A Biochemical Marker of Preeclampsia - Hypertriglyceridemia - and the Impact of Secondary Prevention Therapy

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Changes in lipid metabolism from pregnancies with preeclampsia (PE) are a challenge for the obstetrician, because they contribute to the pathological chain and to some specific severe complications (severe hypertriglyceridemia of pregnancy, acute pancreatitis etc). Patients at risk for PE have higher levels of triglycerides, total and LDL cholesterol, compared to normotensive pregnant women. We searched the link between lipidic changes in pregnancies with PE and the way secondary prophylactic treatments with acetylsalicilic acid or low molecular weight heparin (LMWH) can influence the evolution of pregnancy, avoiding the severe complications of this disease. We identified patients at risk of developing PE and then applied a secondary prophylaxis with either a platelet antiaggregant (acetylsalycilic acid - a group of 36 patients) or an anticoagulant prophylaxis with LMWH – enoxaparin (a second group of 37 patients), aiming a decrease of severe complications of PIH/PE. The control group consisted of 33 pregnant women with risk factors for PE, without any secondary prophylaxis, according to actual guidelines. We periodically determined (at 14, 16-20 and 34 weeks of pregnancy) several biochemical parameters: triglycerides, uric acid, free fatty acids, total cholesterol and albuminemia. In the present paper we present the evolution of triglyceridemia in the studied groups, considering hypertriglyceridemia as an important prognostic factor for maternal complications in pregnancy. The most important result of our study is the statistically significant extremely low rate of complications in the treatment groups.

Keywords: preeclampsia, hypertriglyceridemia, acetylsalycilic acid, LMWH

Pregnancy induced hypertension/preeclampsia (PIH/PE) is a complex condition, originating in the early trophoblast invasion. Key-tissues are the placenta and the endothelium, and both the mother and the fetus are affected [1]. Current worldwide studies attempt to bring screening, early prediction and prevention of PIH/PE as close as possible to daily practice.

The poor invasion of spiral arterioles by the fetal trophoblast is a histopathological certainity, resulting in placental ischaemia and placental hypoperfusion. This creates a hypoxic environment, favoring oxidative aggression and generalised endothelial dysfunction [2]. We searched the link between lipidic changes in pregnancies with PE and the way prophylactic treatments with acetylsalicilic acid or low molecular weight heparines can influence the evolution of pregnancy, avoiding the severe complications of this disease.

Changes in lipid metabolism from pregnancies with preeclampsia are a challenge for the obstetrician, because they contribute to the pathological chain and to some specific severe complications (severe hypertriglyceridemia of pregnancy, acute pancreatitis etc) [3]. The histopathological exams revealed the accumulation of lipid-loaded macrophages in the affected endothelium [4, 5].

In normal pregnancy, an activation by resetting the hypothalamic lipostat, which causes hyperlipidemia [6] is described. Lipid alterations are more marked in pregnant women with PE and major changes are seen in triglycerides- hypertriglyceridemia. This is an aggravating factor for oxidative stress and endothelial dysfunction [7].

Another aggravating factor is the increase in the body mass index, which additionally contributes to the endothelial damage, by activating the generalized inflammation pathways.

Obesity, dyslipidemia and increased insulin resistance are the elements of the so-called gestational metabolic syndrome, with consequences both during pregnancy and later, maintaining a lifetime cardiac and cerebro-vascular risk of these patients.

Patients at risk for PE have higher levels of triglycerides (fig.1), total and LDL cholesterol, compared to normotensive pregnant women [8]. A hypertriglyceridemia over 280 mg/dL at the beginning of the third trimester signals the risk of severe PE, which is a major factor in shaping a pregnancy risk profile.

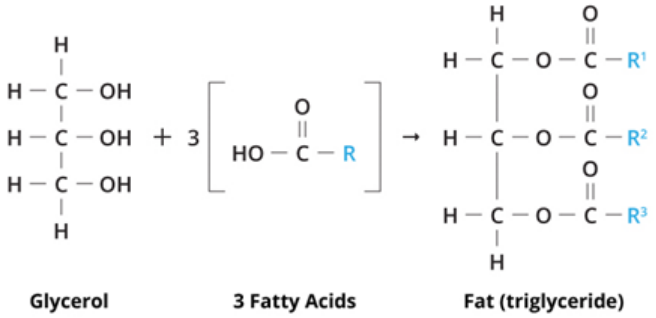

Fig. 1. Triglycerides synthesis

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If the hypertrygliceridemia is a preexisting condition, antepartum weight loss and diet changes are adjustable behavioral factors that we must insist on, as they can help improve prognosis in pregnancy. This concern should continue postpartum, given the long-term, lifetime risks of these women.

Drug prophylaxis of PIH/PE complications can be achieved in two ways:

a.Acetylsalicylic acid (aspirin) at low doses (75-150 mg) (fig. 2)

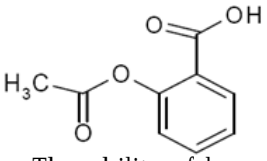

Fig. 2. Acetylsalicylic acid

The ability of low dose aspirin to prevent platelet aggregation was the starting point in its prophylactic administration in various disorders. This is achieved by inhibiting cyclooxigenase activity, decreasing the production of thromboxane A2, and as such, increasing prostacyclin, a powerful vasodilator and inhibitor of platelet aggregation [9]. This is how in preeclamptic patients the intravascular thrombosis and endothelial lesions inside the placenta may be reduced, with improvement in placental perfusion. The benefit is better when aspirin is prescribed from the first trimester of pregnancy (until 32 weeks of prgenancy). It does not increase the risk of abruptio placentae, as some small studies stated [10].

Certain professional organizations have drawn up the following recommendations: aspirin can only be used prophylactically for pregnant women at high risk for preeclampsia (those in whom a Doppler investigation of the uterine arteries in the second trimester detects an increase in the placental resistance to flow), pregnant women with early onset of PIH/PE, those with antiphospholipid antibody syndrome or personal history of PE. According to current guidelines, aspirin is not indicated as routine prophylaxis in all pregnant women with PIH/PE [1].

b.Anticoagulant prophylaxis with low molecular weight heparin (LMWH)(fig.3)

Anticoagulant prophylaxis with LMWH was proposed based on the microscopic characteristics of placenta in pregnancy complicated with preeclampsia. Thus utero-placental ischaemia, syncytial nodosities, intervillous fibrin deposits, distal villous hypoplasia, villous infarction, decidual necrosis and spiral arteries abnormalities (acute atherosclerosis, endothelial hypertrophy, intraluminal thrombosis) are observed. This remains a controversial field, because the formation of thrombus is only a minor component of placental dysfunction [11].

There are currently no conclusive results to allow recommendations on this type of prophylaxis, although many specialists reported beneficial individual outcomes to avoid severe or complicated progression of preeclampsia.

Experimental part

We analysed 497 pregnant women in a two-step study. During the first step, we reviewed retrospectively, over a period of three years, biochemical, ultrasound and placental pathological changes and their correlations in patients who developped PIH, PE (moderate or severe) and eclampsia. The data were collected from the hospitalized gravida and from those who gave birth in the Clinic of Obstetrics and Gynecology from the Bucharest University Emergency Hospital (391 patients).

During the second step, the following two years, we identified patients at risk of developing PE and then applied a secondary prophylaxis with either platelet antiaggregant (aspirin- a group of 36 patients) or an anticoagulant prophylaxis with LMWH - enoxaparin (a second group of 37 patients), aiming a decrease of severe complications of PIH/PE. The risk was assessed by: personal or familial history of thromboembolic disease, more than two abortions, personal history of PIH, PE, eclampsia, intrauterine fetal death, intrauterine growth restriction in previous pregnancies; Doppler study of uterine artery and signs of placental infarction during the current pregnancy. The control group consisted of 33 pregnant women with risk factors for PE, without any secondary prophylaxis, according to actual guidelines. We periodically determined (at 14, 16-20 and 34 weeks of pregnancy) several biochemical parameters: triglycerides, uric acid, free fatty acids, total cholesterol and albuminemia. In the present paper we present the evolution of triglyceridemia in the studied groups, considering hypertriglyceridemia as an important prognostic factor for maternal complications in pregnancy.

Results and discussions

Statistical analysis of casuistry

For the complex case analysis we used the SPSS programme, version 17.0. Quantitative variables have been processed as central and dispersion trend indicators. The resemblance of the Gauss Laplace normal distribution was analyzed using the Shapiro Wilks test. Qualitative variables were analyzed as proportions. The three groups were compared two by two at the same time, using for the quantitative variables the T student test or the Mann Whitney U test, as the case was, and for qualitative variables the Chi2 test (table 1, table 2). Comparison of the same group at different time points was performed with the T test on pairs (table 3).

At all test times, mean triglyceridemia is statistically significant different between the three study groups.

Trygliceridemia values tend to normalize only in the last part of pregnancy in women taking prophylactic treatment, which supports long-terms changes (metabolic syndrome). Although the phenomenon was slow, there was no triglyceride value above 350 mg/dL, which is an effective prophylaxis. Also, none of these patients developed severe preeclampsia.

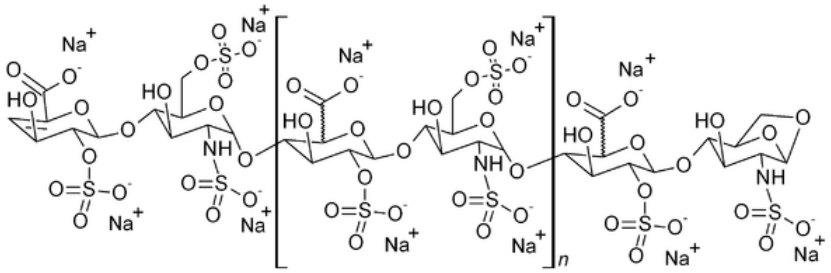

Fig. 3. LMWH - Enoxaparin

ANOVA

		Sum of Squares	df	Mean Square	F	Sig.
TGL_SA 14	Between Groups	21168.141	2	10584.070	28.422	.000
	Within Groups	39845.132	107	372.384		
	Total	61013.273	109			
TGL_SA 16-20	Between Groups	28399.404	2	14199.702	21.764	.000
	Within Groups	69810.968	107	652.439		
	Total	98210.373	109			
TGL_SA 34	Between Groups	10819.250	2	5409.625	7.037	.001
	Within Groups	82259.304	107	768.779		
	Total	93078.555	109			

Table 1
COMPARISON OF TRIGLYCERIDE VALUES AT 14, 16-20 AND 34 WEEKS OF PREGNANCY

	p Anova	p Aspirin vs no treatment	p Aspirin vs LMWH	p no treatment vs LMWH
TGL_SA 14	<0.001	<0.001	<0.001	0.041
TGL_SA 16-20	<0.001	<0.001	<0.001	0.094
TGL_SA 34	=0.001	=0.002	=0.002	0.520

Table 2
LILLIEFORS SIGNIFICANCE CORRECTION

Paired Samples Statistics

Grup (1=aspirin; 2=no treatment; 3=LMWH)			Mean	N	Std. Deviation	Std. Error Mean
1	Pair 1	TGL_SA 14	194.19	37	18.354	3.017
		TGL_SA 16-20	224.73	37	27.903	4.587
	Pair 2	TGL_SA 16-20	224.73	37	27.903	4.587
		TGL_SA 34	242.78	37	28.556	4.695
	Pair 3	TGL_SA 14	194.19	37	18.354	3.017
		TGL_SA 34	242.78	37	28.556	4.695
2	Pair 1	TGL_SA 14	160.79	34	23.253	3.988
		TGL_SA 16-20	186.59	34	27.397	4.699
	Pair 2	TGL_SA 16-20	186.59	34	27.397	4.699
		TGL_SA 34	219.85	34	31.231	5.356
	Pair 3	TGL_SA 14	160.79	34	23.253	3.988
		TGL_SA 34	219.85	34	31.231	5.356

Table 3
PAIRED SAMPLES STATISTICS

3	Pair 1	TGL_SA 14	170.72	39	16.120	2.581
		TGL_SA 16-20	196.26	39	21.158	3.383
	Pair 2	TGL_SA 16-20	196.26	39	21.158	3.383
		TGL_SA 34	224.08	39	23.348	3.739
	Pair 3	TGL_SA 14	170.72	39	16.120	2.581
		TGL_SA 34	224.08	39	23.348	3.739

Table 3
PAIRED SAMPLES STATISTICS
(continuated)

In the group of pregnant women without treatment, there where 12 cases of significant hypertriglyceridemia (over 500 mg/dL) and three cases of severe hypertriglyceridemia (over 750mg/dL), two of them complicated with acute pancreatitis, with complex treatment in the 1st Surgical Clinic.

The most important result of our study is the statistically significant extremely low rate of complications in the treatment groups. The complete absence of major maternal and fetal complications (no case of acute pancreatitis, eclampsia, maternal or fetal death, abruptio placentae, severe intrauterine groth restriction) is an important argument for continuing the studies in this field, in order to find the most appropriate onset and dosages of treatment [12, 13].

We consider as an initial compulsory stage the active detection of pregnant women at risk for developing PE (anamnesis, predictive laboratory and ultrasound markers). In addition to dietary measures (hyperproteic, low fat, low carb and normosodic diet), thorough follow-up during pregnancy (reduction of physical effort, frequent measurement of weight gain, blood pressure and proteinuria) prophylactic administration of acetylsalycilic acid or LMWH is a useful tool in reducing the incidence of severe complications.

Conclusions

From our observations, we propose an interventional therapeutical approach for pregnant women at risk of developing complications of preeclampsia. Beyond an as early as possible diagnosis, we consider utmost important to search how we can exploit the *therapeutic window*, ideally between 16 and 20 weeks of pregnancy [14] or immediately after signs of severity of the disorder are detected [15, 16], to decrease as much as possible the perinatal morbidity or mortality from this condition, which unfortunately remain high in Romania.

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