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Risk Factors for Preeclampsia in Multigravida Women

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Abstract: Hypertensive Diseases in Pregnancy (HDP) are one of the leading causes of maternal and fetal mortality and morbidity. The cause of preeclampsia-eclampsia remains unknown and risk factors for the development of preeclampsia are less well defined. We conducted a case-control study on pregnant women presenting to Tabriz Al-Zahra and Taleghani hospitals from August 2003 to August, 2004. Patients were studied in 2 groups of cases (64) and controls (64). Maternal age and BMI in case group was significantly higher than control group. The difference of education, gravidity, smoking and history of abortion between case and control groups was not significant. Preeclampsia history and inadequate prenatal care in case group were significantly high. The difference of previous SGA newborn, birth interval and same paternity between case and control groups was not significant. Preeclampsia risk factors in multigravida women include: High maternal age and BMI, history of preeclampsia, positive past medical history and inadequate prenatal care.

Key words: Preeclampsia, risk factor, gravidity

INTRODUCTION

Hypertensive Diseases in Pregnancy (HDP) are one of the leading causes of maternal and fetal mortality and morbidity (Leeners *et al*., 2006). There are 4 types of hypertensive disorders in pregnancy: Chronic hypertension, gestational hypertension, preeclampsia and preeclampsia superimposed on chronic hypertension (Fig. 1) (James and Nelson-Piercy, 2004). The term *preeclampsia* refers to the new onset of hypertension (>140/90 mm Hg) and proteinuria after 20 week of gestation in previously normotensive, nonproteinuric women (Table 1) (Skjaerven *et al*., 2005; Wagner, 2004).

Preeclampsia is a common condition and occurs in 5% of pregnancies in the United States and Europe. This condition is the a major cause of maternal, fetal and neonatal morbidity and mortality (Seely and Solomon, 2003; Ian, 2005) and is associated with a five-fold increase in perinatal mortality in developing countries (Lopez-Jaramillo *et al*., 2001). Eclampsia is a life-threatening complication and is characterized by grandmal seizures. A severe variant of preeclampsia also features Hemolysis, Elevated Liver enzymes and Low Platelets (HELLP syndrome). This condition occurs in 1 per 1000 pregnancies (Davison *et al*., 2004).

Although the exact cause of preeclampsia remains unclear, many theories center on problems of placental implantation and the level of trophoblastic invasion. One of the most striking physiologic changes is intense

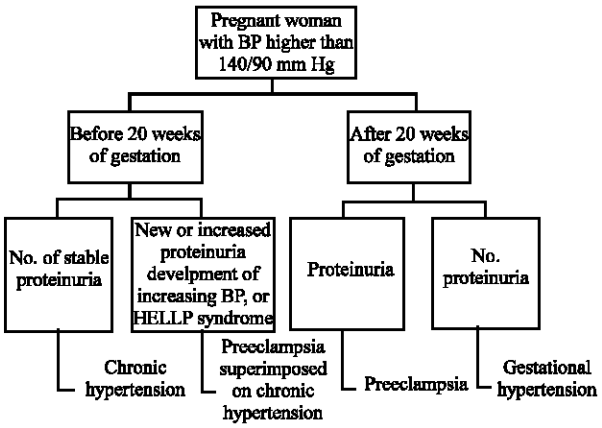

Fig. 1: An algorithm for differentiating among hypertensive disorders in pregnant women, (HELLP = Hemolysis, Elevated Liver Enzymes, Low Platelet Count; BP= Blood Pressure)

systemic vasospasm, which is responsible for decreased perfusion of virtually all organ systems. Perfusion also is diminished because of vascular hemoconcentration and third spacing of intravascular fluids. In addition, preeclampsia is accompanied by an exaggerated inflammatory response and inappropriate endothelial activation. Activation of the coagulation cascade and resultant microthrombi formation further compromise blood flow to organs (Duckitt and Harrington, 2005).

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Table 1: Diagnostic Criteria for Preeclampsia*

Preeclampsia
Blood pressure: 140 mm Hg or higher systolic or 90 mm Hg or higher diastolic after 20 weeks of gestation in a woman with previously normal blood pressure
Proteinuria: 0.3 g or more of protein in a 24 h urine collection (usually corresponds with 1 + or greater on a urine dipstick test)
Severe preeclampsia
Blood pressure: 160 mm Hg or higher systolic or 110 mm Hg or higher diastolic on 2 occasions at least 6 h apart in a woman on bed rest
Proteinuria: 5 g or more of protein in a 24 h urine collection or 3 + or greater on urine dipstick testing of two random urine samples collected at least 4 h apart
Other features: oliguria (less than 500 mL of urine in 24 h), cerebral or visual disturbances, pulmonary edema or cyanosis, epigastric or right upper quadrant pain, impaired liver function, thrombocytopenia, intrauterine growth restriction

*: For the diagnosis of preeclampsia, both hypertension and proteinuria must be present, Information from Wagner, 2004 and ACOG Committee on Obstetric Practice, 2002

The clinical presentation of preeclampsia may be insidious or fulminant. Some women may be asymptomatic at the time they are found to have hypertension and proteinuria; others may present with symptoms of severe preeclampsia, such as visual disturbances, severe headache, upper abdominal pain or HELLP syndrome. Death associated with preeclampsia-eclampsia may be due to cerebrovascular events, renal or hepatic failure, HELLP syndrome, or other complications of hypertension (Mackay *et al*., 2001).

There is no single reliable and cost-effective screening test for preeclampsia and there are no well-established measures for primary prevention. Management before the onset of labor includes close monitoring of maternal and fetal status. Management during delivery includes seizure prophylaxis with magnesium sulfate and, if necessary, medical management of hypertension. Delivery remains the ultimate treatment.

Access to prenatal care, early detection of the disorder, careful monitoring and appropriate management are crucial elements in the prevention of preeclampsia-related deaths (Wagner, 2004).

Risk factors for preeclampsia include medical conditions with the potential to cause microvascular disease (e.g., diabetes mellitus, chronic hypertension, vascular and connective tissue disorders), antiphospholipid antibody syndrome and nephropathy (ACOG Committee on Obstetric Practice, 2002). Other risk factors are associated with pregnancy itself or may be specific to the mother or father of the fetus (Table 2).

Significant risk factors for preeclampsia in a second pregnancy include longer birth interval, previous preterm delivery, previous small-for-gestational-age newborn, renal disease, chronic hypertension, diabetes mellitus, obesity, black race and inadequate prenatal care (Mostello *et al*., 2002).

Table 2: Risk Factors for Preeclampsia

Pregnancy-associated factors
Chromosomal abnormalities
Hydatidiform mole
Hydrops fetalis
Multifetal pregnancy
Oocyte donation or donor insemination
Structural congenital anomalies
Urinary tract infection
Maternal-specific factors
Age greater than 35 years
Age less than 20 years
Black race
Family history of preeclampsia
Nulliparity
Preeclampsia in a previous pregnancy
Specific medical conditions: gestational diabetes, type I diabetes, obesity, chronic hypertension, renal disease, thrombophilias
Stress
Paternal-specific factors
First-time father
Previously fathered a preeclamptic pregnancy in another woman

Information from Duckitt and Harrington, 2005, ACOG Committee on Obstetric Practice, 2002 and Dekker and Sibai, 2001

The purpose of this study was to evaluate the risk factors for preeclampsia in multigravida women of our population in order to identify the important risk factors and prevent them in this group of pregnant women.

MATERIALS AND METHODS

This is a cross-sectional, case-control study performed over pregnant women presenting to Tabriz Taleghani and Al-Zahra hospital since August 2003 to August, 2004.

The simple randomized method of sampling was performed among multigravida women and 128 women were selected. Of all studied women, 64 were preeclamptic (case group) and 64 were without preeclampsia (control group).

The data were collected by questionnaire filling from hospital records and question from the studied women. These data were including individual characteristics, education level, age, height, weight, the history of smoking, gravidity, parity, abortion, stillbirth, hypertension, proteinuria, past medical history, the history of having Small-for-Gestational-Age (SGA) newborn, the interval between past and recent pregnancy, changing paternity of children, prenatal cares in recent pregnancy and the status of newborn in recent delivery.
The criteria for preeclampsia in this study were new onset of hypertension (systolic blood pressure of = 140 mm Hg or diastolic BP of = 90 mm Hg) and proteinuria after 20 week of gestation in previously normotensive, nonproteinuric women.

The criteria for inadequate prenatal care were total care of less than 8 times or initiation of prenatal cares after the first trimester.

The data were analyzed by SPSS statistical software. Chi-square test was used for comparison of two statistical groups and p-value<0.05 was considered statistically significant. Also, Cramer and Phi coefficient were used for determination of severity of correlation between variables.

RESULTS

The most of mothers in at both groups were belong to age range of 26-35 years. All of them had the ages more than 18 years, with average age of 30.71 years (case group) and 28.06 years (control group). The age difference between two groups was significant (PV = 0.25, κ^2 = 7.3, severity of correlation = 24).

The most of mothers in both groups had BMI of = 30 kg m^{-2}, with average BMI of 31.61 kg m^{-2} (case group) and 28.18 kg m^{-2} (control group). The difference of BMI between 2 groups was significant (PV = 0.006, κ^2 = 10.1).

The history of smoking was positive in 2 women of control group and the difference between 2 groups about this history was not significant (PV=0.154, κ^2 = 2.03).

Table 3 shows the age, BMI and the history of smoking in both preeclamptic and control groups.

Thirty three women (51.6%) in case group and 38 women (59.4%) in control group had the elementary and secondary educational levels; and the difference of education level between both groups was not significant (PV = 0.17, κ^2 = 4.9). Twenty nine patients (45.3%) in preeclamptic group and 31 women (48.4%) in control group were gravida II (secundigravida) and the difference of gravidity between 2 groups was not significant (PV = 0.171, κ^2 = 5).

The history of abortion was negative in 49 women (76.6%) in preeclamptic and 52 women (81.3%) in control group and the difference of history of abortion between 2 groups was not significant (PV = 0.635, κ^2 = 0.9).

The history of stillbirth in both groups was same (9.4) with no difference (PV = 1).

Regarding the affection of mothers with diabetes mellitus, chronic hypertension and renal disease, the difference between two groups was not significant (PV = 0.158, κ^2 = 5.2), but the difference between two groups about the history of following conditions was significant (PV = 0.004, κ^2 = 11.2, severity of correlation = 29).

In preeclamptic women, 14 cases (21.9%) had the history of following conditions: Gestational diabetes (1 case), surgery for renal stone (1 case), goiter (1 case), kyphoscoliosis (2 cases), mitral valve prolapse (1 case), genital herpes (1 case), extrauterine pregnancy (1 case), curettage (1 cases), infertility (3 cases), herniorrhaphy (2 cases), apandectomy (2 cases) and tonsillectomy (2 cases).

Table 3: Age, BMI and smoking history of women in both case and control groups

		Case	Control	p-value
Age (years)	>18	0 (0%)	0 (0%)	0.025
	18-25	10 (15.6%)	20(31.3%)	
	26-35	42 (65.6%)	40(62.5%)	
	≥35	12 (18.8%)	4(6.3%)	
	Average age	30.71	28.06	
BMI (kg m^{-2})	Normal (≤25)	6 (9.4%)	20 (31.3%)	0.006
	Overweight (26-29)	23 (35.9%)	21(32.8%)	
	Obese (=30)	35 (54.7%)	23 (35.9%)	
Smoking		0 (0%)	2 (3.1%)	0.154

Table 4: The difference of variables in both case and control groups

		Case (%)	Control (%)	p-value
Gravidity	Gravida 2	29 (45.3)	31(48.4)	0.171
	Gravida 3	20 (31.3)	19 (29.7)	
	Gravida 4 and 5	7 (10.9)	12 (19.4)	
	Gravida ≥6	8 (12.5)	2(3.1)	
Abortion	0	49 (76.6)	52 (81.3)	0.635
	1	8 (12.5)	8 (12.5)	
	≥2	7 (10.9)	5 (6.3)	
History of medical condition	No	45 (70.3)	59 (92.2)	0.025
	Diabetes mellitus	1 (1.6)	0 (0)	
	Chronic hypertension	3 (4.7)	0 (0)	
	Renal disease	1 (1.6)	0 (0)	
	Other	14 (21.9)	5 (7.8)	
History of preeclampsia		14 (21.9)	0 (0)	0.000
History of SGA delivery		11 (17.2)	14 (22.6)	0.504
Paternity change		3 (4.7)	3 (4.7)	1.000
Prenatal care	Sufficient	32 (50)	50 (78.1)	0.001
	Inadequate	32 (50)	14 (22.6)	
Type of delivery	Vaginal	28 (45.2)	28 (44.4)	0.936
	Cesarean	34 (54.8)	34 (55.6)	
Newborn age	Term	24 (38.7)	58 (92.1)	0.000
	Preterm	38 (61.3)	5 (6.3)	
Birth-weight (kg)	≤2.5	25 (40.3)	59 (93.7)	0.000
	2-2.5	12 (19.4)	4 (6.3)	
	1.5-2	11 (17.7)	0 (0)	
	≤1.5	14 (22.6)	0 (0)	

In control group, 5 women (7.8%) had the history of following conditions: goiter (1 case), curettage (1 case), infertility (1 case), surgery for ovarian cyst (1 case) and cholecystectomy (1 case).

The difference of history of preeclampsia in both case and control groups was significant (PV = 0.000, κ^2 = 15, severity of correlation = 35) but the difference of having newborn with SGA in these groups was not significant (PV = 0.504, κ^2 = 0.4) (Table 4).

The time interval between past and recent pregnancy was averagely 6.64 years in preeclamptic and 5.85 years in control group with the minimum and maximum time of 1 and 16 years in both groups; so, the difference of interbirth interval between two groups was not significant (PV = 0.573). Also, the changing of paternity of offsprings between two groups was not significant (PV = 0.000).

The number of women with inadequate prenatal care was 32 (50%) in preeclamptic and 14 (21.9%) in control group. The difference of inadequate care between 2 groups was significant (PV = 0.001, κ^2 = 10.9).

According to the Table 4, there was not significant difference between two groups about the type of delivery (PV = 0.936).

The number of mothers with preterm newborn was 38 (61.3%) and 5 (7.9%) in case and control groups, respectively and this difference was significant (PV = 0.000, κ^2=39, severity of correlation = 56).

The average birth-weight of newborns was 2444.57 g and 3252.14 g in case and control groups, respectively. The difference of number of Low Birth Weight (LBW) newborns in both groups was significant (PV = 0.00, κ^2 = 42, severity of correlation = 58).

The birth-time Apgar score of group case was 0 (6.5%), low (3.2%), intermediate (9.7%) and high (80.6%). In control group, 6.35 of newborns had intermediate Apgar score and remaining had high Apgar score but the difference of Apgar score between 2 groups was not significant (PV = 0.068).

There were 4 cases (6.5%) of stillbirth in preeclamptic women in comparison with no case in control group and this difference was significant (PV = 0.04, κ^2 = 4).

DISCUSSION

In present study the average age of preeclamptic mothers was higher than control mothers. Prior studies have showed that the higher age of mother is associated with higher risk of preeclampsia. Bianco *et al.* (1996) concluded that older gravidas (nulliparas or multiparas) were more likely to develop preeclampsia and the risk of preeclampsia in women with = 40 years old become 2 folds (Bianco *et al.*, 1996). Another study suggested that for any year increase in maternal age, the risk of preeclampsia rises as 30% (Saftlas *et al.*, 1990).

The average Body Mass Index (BMI) of preeclamptic mothers (31.64 kg m^{-2}) was higher than control group (28.18 kg m^{-2}). Most observational studies demonstrate a consistently strong positive association between maternal prepregnancy BMI and the risk of preeclampsia (Obrien *et al.*, 2003; Bodnar *et al.*, 2005). Indeed, BMI is known as a risk factor for preeclampsia (Ohkuchi *et al.*, 2006).

The clinical feature of preeclampsia, including hypertension, proteinuria and varying degrees of ischemic end-organ damage, are caused by widespread endothelial dysfunction. Epidemiologic risk factors for preeclampsia, such as obesity, diabetes and hypertension, are also important risk factors for atherosclerosis. Metabolically, both preeclampsia and atherosclerosis are associated with insulin resistance, dyslipidemia and hypercoagulability (Myles *et al.*, 2001).

Obesity is a validated risk factor for preeclampsia (Nucci *et al.*, 2001) but the mechanism of how it imparts increased risk is not completely understood. Obesity might act through its association with insulin resistance, a syndrome of metabolic derangement characterized by hyperinsulinemia, hyperlipidemia, hypertension and endothelial dysfunction. It also might act through an inflammatory mechanism (Myles *et al.*, 2001; Thadhani *et al.*, 1999).

The education level of preeclamptic mothers was slightly (but not significantly) more than control mothers. Mittendorf *et al.* (1996) demonstrated that the education level of less than high-school is a risk factor of preeclampsia (Mittendorf *et al.*, 1996) but in obstetrics and gynecologic textbooks, the education level has not been considered as a risk factor (Cuningham *et al.*, 2001).

Maternal smoking surprisingly is protective against preeclampsia (Mostello *et al.*, 2002; Lydakis *et al.*, 2001; Mortensen *et al.*, 2001; Odegard *et al.*, 2000; Xiong *et al.*, 2000). In present study, only 2 women in control group were smoker but the difference of number of smoker in both groups was not significant.

The difference of gravidity and history of abortion between case and control groups was not significant. Xiong *et al.* (2002) demonstrated that a single previous abortion was associated with a slightly decreased risk of preeclampsia. However, = 2 abortions were not associated with a decreased risk of preeclampsia (Xiong *et al.*, 2002). It seems that there is no significant relation between the history of abortion and preeclampsia.

Mittendorf *et al.* (1996) and Mostello *et al.* (2002) showed that the history of chronic disease, such as chronic hypertension, diabetes mellitus and renal disease are risk factors for preeclampsia; but in present study, the history of chronic disease, such as chronic hypertension, diabetes mellitus and renal disease, was not significantly different between two groups.

Of all preeclamptic women 21.9% had the history of preeclampsia in comparison with none of control group. In a study of Mostello *et al.* (2002), there was history of preeclampsia in 34.4% of case group and 5.2% of control group which is compatible with our study. Other studies had also similar findings (Wagner, 2004; Duckitt and Harrington, 2005; Lydakis *et al.*, 2001; Eskenazi *et al.*, 1991).

The history of previous SGA newborn was 17.2% and 21.9% in case and control groups respectively with no significant difference between two groups; this result is incompatible with Mostello *et al.* (2002) study in which these ratio were 16.4 and 9.9%, respectively with significant difference.

In present study the difference of interbirth interval between 2 groups was not significant but other studies demonstrated that a longer birth interval is a significant risk factor for preeclampsia in a second pregnancy (Mostello *et al*., 2002; Skavenjen *et al*., 2002).

Longer interbirth interval may be associated with both a change of partner and a higher risk of preeclampsia (Mostello *et al*., 2002). A study by Li and Wi (2000) showed that the effect of changing paternity depends on the history of preeclampsia/eclampsia with the previous partner and support the hypothesis that parental human leukocyte antigen sharing may play a role in the etiology of preeclampsia/eclampsia. In their study, changing of paternity in case group was significantly more prevalent than control group. These finding is incompatible with our study in which the ratio of changing of paternity in both groups was similar.

Preeclampsia is hypothesized to be a maternal immunologic response to foreign fetal antigen derived from the father's sperm. This response may be reduced by prolonged exposure to father's antigen (Trupin *et al*., 1996) which may explain why preeclampsia is more prevalent in changing of paternity.

In the study of Mostello *et al*. (2002) the inadequate prenatal care in case and control groups was 21.1 and 16.3%, respectively. In present study the inadequate prenatal care in case group was significantly more than control group (50% vs. 21.9%) and also more than the results of their study.

A study by Lydakis *et al*. (2001) showed that in pregnancies with hypertensive complications (with or without PE) there was a trend towards higher rates of preterm delivery (<37 weeks), caesarean section, small for gestational age babies, stillbirth and lower baby birth weight (25). All of these findings are compatible with our study results.

CONCLUSION

We concluded that the risk factors of preeclampsia in multigravida women in our region are including previous history of preeclampsia, inadequate prenatal care in recent pregnancy, higher maternal age, higher pregravid BMI and the history of medical conditions.

The education level of mother, smoking, gravidity, history of abortion, previous small-for-gestational-age newborn, interbirth interval and paternity change have no effect on development of preeclamosia.

The fetal complications including preterm delivery, small for gestational age babies, stillbirth and lower baby birth weight were more prevalent in preeclamptic mothers.

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