PERINATAL EPIDEMIOLOGICAL RISK FACTORS FOR PREECLAMPSIA

Mirna Vuković Bobić[1], Dubravko Habek[2] and Jasna Čerkez Habek[3]

[1]University Department of Obstetrics and Gynecology, Kaiser Franz Joseph University Hospital, Vienna, Austria; [2]University Department of Obstetrics and Gynecology, [3]University Department of Internal Diseases, Sveti Duh University Hospital, Croatian Catholic University, Zagreb, Croatia

SUMMARY – In the present study, the impact of the potential perinatal epidemiological factors on preeclampsia development was assessed. This clinical study included 55 pregnant women with preeclampsia and control group of 50 healthy pregnant women. Positive family history of cardiovascular disease, diabetes mellitus or thromboembolic disease was recorded in 50% of women with preeclampsia *versus* 28% of control group women. Positive personal history of this disease was recorded in 15% of women with preeclampsia, whereas all control group women had negative personal history of preeclampsia. Dietary habits, i.e. the intake of meat and meat products, fruit and vegetables, coffee and alcohol drinks were similar in the two groups, without statistically significant differences. The women with preeclampsia and control women reported comparable habits; there was no difference in the consumption of meat, fruit, vegetables, coffee and alcohol, smoking, use of folate and oral hormonal contraception before pregnancy, or in physical activity as the potential risk factors for preeclampsia in current pregnancy. However, personal and family history of vascular disease proved to be significant risk factors for the occurrence of preeclampsia, emphasizing the need of lifestyle and dietary modifications with healthy dietary habits, while avoiding adverse habits in pregnancy.

Key words: *Preeclampsia – epidemiology; Risk factors; Pregnancy; Lifestyle*

Introduction

Preeclampsia is a multiorgan syndrome carrying a risk of subsequent development of vascular disease due to the still questionable yet accepted theories of immune reaction and inflammation with atherogenesis. The incidence of preeclampsia is estimated to 2%-7% in industrialized western countries, whereas in developing countries it rises to 10% of all pregnancies[1], or to 7% according to other reports, with a rising tendency recorded in recent years[2,3]. Lifestyle and habits of pregnant women can play a role in the occurrence of preeclampsia, e.g., obesity, tobacco smoking, use of alcohol and coffee, which all directly influence the level of homocysteine (increased intake of these substances results in elevated homocysteine levels). Diet is also very important since inadequate intake of fruit, fresh vegetable and fish, or food overheating reduces the intake of vitamins, thus increasing blood homocysteine level as a risk factor for preeclampsia. On the other hand, physical activity and blood homocysteine level are inversely proportional[4,5]. In the present study, the impact of the potential perinatal epidemiological factors such as habits, diet, medication and folic acid supplementation, and of maternal history data on preeclampsia development was assessed.

Correspondence to: *Prof. Dubravko Habek, MD, PhD*, University Department of Obstetrics and Gynecology, Sveti Duh University Hospital, Sveti Duh 64, HR-10000 Zagreb, Croatia
E-mail: dubravko.habek@os.t-com.hr

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Material and Methods

This clinical study included 55 pregnant women with defined preeclampsia (blood pressure measurements on at least two occasions at minimum 4-h interval ≥140/90 mm Hg, and with positive proteinuria after 20th week of gestation) and control group of 50 pregnant women after >20th week of gestation with normal course of pregnancy. The study was approved by Ethics Committee of the Osijek University Hospital Center. Prior to entering the study, all women were explained the purpose, protocol and objectives of the study. Data were collected on personal history and hetero-history, lifestyle, gestational age, parity, physical activity, smoking, alcohol drinking, food, folic acid supplementation and oral contraceptive use. The selected descriptive statistics parameters were determined for the variables denoting particular characteristics of study subjects. The Shapiro-Wilks test was used because of the relatively small number of study subjects. The χ^2-test was used on testing the hypothesis, while differences were considered statistically significant at the level of $p<0.05$. Data were processed by use of the Microsoft Excel table calculator, while the SPSS and Statistica softwares were employed on data processing.

Results

Study results revealed the mean gestational age in the group of women with preeclampsia (250.982 (35+5)±24.692 days) to be lower than the mean gestational age in the control group (274.720 (39+1)±10.610 days). The Mann-Whitney test yielded a statistically significant difference in gestational age between the group of women with preeclampsia and control group ($Z=-5.8$, $p=0.000$). There was no statistically significant between-group difference according to parity. Study results showed that almost 50% of women with preeclampsia had positive family history of cardiovascular disease, diabetes mellitus or thromboembolic disease *versus* 28% in the control group; 15% of women with preeclampsia had already had positive personal history of cardiovascular disease, diabetes mellitus or thromboembolic disease, whereas the control group of women had negative personal history of these dis-

Table 1. Family and personal history data

Parameter	Family history		Personal history	
	Preeclampsia group	Control group	Preeclampsia group	Control group
Negative history	28 (50.91%)	36 (72%)	47 (85.45%)	50 (100.00%)
Cardiovascular morbidity	11 (20.00%)	7 (14.00%)	1 (1.82%)	0 (0.00%)
Diabetes	7 (12.73%)	4 (8.00%)	3 (5.45%)	0 (0.00%)
Thromboembolism	2 (3.64%)	1 (2.00%)	3 (5.45%)	0 (0.00%)
2-3 diseases	7 (12.73)	2 (4.00%)	1 (1.82%)	0 (0.00%)
Total	55 (100.00%)	50 (100.00%)	55 (100.00%)	50 (100.00%)

Table 2. Previous pregnancy comorbidity and complications

Previous pregnancy	Preeclampsia group	Control group
Normal pregnancy	32 (58.18%)	47 (94.00%)
Preeclampsia	10 (18.18%)	0 (0.00%)
Gestational diabetes	1 (1.82%)	2 (4.00%)
Antiphospholipid syndrome	1 (1.82%)	0 (0.00%)
Intrauterine fetal death	2 (3.64%)	1 (2.00%)
Spontaneous miscarriage	8 (14.55%)	1 (2.00%)
Intrauterine growth retardation	1 (1.82%)	0 (0.00%)
Total	55 (100.00%)	0 (0.00%)

eases. According to study results, about 40% of women with preeclampsia had developed some pregnancy complications in their previous pregnancies, which could have been related to vascular disorders underlying preeclampsia, in contrast to the control group where 94% of women had normal previous pregnancies; the difference was statistically significant (Tables 1 and 2). Dietary habits, i.e. the intake of meat and meat products, fruit and vegetables, the consumption of coffee and alcohol drinks were also similar in the two groups, without statistically significant between-group difference. The use of oral hormonal contraception and the rate of physical activity during pregnancy were also comparable between the group of women with preeclampsia and control group of women without preeclampsia, yielding no statistically significant difference. There was no between-group difference according to the frequency and level of cigarette smoking either. The results showed that almost one-third of women from both groups did not take folate during pregnancy; however, a greater proportion of control group women had been taking folate before pregnancy as compared to the preeclampsia group who had mostly started taking folate just during pregnancy (Tables 3-5).

Discussion and Conclusion

The women having developed preeclampsia in previous pregnancies are at a higher long-term risk

Table 3. Meat and fruit/vegetable intake in pregnancy

Meat intake	Preeclampsia group	Control group	Fruit and vegetable intake	Preeclampsia group	Control group
No	1 (1.82%)	2 (4.00%)	No	12 (21.82%)	8 (16.00%)
1-3 *per* week	21 (38.18%)	12 (24.00%)	1-3 daily	37 (67.27%)	36 (72.00%)
3-5 *per* week	26 (47.27%)	28 (56.00%)	>3 daily	6 (10.91%)	6 (12.00%)
Daily	7 (12.73%)	8 (16.00%)			
Total	55 (100.00%)	50 (100.00%)	Total	55 (100.00%)	50 (100.00%)

Table 4. Coffee and alcohol intake

Coffee intake	Preeclampsia group	Control group	Alcohol intake	Preeclampsia group	Control group
No	16 (29.09%)	18 (36.00%)	No	54 (98.18%)	47 (94.00%)
1-3 daily	37 (67.27%)	30 (60.00%)	Occasionally	1 (1.82%)	3 (6.00%)
>3 daily	2 (3.64%)	2 (4.00%)	Daily	0 (0.00%)	0 (0.00%)
Total	55 (100.00%)	50 (100.00%)	Total	55 (100.00%)	50 (100.00%)

Table 5. Cigarette smoking and folic acid supplementation

Cigarette smoking	Preeclampsia group	Control group	Folate supplementation	Preeclampsia group	Control group
No smoking	37 (67.27%)	33 (66.00%)	No	16 (29.09%)	14 (28.00%)
<5 cigarettes daily	13 (23.64%)	13 (26.00%)	Before pregnancy	2 (3.64%)	11 (22.00%)
5-20 cigarettes daily	5 (9.09%)	4 (8.00%)	During pregnancy	37 (67.27%)	25 (50.00%)
>20 cigarettes daily	0 (0.00%)	0 (0.00%)			
Total	55 (100.00%)	50 (100.00%)	Total	55 (100.00%)	50 (100.00%)

of cardiovascular and cerebrovascular events in comparison the women with normotensive pregnancies. Many risk factors and pathophysiological abnormalities associated with preeclampsia actually resemble the events seen in coronary artery disease. Ramsay *et al*. were the first to demonstrate microvascular function impairment in preeclamptic pregnancies. Insulin resistance is frequently reported as a common factor. Accordingly, microvascular dysfunction associated with insulin resistance can predispose the woman to both coronary disease and preeclampsia later in life[6-9]. And *vice versa*, pregnancies complicated with preeclampsia can identify women at risk of subsequent development of vascular disease and indicate the need of lifestyle and risk factor modification[10]. In a retrospective study that included more than one million Canadian women, those with any of the following events: preeclampsia, gestational hypertension, abruptio placentae and placental infarction in previous pregnancies were at a twofold higher risk of premature cardiovascular disease at the mean follow up of 8.7 years as compared with the women free from placental symptomatology[11]. In addition, the women with preexisting metabolic, vascular or renal diseases are at a higher risk of superimposed preeclampsia, probably due to their increased susceptibility to normal physiologic changes in pregnancy[12]. The exact mechanism by which obesity or insulin resistance is associated with preeclampsia has not yet been fully elucidated. It may possibly be explained by increased stress along with hyperdynamic circulation, dyslipidemia, or increased cytokine mediated oxidative stress, increased sympathetic activity, increased renal sodium resorption, and direct interference of insulin resistance and hyperinsulinism with placentation[6,13]. In our study group, 50% of the women with preeclampsia had positive family history of microangiopathic etiopathogenesis; about 40% of the women with preeclampsia had developed some pregnancy complication that could have been related to vascular disorders underlying preeclampsia in their previous pregnancies. Although quite unusual and unadvisable, smoking up to 5 cigarettes a day has been demonstrated to reduce the risk of preeclampsia[14], but later on it significantly increases both early and late neonatal morbidity[15]. Deficiency of vitamin B complex, necessary for homocysteine metabolism (folic acid, vitamins B12 and B6), can cause hyperhomocysteinemia in more than 90% of cases. According to the recent ARIC study, even isolated vitamin B6 deficiency is considered as an independent risk factor for development of atherosclerosis[16]. Folate deficit is the most common hypovitaminosis in Europe, in particular due to inadequate fresh fruit and vegetables in diet. About 90% of folate is lost by food processing because it is heat and light sensitive. Makedos *et al.* compared homocysteine levels between the groups of pregnant women with and without preeclampsia, and found the mean homocysteine level to be significantly increased in the former (11.11 *vs*. 6.40 μmol/L)[17]. The authors paid special attention to the possible etiologic factors of hyperhomocysteinemia (folate and vitamin B12 concentration and genetic polymorphisms) for which association with hyperhomocysteinemia has not yet been demonstrated. Then they speculated on the potential causative effect of hyperhomocysteinemia on the occurrence of preeclampsia *via* oxidative stress and endothelial dysfunction (which was also our hypothesis) and found the available studies to show non-uniform entry data, poor correlation of the factors investigated and lack of biologic plausibility; therefore, they believe that these literature data cannot explain the association of hyperhomocysteinemia and preeclampsia[18]. In our study, the women with preeclampsia and control women reported comparable habits; there was no difference in the consumption of meat, fruit, vegetables, coffee and alcohol, smoking, use of folate and oral hormonal contraception before pregnancy, or in physical activity as the potential risk factors for preeclampsia in current pregnancy, which is consistent with literature data. However, personal and family history of vascular disease proved to be significant risk factors for the occurrence of preeclampsia, emphasizing the need of lifestyle and dietary modifications with healthy dietary habits, while avoiding adverse habits in pregnancy.

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Sažetak

PERINATALNI EPIDEMIOLOŠKI ČIMBENICI RIZIKA ZA PREEKLAMPSIJU

M. Vuković Bobić, D. Habek i *J. Čerkez Habek*

U ovom istraživanju ispitan je utjecaj potencijalnih perinatalnih epidemioloških čimbenika na razvoj preeklampsije. U kliničko istraživanje je bilo uključeno 55 trudnica s preeklampsijom i kontrolna skupina od 50 zdravih trudnica. Pozitivna obiteljska anamneza kardiovaskularnih bolesti, šećerne bolesti ili tromboembolija zabilježena je u 50% žena s preeklampsijom u odnosu na 28% u kontrolnoj skupini trudnica. Pozitivna anamneza prethodne preeklampsije zabilježena je u 15% žena u skupini s aktualnom preeklampsijom, dok su sve žene kontrolne skupine imale negativnu anamnezu preeklampsije. Prehrambene navike, odnosno uzimanje mesa i mesnih proizvoda, voća i povrća, kave i alkoholnih pića bile su slične u objema skupinama, bez statistički značajne razlike, kao i primjena oralne hormonske kontracepcije i fizičke aktivnosti prije trudnoće. Međutim, osobna i obiteljska anamneza krvožilnih bolesti pokazale su se značajnim čimbenicima rizika za pojavu preeklampsije, naglašavajući potrebu promjene načina života uz zdrave prehrambene navike i izbjegavanje štetnih navika u trudnoći.

Ključne riječi: *Preeklampsija – epidemiologija; Čimbenici rizika; Trudnoća; Način života*