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Obstetrics & Gynecology International Journal

Research Article

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Maternal plasma lipid concentration in first and second trimester of pregnancy and risk of preeclampsia

Abstract

Background: Numerous studies have shown that high maternal pre-pregnancy body mass index is a strong, modifiable risk factor for preeclampsia. Overweight is associated with alterations in lipid concentrations and an activation of inflammatory markers and both of these metabolic abnormalities are characteristic of preeclamptic pregnancies before the onset of clinically evident disease. We investigated the relationship between early pregnancy and midpregnancy plasma lipid concentration and risk of mild and severe preeclampsia.

Methods: The study included 400 participants, divided in three groups: control group (n=300 normotensive pregnancies); group with mild preeclampsia (n=67) and group with severe preeclampsia (n=33). Maternal serum collected at: 8-12; 20-24; and 28-32 weeks, was used to measure lipid profile.

Results: The groups were similar with respect to age and parity. Women with mild preeclamsia had higher levels of total cholesterol and LDL than control subjects from the first trimester (4.28±0.53 vs. 4.74±0.74mmol/l; 1.37±0.3 vs.1.98±0.45mmol/l; $p<0.05$). HDL values were lower in preeclamptic group (1.38±0.21 vs. 1.16±0.24mmol/l; $p<0.05$). The values of cholesterol and LDL were most increased in the group with severe preeclampsia (5.48±0.91 and 2.36±0.6mmol/l), but HDL values were most increased (0.96±0.15mmol/l). This is in correlation with increased BMI, and this difference is maintained until the end of the pregnancy.

Conclusion: Plasma lipid profile assay in first and second trimester of pregnancy is noticeable to predict probability and severity of preeclampsia, especially in combination with blood pressure values in the same periods.

Keywords: dyslipidemia, preeclampsia, risk

Volume 10 Issue 4 - 2019

Emilija Jasovic-Siveska,[1] Daniel Milkovski[2]

[1]PHO Medihelp, Bitola, University St. Clement Of Ohrid, Bitola North Macedonia

[2]University Clinic of Obstetrics and Gynecology, University St Cyril and Methodius, North Macedonia

Correspondence: Emilija Jasovic-Siveska, PhD, MSc, MD, gynecologist & obstetrician, PHO Medihelp, Bitola, University St. Clement Of Ohrid, Bitola North Macedonia, Tel +38970782100, Email medihlp@t.mk

Received: June 25, 2019 | **Published:** August 20, 2019

Introduction

Preeclampsia is a multi-system disorder of unknown etiology. Women with preeclampsia usually develop raised blood pressure and proteinuria. Preeclampsia is also associated with abnormalities of coagulation system, disturbed liver function, renal failure and cerebral ischemia.[1] Preeclampsia is characterized by vasospasm, increased peripheral vascular resistance, and thus reduced organ perfusion.[1,2] It complicates an estimated 2–30% of pregnancies and is a major cause of maternal morbidity, prenatal death and premature delivery, although outcome for most women is good.[2,3]

The pathogenesis of preeclampsia (PE) is complex (genetic, immunologic and environmental factors interact). It has been suggested that PE is a two-stage disease[4,5]: Stage 1: asymptomatic, characterized by abnormal placental development during the first trimester resulting in placental insufficiency. This in turn leads to symptomatic, stage 2, wherein the pregnant women develops characteristic hypertension, renal impairment, and proteinuria and is at risk for the HELLP syndrome, eclampsia and other endorgan damage.

Numerous studies have shown that high maternal pre-pregnancy body mass index (BMI; weight (kg)/height $(m)^2$) is a strong risk factor for preeclampsia.[6–8] Overweight is associated with alterations in lipid concentrations and an activation of inflammatory markers and both of these metabolic abnormalities are characteristic of preeclamptic pregnancies before the onset of clinically evident disease.[5,9]

We investigated the relationship between early pregnancy and midpregnancy plasma lipid concentration and risk of mild and severe preeclampsia. We've made hypotheses that in first and second trimester exist dyslipidemia and that increased lipid parameters play a key role in the development of the clinical symptoms of preeclampsia. Higher lipid level concentration is related to more severe manifestation of preeclampsia.

Material and methods

Study population

The research was conducted in the Clinical Hospital "Dr Trifun Panovski" in Bitola, Macedonia, Department of 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, Macedonia and the Ethics committee of School of Medicine University of Belgrade, Serbia. A written consent was provided by all participants. The study included 400 participants. Considering recommendations of Ethics committee, this prospective study should be based on 300 normotensive pregnant (control group) and 100 preeclamptic pregnant (study group). 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 timeline and when we reach the required numbers of patients, we stopped further research.

The study included 400 participants, divided in three groups: control group (group K, n=300 normotensive pregnancies); group with mild preeclampsia (group MP, n=67) and group with severe preeclampsia (group SP, n=33).

The participants were 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 with multiple fetuses, without valid data on the last menstrual period and valid ultrasound measurement and chronic maternal disease were excluded.

The criteria to determine the exact pregnancy stage is based on the following reliable criteria: anamnestical, 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 of 6-12wg.

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

Forty nine women were excluded from the study, which in the period of the research, weren't regularly following the scheduled appointments, women which did not performed necessary laboratory analyzes (21 women), have artificial or spontaneous abortion (26 women), and 2 women in which was discovered fatal anomaly.

Definition of study variable

We reviewed age, education, nationality, parity, smoking status, week of PIH onset, duration of PIH, duration of pregnancy, birth weight and length, and birth weight in percentile. Smoking status and level of education was determined by self-report.

All subjects 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. Birth weight (to the nearest gram) was classified into five categories: very low birth weight (<5th percentile), low (5 -9,9), normal (10-89.9), high (90-94.9) and very high (>95).

Prepregnancy BMI was based on measured height and maternal weight at the initial visit (6-12w.g.) and maternal self report of prepregnancy weight. Height was measured by using a portable stadiometer, accurate to 1 mm. Weight was determined by using the average of two measurements, with the woman lightly clothed. A scale accurate 0.2kg was used. Prepregnancy BMI was categorized as: underweight (<19.9), normal (20.0-24.9), overweight (25.0-29.9) or obese (>30.0).[10] Total maternal weight gain during pregnancy was recorded on admission to delivery ward.

Laboratory measurements

Venous blood obtained after an overnight fast (>10h). The blood was collected by veinpuncture of the antecubital vein of each pregnant in the next periods: first trimester (between 8-12w.g.), second trimester (between 20-24w.g.) and third trimester (28-32w.g). Women attended for participation in the study underwent testing between 07.00 and 09.00h. After liquefying frozen plasma's samples, standard enzymatically assays of plasma lipids were performed on all three groups. Enzymatic colorimetric test was used to define serum total cholesterol and low-density lipoprotein cholesterol (LDL) and High density lipoprotein cholesterol (HDL). All analyses were performed blinded to pregnancy diagnosis.

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.

Mild Preeclampsia was defined by the occurrence of two or more systolic pressure ≥140mmHg and/or diastolic pressure ≥90mmHg, diastolic blood pressure measurements, with the first elevated blood pressure occurring after 20 weeks' gestation up to 24 hours after delivery, combined with proteinuria at least 0.3g or "1+ protein" per 24 hours.[11,12]

Severe preeclampsia was defined as a systolic blood pressure of 160mmHg or greater and diastolic blood pressure of 110mmHg 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 ≥3.5g of protein or two urine samples of "3+ protein" or greater taken at least 4 hours apart. The syndrome of haemolysis elevated liver enzymes, and low platelets and eclampsia was also categorized as severe PE.[11,12]

Statistical analysis

Quantitative data are presented as the mean values ± standard deviation and relative numbers of each group. Also, during the research the methods used were: Student's t test, chi-squared test, Spearman correlation coefficient, ANOVA multivariate and univariate analysis and post-hoc test was used to make the statistical differences and comparisons among the normal, mild preeclamptic and severe preeclamptic pregnant patients. For all comparisons, two-tailed tests were accepted as significant when $p<0.05$. The data are presented in tables.

Results

Table 1 shows the demographic and clinical characteristics of the women studied. Women were similar with respect to age and parity.

We found a decreased risk of mild and severe preeclampsia among women who smoked during pregnancy. We did not analyse the impact of smoking on preterm delivery and/or lower birth weight.

Women who developed preeclampsia had higher rates of overweight prior to pregnancy and gained more weight during pregnancy.

The severe vs. mild preeclampsia, occurs earlier in pregnancy 30.42±4.5 (21-38w.g.) vs. 34.46±2.73 (26-38) and lasts longer (7.97±4.31 vs. 4.79±2.59 weeks). Regarding values of blood pressure measurements (Table 2). We may conclude that values of blood pressure, especially diastolic and mean pressure are in positive correlation with levels of total cholesterol and LDL.

Women with severe preeclampsia had high significantly shorter gestations than the other two patient groups ($p<0.01$). The lower birth weight and length at birth, underline the severity of the disease in the preeclamptic groups.

Results of plasma lipid from all three trimesters are displayed in Table 2.

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)	p>0.05†
Parity (%)				
Primipara	46.67	65.67	60.61	
Secundipara	43.67	26.87	21.21	p>0.05†
Tertipara	8.66	7.46	12.12	
multipara	1	0	6.06	
Education (years)				
0-8	27.66	46.27	48.48	
12-Sep	53	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‡
BMI	22.65±1.698	25.53±1.58	25.8±2.15	p<0.01§
	(19.06-27.63)	(21.8-27.91)	(21.68-29.06)	
<19.99	1.67	0	0	
20.0-24.99	87.33	23.88	30.3	
25.0-29.99	11	76.12	69.7	p<0.01§
>30	0	0	0	
Weight gain (kg)	13.95±3.1 (7-29)	19.59±3.78 (13-31)	20.24±7.36 (10-39)	
Week of Preeclampsia onset				
<25	-	0	18.18	
26-30		7.46	24.24	p<0.01‡
>31		92.54	57.58	
Duration of hypertension (weeks±days)	-	4.79±2.59 (1-14)	7.97±4.31 (2-16)	p<0.01§§
Duration of pregnancy (weeks±days)	39.57±0.9 (37-42)	39.09±0.92 (37-40)	37.48±2.04 (32-40)	p<0.01†
Birth weight (g)	3427.77±332.36	2989.25±256.19	2582.42±407.85	p<0.05†
Birth length (cm)	50.65±1.2	48.67±1.33	46.42±2.36	p<0.05†
Birth weight in percentile for GA				
<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 not available; n, number of subjects; GA, gestational age; BMI, body mass index

*Data are given as median, standard deviation and range

†multivariate analysis

‡chi-squared test

§multivariate analysis, univariate ANOVA and Spearman correlation coefficient

§§Student's t test

Citation: Jasovic-Siveska E, Milkovski D. Maternal plasma lipid concentration in first and second trimester of pregnancy and risk of preeclampsia. *Obstet Gynecol Int J.* 2019;10(4):299–304. DOI: 10.15406/ogij.2019.10.00458

Table 2 Lipid parameters and blood pressure during pregnancy*

Characteristics	Controls normal pregnancies n=300	mild preeclampsia n=67	severe preeclampsia n=33	P value
First trimester (8-12 week of gestation)				
Cholesterol (mmol/liter)	4.28± 0.53 (3.4-5.71)	4.74± 0.74 (3.7-6.33)	5.48± 0.91 (3.8- 6.7)	
HDL(mmol/liter)	1.38± 0.21 (0.9-2.1)	1.16± 0.24 (0.8-1.7)	0.96± 0.15 (0.7- 1.5)	p<0.05†
LDL(mmol/liter)	1.37± 0.3 (0.9-2.11)	1.98± 0.45 (1.07-3.2)	2.36± 0.6 (1.3- 3.4)	
Systolic blood pressure	102.18±7.38	111.79±8.73	114.24±10.47	p>0.05‡
Diastolic blood pressure	63.72±4.87	73.36±7.51	75.45±8.23	p<0.05**
Mean arterial pressure	76.54±5.4	86.16± 7.66	88.38±8.6	p<0.05
Second trimester (20-24 week of gestation)				
Cholesterol (mmol/liter)	4.06± 0.56 (3.2- 5.5)	4.97± 0.77 (3.5- 6.5)	5.93± 0.9 (3.57- 7.1)	
HDL(mmol/liter)	1.24± 0.21 (1.05-1.9)	1.18± 0.21 (0.9-1.7)	1.11± 0.16 (0.8- 1.35)	p<0.05†
LDL(mmol/liter)	1.3± 0.31 (0.8-2.02)	2.16± 0.52 (1.0- 3.1)	2.6± 0.64 (1.1- 3.7)	
Systolic blood pressure	107.55±6.49	121.34±10.25	133.33±15.3	P<0.05‡
Diastolic blood pressure	67.92±4.72	80.52±7. 81	88.03±11.85	p<0.05
Mean arterial pressure (mmHg)	81.12±5.2	94.13± 7.99	103.13±12.85	p<0.05
Third trimester (28-32 week of gestation)				
Cholesterol (mmol/liter)	4.12± 0.56 (3.1-5.35	4.91± 0.76 (3.2-6.32)	5.86± 0.87 (3.6-7.1)	
HDL(mmol/liter)	1.28± 0.19 (1.01-1.71)	1.2± 0.2 (0.7-1.56)	1.06± 0.17 (0.7-1.5)	p<0.05†
LDL(mmol/liter)	1.37± 0.32 (0.9-2.3)	2.13± 0.52 (1.01-3.1)	2.64± 0.68 (1.01-4.2)	
Systolic blood pressure	102.18±7.38	111.79±8.73	114.24±10.47	p>0.05‡
Diastolic blood pressure	63.72±4.87	73.36±7.51	75.45±8.23	p<0.05
Mean arterial pressure	82.35±5.05	96.81± 8.2	115.35±16.33	p<0.05

n, number of subjects

*Data are given as mean, SD and range

†Multivariate analysis for proportion and one-way parametric ANOVA

‡parametric and non parametric one-way ANOVA in dependent of normal distribution

**p<0.05 control vs. severe preclampsia; between group p>0.05

Differences of lipoprotein parameters of normotensive and mild and severe preeclamptic women were tested for significance using the multivariate analysis for proportion and one-factor parametric ANOVA. There was a significant difference in all of the plasma lipid concentrations in all three trimesters between all three groups. Mild and severe preeclampsia groups had more total cholesterol and LDL concentrations in comparison to the control groups. This is in correlation with the increased BMI, and this difference maintained by the end of pregnancy. The HDL concentration among mild and severe preeclamptic groups was less than control groups.

Regarding all lipid parameters, our results show that in normotensive women in the second trimester comes to a slight decrease in value of all parameters, which are then slightly increased in the third trimester. In the control group during the third trimester the total cholesterol and HDL levels were lower compared to the first trimester while LDL values returning to levels first trimester. In

women with mild and severe preeclampsia exists continual increase in all lipid parameters during the pregnancy.

Discussion

Endothelial cell dysfunction would seem to be the common denominator in the various stages of preeclampsia and appears to be present from the first trimester of pregnancy.

The physiological response of pregnancy represents a transient excursion into a metabolic syndrome where several components are acquired: a relative insulin resistance, significant hyperlipidemia and an increase in coagulation factors.[13] In the later stage of second trimester an increased concentration of free fatty acids (FFA) is observed. This increased delivery of FFA to the liver results in increased synthesis of triglycerides and very-low-density lipoprotein cholesterol (VLDL). HDL also increases in pregnancy, achieving a peak around 24wg. LDL achieves a less significant elevation, although as concentration of triglyceride rise, a threshold is reached after which proportionally more production of the LDL takes place. In the oxidized form, this molecule is believed to be highly atherogenic, promoting foam-cell production and initiating endothelial dysfunction. Normal pregnancy also involves up-regulation of the inflammatory cascade. In the non-pregnant women, inflammatory markers (C-reactive protein, interleukin-6, white-cell count) have all been found independently to predict future risk of cardiovascular events and diabetes.[14]

Preeclampsia is associated with accentuation of many features of the metabolic syndrome, including insulin resistance, hypertriglyceridemia, elevated FFA and LDL, low HDL cholesterol, hyperuricemia and abnormalities in the fibrinolytic system.[5]

By design, the groups in our study did not differ by age and parity. Women who developed preeclampsia had higher rates of overweight prior to pregnancy and gained more weight during pregnancy. Main weight gain during pregnancy in control groups was 13.95±3.1kg vs. mild preeclamptic women 19.59±3.78kg and severe preeclamptic women 20.24±7.36kg ($p<0.01$). Our results confirmed previous findings that prepregnancy BMI is a strong independent risk factor for preeclampsia and they extend previous findings by demonstrating that inflammation and lipids levels at first and second trimesters may be important mediators of the BMI- preeclampsia association.

Regarding lipid parameters, our results are in line with majority of previous studies in this field which have reported significant relationship between hyperlipidemia and preeclampsia.[15–17] Hubel CA and colleagues reported that in their study exist increased levels of cholesterol, LDL and blood pressure values, but low HDL.[18] These results are comparable with our results.

Maternal dyslipidemia and severity of preeclampsia at 15-20wg was evaluated in a study by Baker A. et al.[19] The authors found that women with severe preclampsia had lower levels of LDL than control subjects (normotensive) and a less atherogenic lipid profile than controls. Women with mild preeclampsia had higher levels of triglycerides, total cholesterol and HDL than control subjects. The authors concluded that midgestation mild preclampsia is associated with mild but not severe preeclampsia, and that these finding may elucidating the different pathologic process between mild and severe preeclampsia.[19] That is not comparable with our results.

Barden et al.[20] in a retrospective comparison of 62 preeclamptic and 84 normotensive women, seen antenatally and at 6 weeks and 6 months postpartum, revealed persistent dyslipidemia, increased blood pressure and a high prevalence of obesity in women prior preeclampsia. In this study women with previous preeclampsia reported a greater incidence of family history of hypertension (65% vs 35%).[20]

Comparing our results and those of other studies, it seems the role of dyslipidemia in pathogenesis is seen in majority of studies. However, there is controversy in regards to total cholesterol in several studies.

In that regard, further research that will include diverse population is essential to bring up new view and answer some controversial questions pertaining to the relation between the severity of preeclampsia and plasma lipid concentration.

We recognize that our study has limitations. We did not assess the combined effects of smoking and weight among women developing preeclampsia.

We did not investigate and analyzed inflammatory response as measured by serum CRP and concentration of triglycerides during pregnancy, especially in first and second trimester. These parameters at <20 weeks may be important mediator of the BMI-preeclampsia association.

Our results have shown early changes in plasma lipid concentration, which suggest their role in causation and severity of preeclampsia. The results of this study support the concept that endothelial cell dysfunction in preeclampsia may be a manifestation of lipid-induced injury to those cells. As such it is considered as a significant etiologic and pathophysiologic factor in this important pregnancy complication. Plasma lipid profile assay in first and second trimester of pregnancy is noticeable to predict probability and severity of preeclampsia, especially in combination with blood pressure values in same periods.

The matter of whether lipid parameters share a causative relationship with preeclampsia should be expanded to the study of other lipoprotein particles and microparticles. The collection of blood specimens in early pregnancy, measuring concentration of triglycerides, insulin, glucose and inflammatory markers, alongside anthropomorphic assessment, and then followed by a thorough assessment of clinical outcome through a large cohort study, might optimally address the role lipids and the metabolic syndrome in the causation of preeclampsia. These data provide further rationale to examine the potential benefit of pre-conceptual weight loss and antenatal exercise.

Acknowledgments

None.

Funding

None.

Conflicts of interest

Authors disclose no conflict of interests in publication of this study.

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Citation: Jasovic-Siveska E, Milkovski D. Maternal plasma lipid concentration in first and second trimester of pregnancy and risk of preeclampsia. *Obstet Gynecol Int J.* 2019;10(4):299–304. DOI: 10.15406/ogij.2019.10.00458