

Obstetric History and Risk for Mild and Severe Preeclampsia

Emilija Jasovic-Siveska^{1*} and Vladimir Jasovic²

¹Private Office for Gynecology and Obstetrics Medihelp, Bitola, Macedonia

²Clinical Hospital Dr TrifunPanovski, Bitola, Macedonia

***Corresponding Author:** Emilija Jasovic-Siveska, Department of Gynecology and Obstetrics, Solunska Str. 218a, Bitola, Macedonia.

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Abstract

Objective: The influence of antepartal, intrapartal and early neonatal risk factors, are very important during the pregnancy and the pregnancy outcome, also for the early neonatal period and the forthcoming children development. Our aim is to detect the risks groups of pregnant women that later develop Preeclampsia (PE) and risk factors that precede its appearance.

Materials and Methods: We examined 300 normotensive pregnant and 100 preeclamptic pregnant, divided in 2 groups: 67 pregnant with mild PE and 33 with severe PE. In research are included only single pregnancies and the following parameters: maternal age, parity and previous pregnancy history.

Results: The study is based on 400 pregnancies with a mean age of 27.65 ± 5.04 years. The significant difference in the frequency of categories and age groups was tested with a method of multivariate analysis for proportion. The difference was not statistically significant $p > 0.05$, which clearly shows that the groups are a priori similar and comparable. Our study shows that PE is most commonly developed in primiparas ($p < 0.05$). The difference was at the level $p < 0.001$. Among women with no history of PE, the median inter birth interval was 4.24 years between the previous and actual pregnancy. Among women with mild PE the median inter birth interval was 5.96 and in group with severe PE was 8.08 years. Multiparous women who are pregnant 5, especially 10 years or more after their previous pregnancy are as likely to have preeclampsia as nulliparous women.

Conclusions: PE is most frequently appearing in young primiparas and adult multiparas. Pregnant women with PE got previously newborns with intrauterine growth restriction or were infertile.

Keywords: Mild Preeclampsia; Severe Preeclampsia; Obstetric history; Parity; Risk factors

Abbreviations: CV: cardiovascular; HELLP haemolysis: elevated liver enzymes- low platelets; MP: Mild Preeclampsia; SP: Severe Preeclampsia; PE: preeclampsia

Introduction

Preeclampsia continues to be a massive cause of maternal and perinatal morbidity and mortality. It's a common, incompletely understood syndrome yet; unique for humans only and it is one of the most common complication of pregnancy worldwide. Over 4 million women will develop the disorder worldwide every year, 50.000-100.000 women die from the preeclampsia each year and it's responsible for approximately 300.000 perinatal deaths [1-3].

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Prediction and prevention of PE is very important contribution for maternal health. Primary prevention of PE is identification of the risk factors. Prevention of PE demands knowledge of the pathophysiological mechanism. Availability of techniques for early detection and intervention in the pathophysiological process are necessary. Finally, prevention of PE is a proper antenatal care which provides screening for hypertension and proteinuria, making intervention, such as timely delivery possible. With an organized antenatal care, such in developed countries, the maternal mortality and serious morbidity have decreased. The major value of prevention is to identify women at high risk of PE and to make a medical intervention so that the disorder never occurs or is postponed. The ultimate predictor of PE should presumably identify women with an increased risk of the disorder as early as in the first trimester [5].

Major risk factors for PE are: pregnancy factors (multiple pregnancies, nulliparity, previous PE), maternal age > 40, prior PE, antiphospholipid antibody syndrome, family history of preeclampsia, renal disease, chronic hypertension, diabetes mellitus, multiple gestations, strong family history of CV disease (heart disease or stroke in ≥ 2 first-degree relatives), obesity etc [6].

The risk of PE is at least twice higher during the first pregnancy then during the second or later pregnancies. The hypothesis is that the risk of PE may be reduced with repeated maternal exposure and adaptation to specific foreign antigens of the partner [5,7].

The role of parity for the development of PE is not new. The increased risk of PE is associated with longer interval between pregnancies. The aim of our study is to evaluate the influence and the effect of parity, interval between pregnancies and outcomes of previous pregnancies on the risk of PE in our study group.

Methods and Materials

Our research was conducted in the Clinical Hospital "Dr. TrifunPanovski" in Bitola, Macedonia, Department Gynaecology and Obstetrics. These patients had been admitted during the period of May 1st 2008 to August 1st 2009. This study protocol was approved by the Director of Clinical Hospital in Bitola, and by the Ethics committee of School of Medicine University of Belgrade, Serbia. A written consent was provided by all participants. The research was conducted in the Antenatal Care Ambulance which is part of the Gynecology-Obstetric Department.

The study included 400 participants. Considering the recommendations of the Ethics committee, this prospective study is based on 300 normotensive pregnant and 100 PE pregnant. The PE women later on, based on clinic and laboratory parameters, were divided in two subgroups: women with mild (MP) and severe (SP) PE. This study wasn't limited by a timeframe so when we reached the recommended numbers of patients, we concluded the research.

The research was conditioned with the following criteria:

The criteria to determine the exact pregnancy stage is based on the following: anamnestic, obstetrical and ultrasound scan, which means that the information of the last period is corresponding with the results from the obstetrical examination and the ultrasound scan. The first examination was performed in the period between the 6th-12th week of gestation (wg).

All patients started the pregnancy with normal blood pressure, (on their first visit they didn't have blood pressure above 120/80 mmHg), and we got information that their pressure was never increased.

To participants belonged healthy women with no history of any chronic disease, with singleton pregnancy, without chromosomal or congenital abnormalities, with exact date of the last menstrual period and regular menstrual period.

Women without valid data on the last menstrual period and valid ultrasound measurement and with chronic maternal disease were excluded.

49 women were excluded from the study, which in the period of the research didn't follow the scheduled exams i.e. failed to do the necessary laboratory analyzes (21 women), or had artificial or spontaneous abortion (26 women), and women in which fetal anomaly was discovered [2].

We reviewed age, education, parity, smoking status, week of PE onset and duration of PE, and obstetrical history (outcome of previous pregnancies and interval between pregnancies). Smoking status and level of education were determinate by self-report, and other data was determinates based on medical records.

The interval between pregnancies was calculated as the time between previous birth dates and approximate dates of conception of the actual pregnancies.

All patients were followed until delivery. The gestational age at delivery, obstetric complications if any and neonatal outcome were recorded. For those subjects who subsequently delivered in another hospital, the obstetric information was obtained by telephoning the subject or via contact with staff in other hospital.

Blood pressure measurements at all clinic sites were taken according to a standardized published protocol, and all urine specimens were assessed for protein by dipstick.

PE was defined by the occurrence of two or more systolic pressure ≥ 140 mmHg and/or diastolic pressure ≥ 90 mmHg, with the first elevated blood pressure occurring after the 20th week of gestation up to 24 hours after delivery, combined with proteinuria at least 0.3g or "1+ protein" per 24 hours on a sterile urine [8,9].

Severe PE was defined as a systolic blood pressure of 160 mmHg or greater and diastolic blood pressure of 110 mmHg or greater on at least two occasions, at least 4 hours apart or on one occasion if anti-hypertensive therapy was administered. Severe proteinuria was defined with a 24-hour urine sample containing ≥ 3.5 g of protein or two urine samples of "3+ protein" or greater taken at least 4 hours apart. The HELLP syndrome and eclampsia was also categorized as severe PE [8,9].

Quantitative data are expressed as mean values \pm standard deviation and relative numbers. Also, during the research the following methods were used: chi-square test, multivariate analysis, analysis of variance (ANOVA), Student's t test and post-hoc test used to determine the statistical differences and comparison of proportion between groups. A p value < 0.05 was considered statistically significant. The data is presented in tables.

Results and Discussion

All of the studied women were married and all of their pregnancies were conceived with the same partner. Maternal age and parity are shown in the Table 1. The significant difference between the categories was tested with a method of multivariate analysis for proportion.

The difference was not statistically significant $p > 0.05$, which clearly shows that the groups are a priori similar and comparable. Despite this, with detailed analysis between the groups we noticed an increasing trend of mild forms of PE in pregnant women of age up to 25 years, while severe forms of PE are more frequently associated with pregnant women of age 31 years and older.

The significant difference in the frequency of categories and parity groups was tested with a method of multivariate analysis for proportion. The difference was statistically significant $p < 0.05$. The difference in the frequency of categories and primipara age was tested with a method of multivariate analysis for proportion. The difference was not statistically significant $p > 0.05$, which clearly shows that the groups are a priori similar and comparable.

However, based on a relative numbers, the disorder appears more often when patients are younger than 20 years and / or older than 31 and especially older than 36 years. Pregnancy outcome, week of PE onset and duration of PE for the three study groups are shown in the Table 2. The severe, occurs earlier in pregnancy than mild preeclampsia: 30.4 ± 4.5 (21-38 w.g.) vs. 34.5 ± 2.7 (26-38) and in the consequence the hypertension is much longer lasting (8.0 ± 4.3 vs. 4.8 ± 2.6).

Previous patients' pregnancy status is displayed in table 3. The difference between the groups regarding the obstetrical anamnesis was tested with a method of multivariate analysis for proportion. In this analysis, large differences exist only in categories of intrauterine growth restriction (IUGR) and infertility at the level of $p < 0.01$. IUGR and history of infertility are significantly associated with the appearance of PE, so they can be considered as significant risk factors for the development of PE.

For the multiparous women the interval between pregnancies was analyzed. The difference between the groups and categories of inter birth interval was tested with the ANOVA. The difference was at the level $p < 0.001$. We concluded that the inter birth interval constitutes the major risk factor for PE. Moreover, more severe forms of preeclampsia are associated with longer inter birth intervals, especially more than 10 years. Obtained results are shown in tables 4 and 5.

The influence of antepartal, intrapartal and early neonatal risk factors, is very important during the pregnancy and the pregnancy outcome, also for the early neonatal period and the forthcoming children development [10]. To identify particular potential factors in cases of PE in some population requires a lot of effort. For some cases the cause factors for PE were evident; however for most of the cases we couldn't prove any connection. Before beginning the antenatal care, women should be assessed for risk factors predisposing PE such as: age, parity, interval between pregnancies, family history, previous PE, blood pressure, proteinuria, multiple pregnancy body mass index, smoking, and underlying medical condition (pre-existing hypertension, renal disease, diabetes etc.) [11].

Regarding the age and parity, based on world literature, PE is more often developed at young primiparas and older multiparas; actually it has a bimodal probability [12,13]. Our study, which includes 300 normotensive and 100 pregnancies with developed PE during the pregnancy, we concluded that PE is most commonly developed in primiparas.

Women aged above 40 have the risk of developing PE twice high as younger women, when they were primiparous or multiparous. Nulliparity almost triples the risk for PE [11]. The higher risk of PE in elderly women may be in part explained by the higher incidence of chronic disease (women with latent chronic hypertension or other chronic disease who are misdiagnosed).

Women with a history of abortion (artificial or spontaneous), who conceived again with same partner, had nearly half risk of PE. Contrary, women with abortion history who conceived with a new partner had the same risk of PE, as women without history of abortion. An immune based etiologic mechanism is proposed, whereby prolonged exposure to foetal antigens from a previous pregnancy protects against PE in a subsequent pregnancy with the same father [14]. In a large cohort study, some authors presented no reduction in incidence of PE or eclampsia among women who had one or two previous abortions [15].

In our research the number of previous abortions presents no relation with the appearance of PE. Based on our data from the obstetrics anamnesis, we found that only IUGR in previous pregnancy, as well as previous infertility, is closely associated with the development of PE, and represent a risk factor for PE.

Among women with no history of PE, the median inter birth interval was 4.24 years. But among women with mild PE the median inter birth interval was 5.96 years and in group with severe PE was 8.08 years. We found that multiparous women who get pregnant 10 years or more after previous pregnancy are more likely to develop PE as nulliparous women. PE is commonly described as disorder of the first pregnancy. Our data confirm that the risk of PE is reduced after the first pregnancy.

Characteristics	Controls n = 300	MP n = 67	SP n = 33	p Value
Maternal age (years)*	27.52 ± 5.04 (17-42)	27.43 ± 5.85 (17-42)	29.24 ± 5.77 (16-43)	p>0.05†
< 20	5.33	8.96	9.1	
20-25	29.0	40.3	12.12	
26-30	40.0	19.4	42.42	
31-35	21.0	19.4	24.24	
>35	4.67	11.94	12.12	
Parity (%)				
Primipara	46.67	65.67	60.61	P < 0.05†
Multipara	53.33	34.33	39.39	
Maternal age (years)* of primiparas (%)	N = 140 25.9 ± 4.5	N = 44 25.7 ± 5.5	N = 20 27.2 ± 6.3	P < 0.05†
< 20	10.0	13.6	15.0	
20-25	38.6	47.7	20.0	
26-30	35.0	20.5	45.0	
31-35	13.6	11.4	10.0	
>35	2.8	6.8	10.0	
Maternal age (years)* of multiparas (%)	N = 160 28.9 ± 4.5	N = 23 30.7 ± 5.2	N = 13 32.38 ± 2.8	P = 0.058†
< 20	1.3	0	0	
20-25	20.6	26.1	0	
26-30	44.4	17.4	38.5	
31-35	27.5	34.8	46.1	
> 35	6.2	21.7	15.4	

Table 1: Maternal age and parity by study groups.

Data are given as mean, standard deviation and % unless otherwise specified; n: number of subjects; Controls: normal pregnancies; MP: Mild preeclampsia, SP: Severe preeclampsia; † multivariate analysis;

We considered the possibility that the increase in the risk of preeclampsia with an increasing interval between pregnancies could be confounded by an association between preeclampsia and subfertility.

A Danish cohort study found that a long interval between pregnancies was associated with a significantly higher risk of PE in a second pregnancy when PE had not been presented in the first pregnancy and paternity had not been changed [16].

In Norwegian population of women who had two, three or more singleton deliveries (1967-1998), the association between the risk of PE and interval was more significant than the association between the risk and a change of partner. When the interval was 10 years or more the risk of PE was about the same as that in nulliparous women [17].

PE has been described as “a disease of first pregnancy” and is sometimes defined as occurring only among nulliparous women [5,7]. Our results presented that the risk of PE falls sharply after the first pregnancy, and we also found that the risk subsequently increases over time. This striking increase in risk with an increasing interval between pregnancies suggests that the benefit of higher parity in terms of the risk of PE is only transient [18].

Characteristics	Controls n = 300	MP n = 67	SP n = 33	p Value
Week of Preeclampsia onset (%)				p < 0.01‡
< 25	-	0	18.18	
26-30	-	7.46	24.24	
> 31	-	92.54	57.58	
Duration of hypertension (weeks)	-	4.79 ± 2.59 (1-14)	7.97 ± 4.31 (2-16)	p < 0.01§§
Duration of pregnancy (weeks)	39.57 ± 0.9 (37-42)	39.09 ± 0.92 (37-40)	37.48 ± 2.04 (32-40)	p < 0.01†
Birth weight in percentile for gestational age (%)				
< 5	0	5.97	33.34	p < 0.05†
5-9.90	3	23.88	30.31	
10-89.90	93.33	70.15	36.36	
90-94.9	1.34	0	0	
> 95	2.33	0	0	

Table 2: Preeclampsia onset, duration and pregnancy outcome.

Data are given as mean, standard deviation and % unless otherwise specified; n: number of subjects; Controls: normal pregnancies; MP: Mild preeclampsia, SP: Severe preeclampsia; † multivariate analysis; ‡ chi-squared test; §§ Student's t test.

Obstetrical History	Normal Pregnancies		Mild Preeclampsia		Severe Preeclampsia	
	n	%	n	%	N	%
Artificial Abortus	9/300	3	5/67	7,46	1/33	3,03
Spontaneous Abortus	22/300	7,33	2/67	2,99	1/33	0,00
IUGR	23/160	14,37	7/23	30,43	6/13	46,15
Previous foetal death	1/160	0,625	0/23	0,00	0/13	0,00
Previous neonatal death	1/160	0,625	0/23	0,00	0/13	0,00
Foetal anomalies	0/160	0	0/23	0,00	1/13	7,69
Infertility	4/300	1,33	7/63	10,45	6/33	18,18

Table 3: Obstetrical history.

Interval between pregnancies	Normal pregnancies	Mild preeclampsia	Severe preeclampsia
	n = 160	n = 23	n = 13
Mean value of interval between pregnancies	4.24 ± 2.39	5.96 ± 4.02	8.08 ± 3.48
95% CI for mean	3.816-4.659	4.845-7.068	6.598-9.556

Table 4: Interval between pregnancies.

Interval between pregnancies	Normal pregnancies n = 160	Mild preeclampsia n = 23	Severe preeclampsia n = 13
1-4.9	63.8	47.8	30.8
5-9.9	31.2	34.8	30.8
≥ 10	5.0	17.4	38.4

Table 5: Interval between pregnancies.

N: number of pregnant; †† ANOVA; p < 0.001

Conclusion

Based on our research it can be concluded that multiparous women who are pregnant five and especially 10 years or more after their previous pregnancy are as likely to have preeclampsia as nulliparous women. Pregnant women with PE got previously newborns with intrauterine growth restriction or were infertile.

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