The Open Access Journal of Science and Technology
Vol. 2 (2014), Article ID 101065, 6 pages
doi:10.11131/2014/101065

AgiAl Publishing House
http://www.agialpress.com/

Research Article

The Interval Between Pregnancies as A Risk Factor for Mild and Severe Forms of Preeclampsia

Emilija I. Jasovic-Siveska[1] and Vladimir I. Jasovic[2]

[1]*PHO Medihelp, Bitola, Macedonia*
[2]*Clinical Hospital "Dr Trifun Panovski", Bitola, Macedonia*

Corresponding Author: Emilija I. Jasovic-Siveska; email: medihelp@t-home.mk

Received 22 December 2013; Accepted 1 May 2014

Academic Editors: Shalev Eliezer and Edward Araújo Júnior

Abstract. We studied 300 normotensive and 100 PE pregnancies divided into two subgroups: mild ($n = 67$) and severe ($n = 33$) PE. This research has included only single pregnancies and the following parameters: maternal age, parity, previous pregnancy history and interval between pregnancies. 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 interbirth interval was 4.24 years between the previous and actual pregnancy. Among women with mild PE the median interbirth 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.

Keywords: pre-eclampsia; risk; interbirth interval; parity

1. Introduction

Worldwide, pre-eclampsia (PE) and eclampsia contribute to the death of a pregnant woman every 3 min. The management of pregnancies complicated by hypertension has not significantly changed for many years, possibly as a result of little progress being made in our understanding of the condition [1].

PE is a multi-system disorder, of unknown aetiology, usually associated with elevated blood pressure and proteinuria [2]. There are many terminologies used for this maternal disease, which appears after 20 weeks gestation and has spontaneous resolution after delivery [3, 4].

Risk factors for PE include socio-demographical factors (extremes of reproductive age, socio-economic status, ethnic group), genetic factors, pregnancy factors (multiple pregnancies, primigravidae, previous PE) or personal medical history (obesity, chronic renal disease, chronic hypertension, diabetes mellitus, trombophilia) [5].

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 [6, 7].

The finding that parity plays a role for the development of preeclampsia is not new. The increased risk of PE is associated with longer interbirth interval. The aim of this study is to evaluate and confirm the influence and the effect of parity and the interbirth interval on the risk of PE in our population.

2. Materials and Methods

The research was conducted in the Clinical Hospital "Dr Trifun Panovski" 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. Approximately, this ambulance provides treatment to 900–1000 patients annually, while at the Gynecology-Obstetric Department approximately 1600 pregnancies are delivered annually.

The study included 400 participants. Considering the recommendations of the Ethics committee, this prospective study is based on 300 normotensive pregnant and 100 preeclamptic pregnant. The preeclamptic women later on, based on clinic and laboratory parameters, were divided in two subgroups: women with mild and severe preeclampsia. 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 6–12th week of gestation (wg). Ultrsound scans were performed in the following weeks: 16, 20, 24, 28, 32, 36, 38, and 40. The participants who were delivered before 40 wg were excluded. The ultrasound scanning was performed using the ultrasound unit *GE Logiq CX 200*, with a convex transabdominal transducer of 3,5 MHz.

All patients commenced the pregnancy with normal blood pressure, that is, on their first visit they didn't have artery pressure above 120/80 mmHg, and anamnestically 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, that is, 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). From the study were excluded 47 normotensive and 2 preeclamptic women, because in the certain moment we achieved the required total numbers of normotensive and preeclamptic pregnant. We reviewed age, education, parity, smoking status, week of PE onset and duration of PE, and obstetrical history. Smoking status and level of education were determinate by self-report, and other data was determinates based on medical records.

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.

Preeclampsia was defined by the occurrence of two or more systolic pressure $\geq$140 mmHg and/or diastolic pressure $\geq$90 mmHg, diastolic blood pressure measurements, 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 [3, 4].

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 antihypertensive therapy was administered. Severe proteinuria was defined with a 24-hour urine sample containing $\geq$3.5 g of protein or two urine samples of "3+ protein" or greater taken at least 4 hours apart. The syndrome of haemolysis elevated liver enzymes, low platelets and eclampsia was also categorized as severe PE [3, 4].

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

Statistical analysis. 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.

3. Results

The research is based on 400 pregnancies with average age of 27,7±5,0 years (min15-max 43; median=27). All of the studied women were married and all of their pregnancies were conceived with the same partner. Maternal characteristics and pregnancy outcome for the three study groups 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.

A chi-square test was used for testing in the differences in frequency of categories of education of the monitored pregnant women. The difference is statistically significant ($P < 0.05$). In the group with severe form of PE, the most dominant were pregnant women with lower education (primary school). In the control group and the group with mild PE, over 50% of the women had secondary education. It is very important at this point to remember that most of analyzed women are at a similar age.

We found a decreased risk of mild and severe preeclampsia among women who smoked during pregnancy.

The severe, occurs earlier in pregnancy than mild prreclampsia: 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 2. 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.

Other of obstetrical anamnesis were not significantly associated with PE.

For the mulitparous women the interbirth interval was analyzed. The difference between the groups and categories of interbirth interval was tested with the ANOVA. The difference was at the level $P < 0.001$. We concluded that the interbirth interval constitutes the major risk factor for PE. Moreover, more severe forms of preeclampsia are associated with longer interbirth intervals, especially more than 10 years. Obtained results are shown in Tables 3 and 4.

4. Discussion

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, interbirth interval, body mass index, smoking, family history, previous PE, blood pressure, proteinuria, multiple pregnancy and underlying medical condition (pre-existing hypertension, renal disease, diabetes etc.) [8].

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 [9, 10]. Our study, which includes 300 normotensive and 100 pregnancies with developed PE during the pregnancy, conculded that PE is most commonly developed in primiparas.

Women aged above 40 have the risk of developing PE twice *s* high as younger women, when they were primiparous or multiparous. Nulliparity almost triples the risk for PE. Women with PE are twice as likely to be nuliparous as women without PE [8]. 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).

Our study shows an inverse correlation between smoking and PE. Smoking is associated with lower maternal sFlt-1 concentrations during pregnancy and PE. Based on this data, cigarette smoking exposure may decrease the risk of PE in part by moderating the anti-angiogenic phenotype observed in this syndrome [11].

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 [12]. 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 [13].

Table 1: Description of maternal characteristics and pregnancy outcome by study groups.

Characteristics	Controls normal pregnancies $n = 300$	mild preeclampsia $n = 67$	severe preeclampsia $n = 33$	P value
Maternal age (years)*	27.52±5.04 (17–42)	27.43±5.85 (17–42)	29.24±5.77 (16–43)	
<20	5.33	8.96	9.1	
20–25	29.0	40.3	12.12	$P > 0.05$†
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	
Education (years) (%)				
0–8	27.66	46.27	48.48	
9–12	53.0	38.8	36.37	$P < 0,05$‡
>12	19.34	14.93	15.15	
Smoking status (%)	10.33	1.49	30.3	$P < 0.05$‡
Nationality (%)				
Macedonian	83.67	68.66	66.67	$P < 0.05$‡
Muslims	14	31.34	30.3	
Other	2.33	0	3.03	
BMI(%)*	22.65±1.698	25.53±1.58	25.8±2.15	
<19.99	1.67	0	0	
20.0–24.99	87.33	23.88	30.3	$P < 0.01$§
25.0–29.99	11.0	76.12	69.7	
>30 Weight gain (kg)	0 13.95±3.1 (7–29)	0 19.59±3.78 (13–31)	0 20.24±7.36 (10–39)	
Week of Preeclampsia onset (%)	-			
<25		0	18.18	$P < 0.01$‡
26-30		7.46	24.24	
>31		92.54	57.58	
Duration of hypertension	-	4.79±2.59 (1–14)	7.97±4.31 (2–16)	$P < 0.01$§§
Duration of pregnancy	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	
5–9.90	3	23.88	30.31	
10–89.90	93.33	70.15	36.36	$P < 0.05$†
90–94.9	1.34	0	0	
>95	2.33	0	0	

Data are given as mean, standard deviation and % unless otherwise specified; n = number of subjects; Controls = normal pregnancies; MP- Mild preeclampsia, SP- Severe preeclampsia; BMI- body mass index; † multivariate analysis; ‡ chi-squared test; §multivariate analysis, univariate ANOVA and Spearman correlation coefficient; §§Student's t test.

Table 2: Obstetrical history*.

Obstetrical history	Normal pregnancies		Mild preeclampsia		Severe preeclampsia	
	n	%	*n*	%	*n*	%
Artefitial abortus	9/300	3	5/67	7,46	1/33	3,03
Sponatneus 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	7/67	10,45	6/33	18,18

Table 3: Interval between pregnancies*.

Interval between pregnancies	Normal pregnancies		Mild preeclampsia		Severe preeclampsia	
	n = 160	%	*n* = 23	%	*n* = 13	%
<1	0	0	0	0	0	0
1-1,9	8	5	0	0	0	0
2-2,9	33	20,6	5	21,7	2	15,4
3-3,9	33	20,6	6	26,1	1	7,7
4-4,9	28	17,5	0	0	1	7,7
5-5,9	21	13,1	1	4,3	1	7,7
6-6,9	14	8,8	2	8,7	0	0
7-7,9	6	3,8	0	0	0	0
8-8,9	5	3,1	4	17,4	1	7,7
9-9,9	4	2,5	1	4,3	2	15,4
≥10	8	5.0	4	17,4	5	38,4
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	

*- The significant difference in the frequency of the category of time between the pregnancies was tested with the ANOVA; *n*- number of pregnant; **- data are expressed as mean ± standard deviation

In our research the number of previous abortions present 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 interbirth interval was 4.24 years. But among women with mild PE the median interbirth 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.

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

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 [14].

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 [15].

Preeclampsia has been described as “a disease of first pregnancy” and is sometimes defined as occurring only among nulliparous women [6, 7]. In contrary our data present, that the risk of preeclampsia 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 interbirth interval suggests that the benefit of higher parity in terms of the risk of preeclampsia is only transient [16, 17].

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

n- number of pregnant; †† ANOVA; $P < 0.001$

We recognize that our study has limitations. We did not assess the combined effects of smoking and BMI among women developing preeclampsia. As is was mentioned before, smoking is associated with reduction the risk of preeclampsia [6, 11]. The next parameter that is connected with higher risk of PE is obesity. The risk of obesity increases with a woman's age and parity [5, 13].

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 IUGR newborn or were infertile.

Acknowledgment

The authors thank Prof. Dr. Tatjana Ille, specialist in medical statistics and informatics, Director od Department for Biostatistics, Medical informatics, and researches in Medicine Medical Faculty, University of Belgrade, Serbia, for her assistance in statistical analysis and interpretation of data. The authors also thank Prof.Dr. Mladenko Vasiljevic, specialist of gynecology and obstetrics, professor of Gynecology and Obstetrics, in Medicine Medical Faculty, University of Belgrade, Serbia mentor of PhD Thesis, for their helpful comments, supervision and revision regarding the manuscript.

References

[1] J. E. Myers and P. N. Baker, Baker PN. Hypertensive diseases and eclampsia, *Curr Opin Obstet Gynecol*, **14**, 119–125, (2002).

[2] L. Duley, Pre-eclampsia and the hypertensive disorders of pregnancy, *British Medical Bulletin*, **67**, 161–176, (2003).

[3] A. R. Nort, Classification and diagnosis of pre-eclampsia, in *Pre-eclampsia, Etiology and Clinical Practice*, F. Lyall and M. Belfort, Eds., 243–257, Cambridge University Press, Cambridge, 2007.

[4] R. Hayman and J. Myers, Definition and classification, in *Pre-eclampsia, Current Perspectives on Management*, N. P. Baker and C. P. J. Kingdom, Eds., 11–13, Parthenon Publishing Group, New York, 2004.

[5] R. A. Smith and P. N. Baker, Risk factors, prevention and treatment of hypertension in pregnancy, *Minerva Ginecologica*, **57**, no. 4, 379–388, (2005).

[6] F. Broughton Pipkin, Risk factors for preeclampsia: Editorial, *New England Journal of Medicine*, **344**, no. 12, 925–926, (2001).

[7] G. Dekker and B. Sibai, Primary, secondary, and tertiary prevention of pre-eclampsia, *Lancet*, **357**, no. 9251, 209–215, (2001).

[8] K. Duckitt and D. Harrington, Risk factors for pre-eclampsia at antenatal booking: Systematic review of controlled studies, *British Medical Journal*, **330**, no. 7491, 565–567, (2005).

[9] S. Baumwell and S. A. Karumanchi, Pre-eclampsia: Clinical manifestations and molecular mechanisms, *Nephron - Clinical Practice*, **106**, no. 2, c72–c81, (2007).

[10] G. A. Dildy III, M. A. Belfort, and J. C. Smulian, Preeclampsia Recurrence and Prevention, *Seminars in Perinatology*, **31**, no. 3, 135–141, (2007).

[11] A. Jeyabalan, R. W. Powers, A. R. Durica, G. F. Harger, J. M. Roberts, and R. B. Ness, Cigarette smoke exposure and angiogenic factors in pregnancy and preeclampsia, *American Journal of Hypertension*, **21**, no. 8, 943–947, (2008).

[12] A. F. Saftlas, R. J. Levine, M. A. Klebanoff, K. L. Martz, M. G. Ewell, C. D. Morris, and B. M. Sibai, Abortion, changed paternity, and risk of preeclampsia in nulliparous women, *American Journal of Epidemiology*, **157**, no. 12, 1108–1114, (2003).

[13] J. Zhang, J. Zeisler, M. C. Hatch, and G. Berkowitz, Epidemiology of pregnancy-induced hypertension, *Epidemiologic Reviews*, **19**, no. 2, 218–232, (1997).

[14] R. Sjaerven, J. A. Wilcox, and T. R. Lie, The interval between pregnancies and the risk of preeclampsia, *N Engl J Med*, **345**, 33–38, (2003).

[15] O. Basso, K. Christensen, and J. Olsen, Higher risk of pre-eclampsia after change of partner. An effect of longer interpregnancy intervals? *Epidemiology*, **12**, no. 6, 624–629, (2001).

[16] L. Trogstad, P. Magnus, R. Skjærven, and C. Stoltenberg, Previous abortions and risk of pre-eclampsia, *International Journal of Epidemiology*, **37**, no. 6, 1333–1340, (2008).

[17] L. Trogstad, P. Magnus, A. Moffett, and C. Stoltenberg, The effect of recurrent miscarriage and infertility on the risk of pre-eclampsia, *BJOG: An International Journal of Obstetrics and Gynaecology*, **116**, no. 1, 108–113, (2009).