previous studies[11,14].

Nulliparity was associated with a significantly increased risk of preeclampsia in the present study. This was consistent with previous studies[4,8,15]. It is believed that this is related to the maternal first exposure to trophoblasts, which are of fetal origin[16].

Obestiy (prepregnancy body mass index ≥ 30 kg/m^2) was associated with a significantly increased risk of preeclampsia in the present study. This was consistent with previous studies[8,15]. A prepregnancy body mass index < 20 kg/m^2 was found to be a protective factor against the development of preeclampsia as in a previous study[5]. The reason for obesity being associated with an increased risk of preeclampsia was explained by increased levels of serum triglycerides, very low-density lipoproteins, and formation of small dense low-density lipoprotein particles in obese women[17]. This lipid profile was also found in women with preeclampsia[18]. These lipid alterations have been suggested to promote oxidative stress, caused by ischemia-reperfusion mechanism or activated neutrophils, which leads to endothelial cell dysfunction[1,19,20].

Nulliparity, multifetal pregnancy, history of preeclampsia in previous pregnancy and chronic hypertension were associated with a significantly

Table 3. Risk factors for preeclampsia

Risk factors	Preeclampsia (n = 309)	Control (n = 309)	p-value
Age (years)			
< 20	15 (4.9%)	28 (9.1%)	0.084
20-34	223 (72.1%)	234 (75.7%)	Reference
≥ 35	71 (23%)	47 (15.2%)	0.028
Parity			
Multiparity	111 (35.9%)	160 (51.8%)	Reference
Nulliparity	198 (64.1%)	149 (48.2%)	<0.001
Previous abortion			
No	243 (78.6%)	244 (79%)	Reference
Yes	66 (21.4%)	65 (21%)	0.922
History of chornic hypertension			
No	288 (93.2%)	307 (99.7%)	Reference
Yes	21 (6.8%)	1 (0.3%)	0.002
Mother's Rh			
Positive	307 (99.4%)	308 (99.7%)	Reference
Negative	2 (0.6%)	1 (0.3%)	0.571
Gestational age at first ANC (weeks)			
1-13	123 (39.8%)	179 (57.9%)	Reference
14-26	87 (28.2%)	109 (35.3%)	0.419
≥ 27	99 (32%)	21 (6.8%)	<0.001
Prepregnancy BMI (kg/m^2)			
< 20	55 (17.8%)	126 (40.8%)	<0.001
20-24.9	151 (48.9%)	133 (43%)	Reference
25-29.9	64 (20.7%)	37 (12%)	0.077
≥ 30	39 (12.6%)	13 (4.2%)	0.004
Cigarette smoking			
No	309 (100%)	307 (99.4%)	Reference
Yes	0	2 (0.6%)	0.586
Multiplicity of pregnancy			
Single	287 (92.9%)	300 (97.1%)	Reference
Multiple	22 (7.1%)	9 (2.9%)	0.02
Infant's sex			
Male	138 (44.7%)	160 (51.8%)	Reference
Female	171 (55.3%)	149 (48.2%)	0.207
Diabetes mellitus			
No	301 (97.4%)	302 (97.7%)	Reference
GDM/Pregestational DM	8 (2.6%)	7 (2.3%)	0.794
Calcium used			
No	283 (91.6%)	291 (94.2%)	Reference
Yes	26 (8.4%)	18 (5.8%)	0.281
History of preeclampsia in previous pregnancy			
No	295 (95.5%)	307 (99.4%)	Reference
Yes	14 (4.5%)	2 (0.6%)	0.009
Family history of DM			
No	250 (80.9%)	240 (77.7%)	Reference
Yes	59 (19.1%)	69 (22.3%)	0.321
Family history of HT			
No	248 (80.3%)	262 (84.8%)	Reference
Yes	61 (19.7%)	47 (15.2%)	0.139

DM = diabetes mellitus; HT = hypertension

Table 4. Results of multivariate logistic regression analysis

Risk factors	Adjusted ORs	95% CI
Age < 20	0.4	0.2, 0.9
Age ≥ 35	1.7	1.1, 2.9
Prepregnancy body mass index ≥ 30 kg/m^2	3.0	1.4, 6.3
Prepregnancy body mass index < 20 kg/m^2	0.4	0.2, 0.6
Multiplicity	2.8	1.2, 7.1
History of preeclampsia in previous pregnancy	17.0	3.3, 87.6
History of chronic hypertension	19.5	2.4, 155.7
Nulliparity	3.8	2.5, 5.7

increased risk of preeclampsia in the present study. This was consistent with the hypothesis that immune maladaptation might play a role in triggering the development of preeclampsia[1].

In contrast with previous studies[8,14], cigarette smoking did not decrease the risk of preeclampsia in the present study. This may be due to the small number of our pregnant women who smoke in Thailand.

The strength of present study was the use of patient interview and data from antenatal care records and delivery records. Thus, the data collection was completed. The limitation of the present study was the small sample size that could not assess the effect of some factors such as smoking and diabetes mellitus.

In conclusion, maternal age ≥ 35 years, nulliparity, prepregnancy body mass index ≥ 30 kg/m^2, multifetal pregnancy, history of preeclampsia in previous pregnancy and chronic hypertension were associated with a significantly increased risk of preeclampsia. This information may be useful for obstetricians in counseling and screening at-risk women. These at-risk women are candidates for further studies of preeclampsia which may have application for prevention and treatment.

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ปัจจัยเสี่ยงของการเกิดภาวะครรภ์เป็นพิษในหญิงไทย

พนิดา เหลือล้น, วรพงศ์ ภู่พงศ์

วัตถุประสงค์*: เพื่อหาปัจจัยเสี่ยงของการเกิดภาวะครรภ์เป็นพิษในโรงพยาบาลมหาวิทยาลัย*

วัสดุและวิธีการ*: ได้ทำการศึกษาแบบ case control ในหญิงตั้งครรภ์ที่มีภาวะครรภ์เป็นพิษ 309 ราย และหญิงตั้งครรภ์ปกติ 309 ราย ที่มาคลอดในโรงพยาบาลจุฬาลงกรณ์ ระหว่างเดือนมิถุนายน พ.ศ. 2551 ถึงพฤษภาคม พ.ศ. 2552 ข้อมูลได้จากการซักถามประวัติ บันทึกของการคลอดและบันทึกของการฝากครรภ์*

ผลการศึกษา*: ปัจจัยเสี่ยงที่มีความสัมพันธ์กับการเกิดภาวะครรภ์เป็นพิษคือ อายุมารดาตั้งแต่ 35 ปี (ORs 1.7; 95% CI 1.1-2.9), การตั้งครรภ์ครั้งแรก (ORs 3.8; 95% CI 2.5-5.7), ดัชนีมวลกายก่อนตั้งครรภ์ตั้งแต่ 30 กิโลกรัมต่อตารางเมตร (ORs 3.0; 95% CI 1.4-6.3), การตั้งครรภ์แฝด (ORs 2.8; 95% CI 1.2-7.1), ประวัติการเกิดภาวะครรภ์เป็นพิษในครรภ์ก่อน (ORs 17.0; 95% CI 3.3-87.6) และภาวะความดันโลหิตสูง (ORs 19.5; 95% CI 2.4-155.7) ส่วนอายุมารดาน้อยกว่า 20 ปี (ORs 0.4; 95% CI 0.2-0.9) และดัชนีมวลกายก่อนตั้งครรภ์น้อยกว่า 20 กิโลกรัมต่อตารางเมตร (ORs 0.4; 95% CI 0.2-0.6) เป็นปัจจัยที่ป้องกันการเกิดภาวะครรภ์เป็นพิษ*

สรุป*: ปัจจัยเสี่ยงของการเกิดภาวะครรภ์เป็นพิษคือ อายุมารดาตั้งแต่ 35 ปี, การตั้งครรภ์ครั้งแรก, ดัชนีมวลกายก่อนตั้งครรภ์ตั้งแต่ 30 กิโลกรัมต่อตารางเมตร, การตั้งครรภ์แฝด, ประวัติการเกิดภาวะครรภ์เป็นพิษในครรภ์ก่อน และภาวะความดันโลหิตสูง ส่วนอายุมารดาน้อยกว่า 20 ปี และดัชนีมวลกายก่อนตั้งครรภ์น้อยกว่า 20 กิโลกรัมต่อตารางเมตรเป็นปัจจัยที่ป้องกันการเกิดภาวะครรภ์เป็นพิษ ปัจจัยเสี่ยงดังกล่าวจะมีประโยชน์ต่อสูติแพทย์ในการให้คำปรึกษาแก่หญิงตั้งครรภ์*