



Full Length Research Article

RISK FACTORS OF EARLY AND LATE ONSET PRE-ECLAMPSIA IN POPULATION ADMITTED AT GUJARAT ADANI INSTITUTE OF MEDICAL SCIENCE, BHUJ, KUTCH, GUJARAT, INDIA

*Dr. Nagajan Bhadarka and Dr. Tarak Nath Mukherjee

Department of Obstetrics and Gynecology, Adani Institute of Medical Science, Bhuj, Gujarat

Accepted 18th February 2016; Published Online 31st March 2016

ABSTRACT

Aim: The aim of this study was to identify the differences in risk factors between early and late onset pre-eclampsia.

Materials and Methods: A case-control study was carried out involving pregnancies with pre-eclampsia and 449 controls at Gujarat Adani institute of medical science, Bhuj, Kutch, Gujarat from August 2011 to May 2014. The data were reviewed from antenatal and delivery records.

Results: Factors which were significantly associated with increased risk for both early and late onset preeclampsia were family history of diabetes mellitus, high pre-pregnancy body mass index ≥ 25 kg/m² and weight gain ≥ 0.5 kg per week. History of chronic hypertension was significantly associated with increased risk for only early onset pre-eclampsia, while family history of chronic hypertension was significantly associated with increased risk for only late onset pre-eclampsia.

Conclusions: The risk factors that differ between early and late onset of pre-eclampsia were history of chronic hypertension and family history of chronic hypertension. Family history of diabetes mellitus, pre-pregnancy body mass index ≥ 25 kg/m² and weight gain ≥ 0.5 kg per week were risk factors of both early and late onset pre-eclampsia.

Key words: Case-control study, Diabetes mellitus, Hypertension, Pre-eclampsia.

INTRODUCTION

Pre-eclampsia is a common obstetric complication. It is one of three common causes of maternal mortality in the world. (WHO, 2008) in severe cases, it causes multiple organ failures, which leads to maternal death. A high fetal morbidity and mortality rate is associated with prematurity, placental insufficiency and intrauterine growth restriction (IUGR), which result from this disorder. (Assis *et al.*, 2008; Sibai *et al.*, 2005) the exact cause of pre-eclampsia is still unknown. The impaired placentation is one possible cause. (Phupong and Dejthevaporn, 2008) There are many studies that aim to evaluate risk factors of pre-eclampsia. Primigravida, previous pregnancy-induced hypertension, obesity, diabetes, hypertension and multiplicity are risk factors. Some factors are protective; one of these is cigarette smoking. (Bainbridge *et al.*, 2005) Some studies demonstrated higher morbidity and mortality from pre-eclampsia at an early gestational age than from that at a late stage. (Duckitt *et al.*, 2005; Hernandez-Diaz *et al.*, 2009; Conde-Agudelo and Belizan, 2000) The early onset of this disorder causes severe morbidity in mothers and a higher preterm birth rate in fetuses. (Mattar and Sibai, 2000) The aim of this study is to find the difference in risk factors between early onset and late onset preeclampsia in the Thai population.

METHODS

This was a case-control study conducted at the Department of Obstetrics and Gynecology, Gujarat Adani institute of medical science, Bhuj, Kutch, Gujarat. The study was approved by the ethical committee of the college and informed consent was obtained from participants. The antenatal and delivery records of all pregnant women with gestational age of 20 weeks or more and estimate fetal weight of 500 g delivered at Gujarat Adani institute of medical science, Bhuj, Kutch, Gujarat from August 2011 to May 2014 were reviewed. Exclusion criteria included abortion, pregnancies complicated with chromosomal or structural anomalies and birth before arrival. Data were divided into three groups as cases and controls. Cases were diagnosed as mild pre-eclampsia, severe pre-eclampsia, eclampsia, or superimposed pre-eclampsia. Cases were divided into two subgroups, early onset and late onset. Controls were normotensive pregnant women who delivered consecutively after pre-eclamptic pregnant women. Data were collected regarding general information, pregnancy information, antenatal care, medical history, and pregnancy outcome. Mild pre-eclampsia was defined as a blood pressure of at least 140/90 mmHg, measured on two occasions at least 6 h apart, with proteinuria of at least 300 mg/ 24 h or at least 1+ on urine dipstick test. Both elevated blood pressure and proteinuria occurred for the first time after gestational age of 20 weeks. Severe preeclampsia was defined on the basis of pre-eclampsia with one or more of the following: blood pressure of at least 160/110 mmHg, proteinuria of at least 5 g/24 h or at least 3+ on urine dipstick test, serum creatinine

*Corresponding author: Dr. Nagajan Bhadarka,
Department of Obstetrics and Gynecology, Adani Institute of Medical Science, Bhuj, Gujarat, India.

>1.2 mg/dL, platelet count <100 000/mL, microangiopathic hemolysis, elevated serum transaminase level, persistent headache or other cerebral or visual disturbance, persistent epigastric pain, pulmonary edema, or intrauterine growth restriction. (ACOG, 2002) The onset of pre-eclampsia was divided into early and late onset; early onset was gestational age less than 34 weeks, and late onset was gestational age of 34 weeks or more. Gestational age was calculated from the time elapsed since the first day of the last menstrual period, or calculated from first-trimester ultrasonography if the last menstrual period was uncertain.

Table 1. Demographic characteristics of study population

Characteristic	Control	Early onset	P value	Late onset	P value
Age	28.5±6.5	31.6 ± 6.4	0.003*	29.4±7.0	0.07
Previous abortion	101	44	0.08	146	0.40
Previous pre-term delivery	13	0	0.87	0	0.004*
Pregestational bodyweight	54.08±10.8	57.6±13.9	0.01*	59.4±13.9	0.003*
Total weight gain (kg)	14±5.8	13.9±5.8	0.9	16.4±5.7	0.0004*

Table 2. Results of multivariate logistic regression analysis

Risk factors	Early onset Late onset Adjusted OR (95% CI)	Adjusted OR (95% CI)
History of chronic hypertension	4.4 (2.1, 9.3)	
Family history of hypertension	—	18 (6, 54)
Family history of diabetes	2.5 (1.1, 5.6)	2.7 (1.6, 4.4)
Pre-pregnancy body mass index 25–29.9 kg/m ²	3.5 (1.3, 8.9)	2.1 (1.2, 3.7)
Pre-pregnancy body mass index ≥ 30 kg/m ²	16.2 (4.5, 58.3)	5.8 (2.8, 11.9)
Pre-pregnancy body mass index < 20 kg/m ²		0.5 (0.3, 0.8)

Sample size calculation was based on the risk factors based on a previous study. (Luealon and Phupong, 2010) Body mass index was the risk factor that gave the largest sample size in the early onset group: 154 women. Multifetal pregnancy was the risk factor that gave the largest sample size in the late onset group: 296 women. The samples in the control group were equal to all women in both case groups: 448 women. The following risk factors were evaluated: age, parity, gestational age, multifetal pregnancies, blood pressure at first visit, height, pre-pregnancy weight, body mass index, weight gain per week, medical illness and family history, drug allergy, medication, previous history of pre-eclampsia, history of gestational hypertension, infant's sex, maternal and fetal complications.

Statistical analysis

Data were presented as mean ± standard deviation and percentage. anova with post-hoc analysis and Kruskal–Wallis were used for continuous variables. The risk factors that were significant on the univariate analysis were entered into a multivariate regression analysis. Adjusted odds ratio (OR) with 95% confidence interval (CI) was calculated. A P-value < 0.05 was considered as statistically significant.

RESULTS

There were a total of 449 consecutive cases with pre-eclampsia. They were divided into 152 women in early onset pre-eclampsia and 297 women in late onset pre-eclampsia and 449 controls. Demographic characteristics are shown in Table 1. Mean maternal age and proportion of multiparity were significantly higher in the early onset pre-eclampsia group

than in controls. The pregestational weight and weight gain per week were significantly higher in both the early and late onset pre-eclampsia groups than in controls. The total weight gain was significantly higher in the late onset pre-eclampsia group than in controls. The proportion of preterm deliveries and cesarean sections were significantly higher in both the early and late onset pre-eclampsia groups than in controls. The control group did not represent a normal population in our institution. The preterm birth rate appeared to be high in the controls.

Neonatal birth weight in the early onset preeclampsia group was significantly less than in controls. From univariate analysis, maternal age ≥35 years, pre-pregnancy BMI 25–29.9 kg/m², weight gain ≥ 0.5 kg per week, female infant, calcium intake, family history of diabetes mellitus (DM), and family history of hypertension were significantly associated with increased risk of both early and late onset preeclampsia. Multiparity, chronic hypertension, pregestational DM or gestational DM, history of pre-eclampsia in previous pregnancy, history of hemolysis, and elevated liver enzyme and low platelet in previous pregnancy were significantly associated with increased risk of early onset pre-eclampsia only. There was no risk factor significantly associated with increased risk of late onset pre-eclampsia only. Gestational age at first antenatal care ≥ 27 weeks and pre-pregnancy BMI < 20 kg/m² were significantly associated with decreased risk of both early and late onset pre-eclampsia.

Gestational age at first antenatal care 14–26 weeks and maternal weight gain < 0.2 kg per week were significantly associated with decreased risk of late onset pre-eclampsia only. Table 3 shows the results of multivariate logistic regression analysis. Risk factors which were significantly associated with increased risk of both early and late onset pre-eclampsia were family history of DM, pre-pregnancy BMI 25–29.9 kg/m², pre-pregnancy BMI ≥30 kg/m² and weight gain ≥ 0.5 kg per week. History of chronic hypertension (OR 4.4; 95% CI 2.1– 9.3) was significantly associated with increased risk of early onset pre-eclampsia only. Family history of chronic hypertension (OR 18; 95% CI 6–54) was significantly associated with increased risk of late onset pre-eclampsia only. Pre-pregnancy BMI < 20 kg/m² was a significant protective factor for both early and late onset pre-eclampsia.

DISCUSSION

This study shows that risk factors that differ between early and late onset pre-eclampsia were a history of chronic hypertension and family history of chronic hypertension. History of chronic hypertension was significantly associated with increased risk of early onset pre-eclampsia only, while family history of chronic hypertension was significantly associated with increased risk of late onset pre-eclampsia only. There has been only one study evaluating the risk factors of early and late onset of pre-eclampsia. Fang *et al.*, 2009 did not find any difference in risk factors between early and late onset pre-eclampsia. (Fang *et al.*, 2009) This may be due to the small sample size of their study. There were only 29 cases of early onset and 121 cases of late onset preeclampsia. They found that pre-pregnancy body mass index >30 kg/m² and failure to use prenatal care services were associated with increased risk of preeclampsia. This study recruited cases as early and late onset pre-eclampsia at the beginning of the study, while Fang *et al.* divided cases into early and late onset pre-eclampsia by subgroup analysis. Poon *et al.*, 2010 developed prediction algorithms for hypertensive disorders based on multivariate analysis of factors from the maternal history and compared the estimated performance of such algorithms in the prediction of early pre-eclampsia, late pre-eclampsia and gestational hypertension.

There were 37 cases with early pre-eclampsia, 128 with late pre-eclampsia, and 140 with gestational hypertension. They found that predictors of early pre-eclampsia were African race, chronic hypertension, prior pre-eclampsia and use of ovulation drugs. Predictors of late onset pre-eclampsia and gestational hypertension were increased maternal age and BMI, and family history or history of pre-eclampsia. The detection rates of early pre-eclampsia, late pre-eclampsia and gestational hypertension in screening by maternal factors were only 37.0, 28.9 and 20.7%, respectively, for a 5% false positive rate. Nanjundan *et al.* evaluated risk factors for early onset severe pre-eclampsia and eclampsia.¹⁴ They found that history of pre-eclampsia or eclampsia in a previous pregnancy, exposure to passive smoking, inadequate antenatal supervision, family history of hypertension in one or more first-degree relatives, living in a joint family, being overweight and lower socioeconomic status were associated with increased risk of early onset pre-eclampsia and eclampsia. The results of the present study were similar to previous studies. (Duckitt and Harrington, 2005; Hernandez-Diaz *et al.*, 2009; Luealon and Phupong, 2010) Overweight and obesity increased the risk of pre-eclampsia, which was explained by increase in triglyceride and free fatty acid levels.

These lipid alterations can produce major factors leading to endothelial cell dysfunction in pre-eclampsia with increased circulating levels of lipid peroxides oxidative stress. This can lead to endothelial cell damage. (Takacs *et al.*, 2001; O'Brien *et al.*, 2003; Cheng and Wang, 2009) Maternal weight gain < 0.2 kg per week was a significant protective factor for early onset pre-eclampsia. Pre-pregnancy BMI < 20 kg/m² was a significant protective factor for late onset pre-eclampsia. This is similar to the previous studies (Lee *et al.*, 2000). History of chronic hypertension was a significant risk factor for early onset pre-eclampsia in the present study. This is in agreement with previous studies that showed that chronic hypertension

was a risk factor for pre-eclampsia. Family history of chronic hypertension was a significant risk factor for late onset preeclampsia in the present study. This is in agreement with previous studies. (Roes *et al.*, 2005; Qiu *et al.*, 2003; Eskenazi *et al.*, 1991) Chronic hypertension can cause end-organ damage and vascular complications.

This may be the reason why chronic hypertension is associated with early onset pre-eclampsia; however, family history of chronic hypertension is associated with late onset preeclampsia. This may be explained by a genetic predisposition. Vascular complications still do not occur in these cases. The limitation of this study was the small number of smokers and the small number of pregnant women who used calcium medication during pregnancy. Thus we could not assess the effect of these factors. In conclusion, the risk factors differing between early and late onset pre-eclampsia were history of chronic hypertension and family history of chronic hypertension. Family history of DM, pre-pregnancy BMI 25 kg/m² and weight gain 0.5 kg per week were risk factors of both early and late onset preeclampsia. These risk factors are valuable to obstetricians for identifying patients at risk for pre-eclampsia and for implementing primary prevention.

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