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RISK FACTORS AND OUTCOME OF PREECLAMPSIA

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A b s t r a c t: *Aim:* To determine differences between groups with hypertension in pregnancy and assess risk factors associated with preeclampsia.

Patients and methods: In the period 2008–10 at the Department of Nephrology in Skopje, Macedonia, a prospective and a longitudinal study study comprising 134 pregnant women was carried out. They had regular monthly check-ups in pregnancy and after delivery (1–8), when groups were defined as gestational hypertension, pre-existing hypertension, superimposed preeclampsia, and preeclampsia. A total of 134 women were regularly controlled by 24-hour ambulatory monitoring of blood pressure (24ABPM), blood and urine, D-dimers, and a resistance index of the Doppler of the umbilical artery (RI a.umb), and a questionnaire on risk factors was filled in for every pregnant woman.

Results: Superimposed preeclampsia was found in 22 (16.4%) and preeclampsia was found in 20 women (14.9%). Daily diastolic blood pressure of 24-hour blood pressure monitoring at the last check-up before delivery was significantly higher in the group with superimposed preeclampsia (SP) 87.6 ± 9.5 and in the group with preeclampsia (PE) 87.9 ± 7.7 mm Hg. Previous preeclampsia (OR = 3.28), primiparity (OR = 2.35), methyldopa (OR = 3.76), number of check-ups (OR = 2.3), positive family history (OR = 1.4) and *in vitro* fertilisation (OR = 1.15) were found as risk factors associated with the occurrence of preeclampsia and preeclampsia superimposed on preexisting hypertension.

Conclusions: Early determination of risk factors should prompt more frequent check-ups in hypertensive pregnancies in order to determine timely delivery and avoid adverse outcomes in the mother and child.

Key words: preeclampsia, risk factors, outcomes.

Introduction

Preeclampsia is the most common complication in pregnancy and its incidence ranges between 2–10% [1]. Preeclampsia comprises blood pressure > 140/90 mm Hg and a new onset of proteinuria after the 20th gestational week, while when there is a history of pre-existing hypertension and a new onset of proteinuria > 0.3 g/du after the 20th gestational week, preeclampsia superimposed on pre-existing hypertension is diagnosed [2].

Since the etiology is not completely known, primary prevention of these conditions is not possible [3]. Therefore, secondary and tertiary prevention are most important in early recognition and timely delivery in order to avoid adverse outcomes for the mother and the child [3].

Unfortunately, available biomarkers cannot predict preeclampsia with a very high probability and therefore early determination of risk factors and risk stratification for every preganant woman with hypertension may be used as a substitute for prediction [4].

The aims of our study were to determine differences between groups with hypertension in pregnancy and assess risk factors associated with preeclampsia.

Material and Methods

A prospective study was carried out on 134 pregnant women, followed every month during pregnancy at the Department of Nephrology and one check-up 2–6 months after delivery (a total of 1–8 check-ups), when it was determined in which group the women belonged. Fifty-one women (38.2%) had pre-existing hypertension (HT), 41 (30.5%) had gestational hypertension (GH), 20 (14.9%) had preeclampsia (PE) and 22 (16.4%) had superimposed preeclampsia (SP). General data on all four groups are shown as mean values and standard deviation. 24-hour blood pressure monitoring profile, proteinuria, birthweight, D-dimers, and resistance index at Doppler of the umbilical artery (RI a.umb.) were determined and compared at the last check up before delivery and shown as mean values and standard deviation in all four groups and differences were tested by ANOVA. A questionnaire was filled in for every pregnant woman, comprising dichotomous data on the following risk factors: family history, smoking, *in vitro* fertilisation, previous preeclampsia, primiparity, administration of therapy (methyldopa), and data were presented as a percentage of a total, difference estimated by χ^2 test and risk factors determined as odds ratio in combined groups of preeclampsia (preeclampsia and superimposed preeclampsia) and no preeclampsia (gestational hypertension and pre-existing hypertension). Data were analysed by the use of SPSS 13.0 for Windows.

Results

General characteristics of pregnant women enrolled in the study are shown in Table 1. The average number of check-ups per pregnant woman was 3.6, ranging from 1 to 8. Mean gestational age at enrolment was 20.39 ± 8.4 years and body mass index (BMI) at enrolment was 31.5 ± 6.3 kg/m^2. Most of the women were multiparas – 85 (63.4%), 20 (15%) had had previous preeclampsia, 4 (3%) had diabetes and 1 (0.74%) had chronic kidney disease. Antihypertensive medication at any point during pregnancy was used in 98 (73%) of all pregnant women.

Table 1 – Табела 1

General characteristics of all groups with hypertension in pregnancy
Општи карактеристики на сите групи со хипертензија во гравидитет

General characteristics of all groups	
Nr of controls at the Department per pregnant woman	3.6 (1–8)
Age (yrs)	30.5 ± 2,3
Gestational age at enrolment	20.39 ± 8,4
BMI (kg/m^2)	31.5 ± 6.3
Nulliparity	49 (36.6 %)
Multiparity	85 (63.4%)
Current smoker	12 (8.9%)
Previous preeclampsia	20 (15%)
Diabetes	4 (3%)
Chronic kidney disease	1 (0.74%)
Antihypertensive medication	98 (73%)

As shown in Table 2, women with superimposed preeclampsia were the oldest (33.78 ± 4.4 years) and had significantly higher BMI (31.55 ± 6.4 kg/m^2) at enrolment. At the last check-up before delivery, women with superimposed preeclampsia had significantly higher daily systolic and diastolic blood pressures (132.4 ± 12.3 and 87.6 ± 9.5 mm Hg, respectively, P = 0.049).

Proteinuria, D-dimers, RI of Doppler of umbilical artery and birthweight, as shown in Table 3, were significantly different in subgroups with preeclampsia. Mean proteinuria in the subgroup with superimposed preeclampsia was 780 ± 300 and in the subgroup with preeclampsia, 1500 ± 400 mg/dU (P = 0.000). In the group with preeclampsia, D-dimers (1317 ± 857 ng/ml) and resistance index on the Doppler of the umbilical artery (0.71 ± 0.08) were higher when compared to other groups (P = 0.001 and P = 0.000 respectively).

Table 2 – Табела 2

Difference in age, BMI and 24-hour blood pressure in groups with hypertension in pregnancy
Разлика во возраста, индексот на телесна маса и 24 часовен мониторинг на крвен притисок меѓу групите со хипертензија во гравидитет

RISK FACTORS	PH	GH	SP	PE	ANOVA (P)
AGE	29.04 ± 4.6	29.5 ± 4.8	33.78 ± 4.4	29.3 ± 5.29	**0.001**
BMI	28.3 ± 6.8	28.7 ± 5.9	31.55 ± 6.4	30 ± 9.65	**0.281**
24 hour ABPM					
Daily systolic blood pressure	130.7 ± 19.2	123.9 ± 12	132,4 ± 12,3	129,9 ± 12,4	**0.088**
Daily diastolic blood pressure	85 ± 14.8	80.6 ± 10.3	87,6 ± 9,5	87,9 ± 7,7	**0.049**
Night systolic blood pressure	120.1 ± 12.5	113.4 ± 8.4	118.4 ± 13.1	118.73 ± 10.2	**0.031**
Night diastolic blood pressure	76 ± 12.4	69.12 ± 8.6	76.7 ± 11.5	79.5 ± 10.35	**0.001**

Table 3 – Табела 3

Differences between groups with hypertension in pregnancy in proteinuria, D-dimer, RI of umbilical artery and birthweight
Разлики меѓу групите со хипертензија во гравидитет во однос на протеинурија, Д-димери, РИ на умбиликална артерија и родилна тежина

RISK FACTORS	PH	GH	SP	PE	ANOVA (P)
PROTEINURIA	0.19 ± 0.14	0.19 ± 0.07	780 ± 300	1500 ± 400	**0.000**
UP TO 1 G/DU	NONE	NONE	18/22 (81%)	6/20 (30%)	
1–2 G	NONE	NONE	4/22 (19%)	5/20 (25%)	
2–5 G	NONE	NONE	0/22 (0%)	9/20 (25%)	
D-DIMER	766 ± 561	791 ± 436	1142 ± 681	1317 ± 857	**0.001**
RI-A.UMB	0.64 ± 0.07	0.6 ± 0.09	0,65 ± 0.09	0.71 ± 0.08	**0.000**
BIRTHWEIGHT of the child (G)	3205 ± 401	3149 ± 527	2733 ± 619	2680 ± 538	**0.000**

Risk factors estimated for combined groups without preeclampsia (gestational hypertension and pre-existing hypertension as one group) and a combined group with preeclampsia (preeclampsia and superimposed preeclampsia) are shown in Table 4. Among the most important factors for the occurrence of preeclampsia were: previous preeclampsia (OR 3.28), use of methyldopa (OR 3.76), primiparity (OR 2.35), family history (1.4) and *in vitro* fertilisation (OR 1.15). Smoking did not appear to be a significant risk factor (OR 0.88).

Table 4 – Табела 4

Risk factors for preeclampsia
Ризик факшори за йреекламйсија

RISK FACTORS	PH + GH	SP + PE	x2	OR (95% CI)
Positive family history	63/92 (68.5%)	18/42 (42.8%)	0.014	1.4 (1.2–2.3)
Smoking	8/92 (8.7%)	4/42 (9.5%)	0.893	0.88 (0.6–1.2)
In vitro fertilisation	5/92 (5.42%)	2/42 (4.8%)	0.798	1,15 (0.9–1.4)
Previous PE	3/92 (3.3%)	9/42 (21.4%)	0.03	3.28 (2.9–3.5)
Primiparity	39/92 (39.1%)	10/42 (23.8%)	0.06	2.35 (2–3.1)
Methyldopa	61/92 (66.3%)	37/42 (88.1%)	0.015	3.76 (3 – 4.2)
Nr.of controls (>3)	80/92 (86.9%)	20/42 (47.6%)	0.03	2.3 (2–2.9)

Discussion

Despite current classifications of preeclampsia and hypertensive disease in pregnancy allowing risk stratification, these criteria are not sufficient to predict an adverse outcome in the mother, according to Menzia *et al.* [5].

Our subgroups with preeclampsia consisted of mild preeclampsia and superimposed preeclampsia, which are less frequently investigated than the groups with severe preeclampsia.

Some of the risk factors that consistently occur as associated with preeclampsia in most studies are the same as common cardiovascular risk factors – family history, age and higher body mass index at enrolment [6] – which was consistent with our findings, particularly in the group with superimposed preeclampsia, where pre-existing hypertension had already been present for several years. Coexistance of diabetes mellitus (DM) [7] and chronic kidney disease (CKD) and pre-existing hypertension [6] are also factors of risk for preeclamp-

sia, although the number of women with these conditions included in our study was small and all of these five women ended up with preeclampsia.

With regular administration of antihypertensive therapy, in our study blood pressure was only slightly higher in the subgroup with preeclampsia, indicating that antihypertensive treatment and the achievement of almost target value of blood pressure does not preclude the emergence of preeclampsia. Women with superimposed preeclampsia had a lower mean proteinuria than those with preeclampsia, probably due to the fact that they were more frequently examined at the Department, and immediately referred to the gynecologist when proteinuria occurred. The number of regular check-ups also appeared as an important risk factor, which is consistent with the work of Mc Duffie *et al.* [8], where observing regular scheduled antenatal visits was important for the outcome of the hypertensive pregnancy.

The D-dimer and resistence index of the umbilical artery appeared significantly higher in the subgroups with superimposed preeclampsia and with preeclampsia, suggesting that these may be used as factors predictive of pure preeclampsia. These findings were confirmed in severe preeclampsia, but few studies with these two factors have been carried out in cases of mild preeclampsia. The study by de Melo refers to Doppler in severe preeclampsia [9] and that by Rey *at al*. [10] refers to low molecular weight heparin (LMWH) in severe and in mild preeclampsia, both as helpful predictors of these conditions.

Women with previous preeclampsia and primiparity deserve more frequent examinations, because these two factors were found to be the most important risk factors in our study. Yet, as suggested by Sep *et al.* [11] predicting the recurrence of these disorders should be done by combining tests of different categories, since prediction based on single variables was disappointing.

Many studies developed to conclude on possible prediction and prevention of preeclampsia [12–16] suggest that a combination of tests and risk stratification be done. We suggest that risk factors, 24-hour blood pressure monitoring, Doppler of the umibilical artery and D-dimers may be used jointly to predict preeclampsia. Early determination of risk factors should prompt more frequent check-ups in hypertensive pregnancies in order to determine timely delivery and avoid adverse outcomes in the mother and child.

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Резиме

РИЗИК ФАКТОРИ И ИСХОД ОД ПРЕЕКЛАМПСИЈА

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Апстракт: *Цел:* Да се одредат разликите меѓу групите со хипертензија во гравидитет и да се проценат ризик факторите асоцирани со преeклампсија.

Пациенти и методи: Во периодот 2008–2010 година, на Клиниката за нефрологија во Скопје, Македонија, беше спроведена проспективна и лонгитудинална студија во која беа вклучени 134 гравидни пациентки. Кај нив се спроведени редовни месечни контроли во текот на бременоста и по породување (1–8), а по породувањето групите беа дефинирани како гестациска хипертензија, преегзистирачка хипертензија, суперпонирана преeклампсија и преeклампсија. Вкупно 134 жени беа редовно следени со 24 часовно амбулаторно мониторирање на крвниот притисок (24 часа АМКП), анализи на крв и урина, Д-димери, и индекс на резистенција на Доплер на умбиликалната артерија и беше пополнет прашалник за ризик факторите кај секоја гравидна пациентка.

Резултати: Суперпонирана преeклампсија беше регистрирана кај 22 (16,4%) пациентки, додека преeклампсија беше регистрирана кај 20 жени (14,9%). Средниот дневен дијастолен крвен притисок на последната контрола пред породувањето бил сигнификантно повисок во групата со суперпонирана преeклампсија (87,6 ± 9,5) и во групата со преeклампсија (87,9 ± 7,7 mm Hg). Претходна преeклампсија (OR = 3,28), примипаритет (OR = 2,35), примањето на метилдопа (OR = 3,76), бројот на контролите (OR = 2,3), позитивната фамилијарна анамнеза (OR = 1,4) и ин витро фертилизацијата (OR = 1,15) беа востановени како ризик фактори асоцирани со појавата на преeклампсија и преeклампсија суперпонирана на преегзистирачка хипертензија.

Заклучоци: Раното одредување на ризик фактори треба да наложи почести контроли кај пациентките со хипертензија во гравидитет, со цел да се спроведе навремено породување и да се избегне несакан исход од гравидитетот кај мајката и детето.

Клучни зборови: преeклампсија, ризик фактори, исход.

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