Biomarkers in Diagnosing Preeclampsia and Their Correlation with Blood Pressure

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Together with their general condition, the ratio of sFlt-1 / PlGF is an objective factor in the assessment of suspected preeclampsia. Recent research has shown that the ratio sFlt-1 / PlGF can be associated with the severity of preeclampsia, providing a short-term prediction about pregnancy. For this follow up study we considered a sample of 30 pregnant woman's all of them having tension problems. Our results confirm a decreased PlGF serum in patients with preeclampsia.

Keywords: pregnancy, hypertension, biomarkers, the ratio of sFlt-1 / PlGF

Pregnancy-induced hypertension is defined as the increase of systolic blood pressure over 140 mmHg and diastolic blood pressure over 90 mmHg in pregnant women who have over 20 weeks of pregnancy and who, previously, were normotensive [1].

HTAIS that is found in pregnancy and may complicate its evolution has a frequency of 5-10% of all pregnancies and in 20% of cases is seen in nulliparous. Due to this incident, it is an important cause of maternal and newborn mortality and morbidity [2]. More than half of pregnant women that will develop HTAIS will present signs and symptoms of preeclampsia, and its frequency is seen in about 4% of all pregnancies [3]. In developing countries the main cause of mortality among pregnant women is due to bleeding (according to OMS -24%) and infection (according to OMS - 14%); in developed countries the leading cause of maternal mortality is represented by complications created by HTAIS [4]. In the United States, the incidence of maternal mortality caused by infections is 2%, by hemorrhages, 13%, and by complications due HTAIS, 16% [5]. Therefore, our efforts should be focused on early detection of HTAIS and appropriate approach of diseases associated with hypertension; if all of these are combined may significantly reduce the incidence of maternal and fetal morbidity and mortality [6].

The normal development of the placenta is a major factor in the fetus's growth and development, whilst the maternal-fetal placental vasculature is essential in this regard. During placentation, there is an ongoing process, which combines angiogenesis with vasculogenesis, as demonstrated by numerous studies, which reveal important roles of various known angiogenic factors, while other studies show the roles of different classes of factors in vascular morphogenesis nonspecific to the placenta [7,8].

Experimental part
Material and method
For this follow up study we considered a sample of 30 pregnant woman's all of them having tension problems. We wanted to proof that a hypertension can conduce to different medical problems. We made several test on this patients in order to see if we can find an association between their age, gestational period (calculated in weeks), fetus weight, Esbach proteinuria and the fact that all of them presented hypertension. There are standardized and automated tests available worldwide to measure the levels of PlGF and sFlt-1 and to ensure accurate diagnosis and monitoring preeclampsia widely.

For the statistical analysis we used the programs Microsoft Excel, EpiInfo v7 and SPSS v17. For the Person coefficients, the coefficients of determination and the associated p – values we used the Regression Model. In the last part we computed a risk analysis, for determining the significance we used a chi square test.

Results and discussions
The treatment of moderate and mild hypertension is controversial. Although it may be beneficial for the mother in order to reduce her BP, it could affect uteroplacental perfusion and jeopardize fetal development, resulting in intrauterine growth retardation [9]. To maintain intrauterine growth, plasma volume increases along with maternal cardiac output and pulse rate, while maternal vascular resistance and blood pressure decrease. While all the processes mentioned above take place in the first trimester, in the second trimester, in order to facilitate fetal vasculature both systolic and diastolic blood pressure reduce by 5-10 mmHg, and in the third trimester they are in the normal range. The decrease of blood pressure dues to a decrease in systemic vascular resistance and remains

Correlation between …	Pearson's correlation coefficient	The coefficient of determination R^2	p - value
Age and Test for Preeclampsia (group 2)	0.076	0.006	0.836
Age and Gestational Period (group 2)	0.024	0.0006	0.949
Gestational period and Test for Preeclampsia (group 2)	0.311	0.097	0.382

Table 1
CORRELATIONS THAT EVALUATES
SUSPICION OF PREECLAMPSIA

the same after delivery. Both the uteroplacental circulation with low resistance and high flux and vasodilation contribute to the decline in the vascular resistance [10].

Together with their general condition, the ratio of sFlt-1 / PlGF is an objective factor in the assessment of suspected preeclampsia. Recent research has shown that the ratio sFlt-1 / PlGF can be associated with the severity of preeclampsia, providing a short-term prediction about pregnancy, which helps identify the women at risk of immediate delivery [11]. There are standardized and automated tests available worldwide to measure the levels of PlGF and sFlt-1 and to ensure accurate diagnosis and monitoring preeclampsia widely. We analyzed the association between the age variable and preeclampsia, between the age of the mother and her gestational period (calculated in weeks) and between the gestational period and preeclampsia and we obtained that these variables are independent. All the results are presented in table1.

From the above table it can be seen that all the variables are independent. The graphical representations can be found in the graphs relating to the table (fig. 1).

Women predisposed to HTAIS have be monitored regularly because of the risks of hypertension. In planning the pregnancy there should be considered the risks for women predisposed to have high blood pressure during pregnancy.

The size of our sample is 30 patients, all of then having hypertension. Most of them delivered their baby's by having a caesarian section (90%, 27 patients). We observed that the average value for delivery in our pregnant patients was 34 weeks, which is significantly lower than in the normal population (p<0,001). Along with the pregnancy evolution the TA values are increasing as well. We saw that if a patient has a high blood pressure when the pregnancy evolves the blood pressure is increasing as well. We wanted to proof that hypertension can conduce to different medical problems. We made several test on this patients in order to see if we can find an association between their age, gestational period (calculated in weeks), fetus weight, Esbach proteinuria and the fact that all of them presented hypertension. The conclusions that we obtained for the systolic blood pressure are the same as for diastolic blood pressure. The only difference is that in the diastolic blood pressure we have a lower variability, so the intensity of correlation is a little bit lower. All the results are presented in table 2, and plotted in figure 2.

During pregnancy, there should be made screening tests for preeclampsia by measuring proteinuria and BP. Proteinuria as a mandatory element in the diagnosis of preeclampsia varies in US and European protocols and thus, studies are needed to assess the importance of this parameter [12-14].

In the second part of the study we wanted to see if smoking during pregnancy can cause an involution on the fetus. For this from our sample we selected only the patients with an advanced gestational period (higher than 34 weak), 18 patients (60%). We split this group in smokers and nonsmokers and we obtained that smoking can be considered as a risk factor for a fetus weight evolution (RR=7.86, p<0.05). All the results are presented in Table 3 and in Fig3. Cigarette smoke contains about 2,500 chemicals, and when the mathers is an active or passive smoker, part of oxygen in her blood is replaced by carbon monoxide [15].
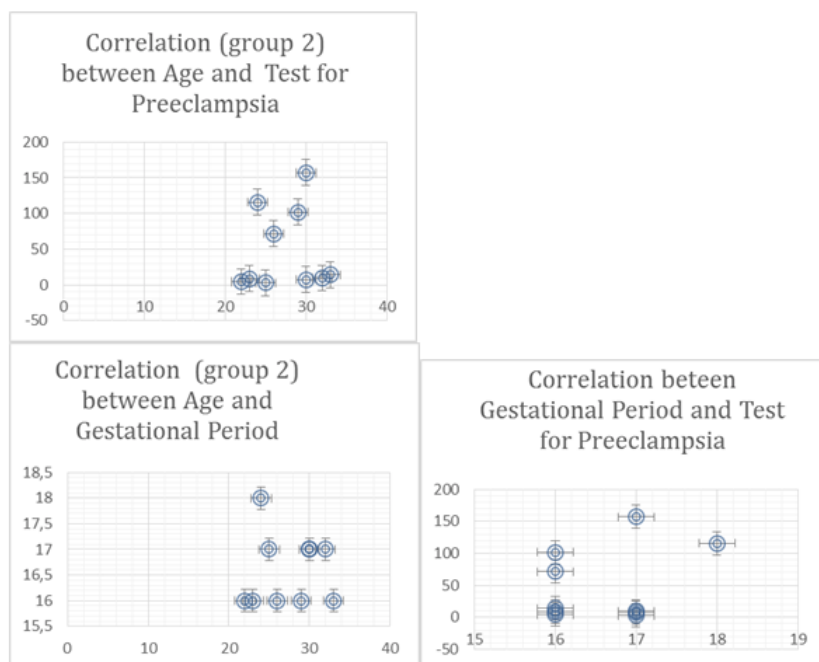

Fig. 1. Different correlations in our study groups

The statistical parameters	The values obtained
Results for the age compared to the systolic blood pressure	
r (Pearson coefficient)	0.49
R^2	0.26
p value	p=0.006
Results for Esbach proteinuria compared to the systolic blood pressure	
r (Pearson coefficient)	0.73
R^2	0.54
p value	p<0.001
Results for the fetus weight compared to the systolic blood pressure	
r (Pearson coefficient)	0.87
R^2	0.76
p value	p<0.001
Results for the pregnancy period compared to the systolic blood pressure	
r (Pearson coefficient)	0.84
R^2	0.71
p value	p<0.001

Table 2
IN THIS TABLE WE COMPUTED THE REGRESSION MODEL IN ORDER TO SEE IF WE HAVE AN ASSOCIATION BETWEEN THE VALES OF AGE, ESBACH PROTEINURIA, FETUS WEIGHT, GESTATIONAL PERIOD (CALCULATED IN WEEKS) AND THE SYSTOLIC BLOOD PRESSURE
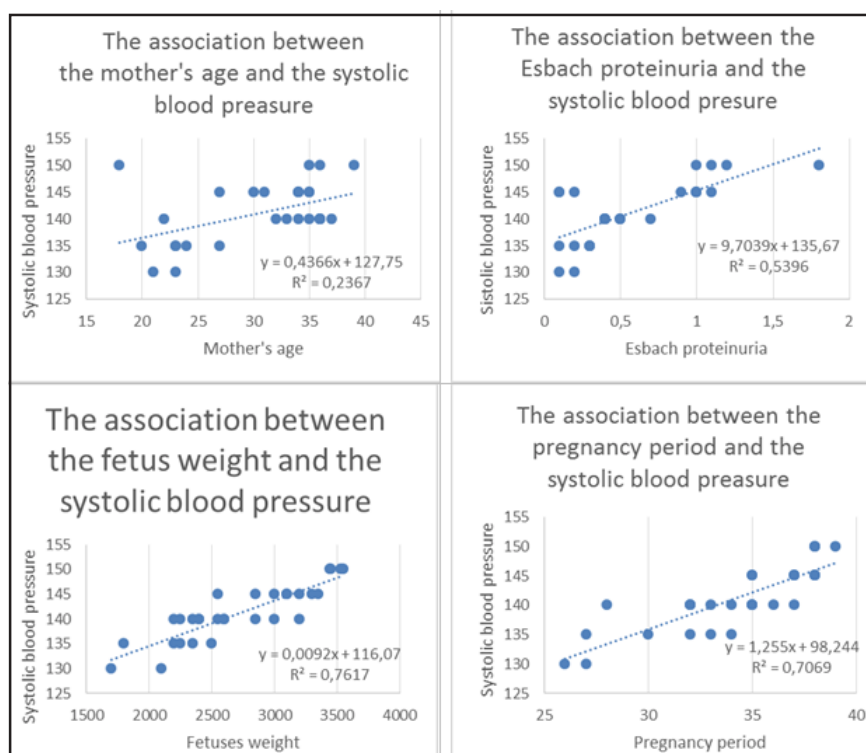

Fig. 2. In this figure we plotted all the regression models presented above

Table 3
IN THIS TABLE WE COMPUTED A RISK ANALYSIS IN ORDER TO SEE IF SMOKING CAN BE CONSIDERED AS A RISK FACTOR FOR A FETUS WEIGHT EVOLUTION

	Less than 3000 gr	More than or equal to 3000 gr	Total	Results
Smoker	5	2	7	RR=7,86
Non - smoker	1	10	11	95% >1
Total	6	12	18	p<0.05

The smoking future mother is more predisposed to have complication during pregnancy, complications such as the premature peeling of the placenta - placenta praevia. Smoking increases the risk of thrombosis and the occurrence of premature labor with repercussions on the fetus, with varying degrees of prematurity and increased risk of infection [16].

For this from our sample we selected only the patients with an advanced gestational period (higher than 34 weak), 18 patients (60%). We split this group in smokers and nonsmokers and we obtained that smoking can be considered as a risk factor for a fetus weight evolution (RR=7.86, p<0.05). All the results are presented in table 3 and in figure 4.

It is known that, during pregnancy there are risk factors for thrombosis resulting in venous stasis on the arterial wall, decreasing peripheral resistance, physiological hypercoagulability and decreasing peripheral resistance [17].

In a previous paper was studied Determining Visfatin/NAMPT Serum Levels by ELISA Technique, in pregnant women with preeclampsia [18].
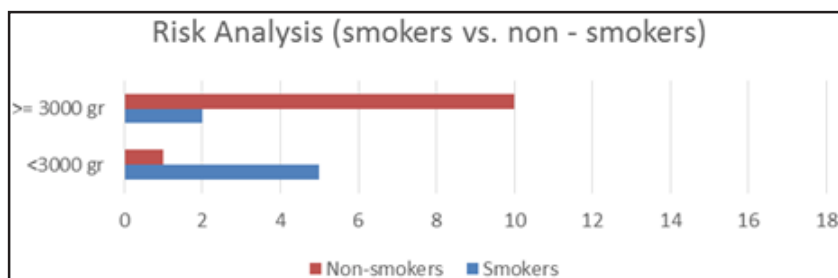
Fig.3. In this figure we plotted the risk analysis in order to highlight that smoking can be considered as a risk factor for a fetus weight evolution

Conclusions

Our results confirm the importance of determining markers for diagnosis and monitoring of pregnant women and at the same time highlight that PlGF levels along with other laboratory results are a good predictor of preeclampsia. Our results confirm a decreased PlGF serum in patients with preeclampsia.

Smoking increases the risk of thrombosis and the occurrence of premature labor with repercussions on the fetus. The risk of premature birth to a smoking mother is about 30%, and the baby may have different problems due to incompletely developed organ functions.

High blood pressure (hypertension) during pregnancy is a major global cause of maternal, fetal and newborn morbidity and mortality, being the most common medical problem in pregnancy.

References

1.*** Report of the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy. Am J Obstet Gynecol 2000; 183:S1-S22.
2.*** ESC Guidelines on the management of cardiovascular diseases during pregnancy. European Heart Journal (2011) 32, 3147–3197.
3.*** https:/ /en.wikipedia. org/wiki/Pre-eclampsia.
4.*** ESC Guidelines on the management of cardiovascular diseases during pregnancy. European Heart Journal (2011) 32, 3147–3197.
5.**** ESH/ESC Guidelines for the management of arterial hypertension. European Heart Journal (2013) 34, 2159–2219.
6.PETRE, I., BERNAD,E., CRAINA, M., CITU,C., BOLINTINEANU, S., POP, E., STOIAN, D., SIPOS, S., LUNGEANU,D., FURAU, C., FURAU, Gh., PANTEA, S., IONITA, I., Determining markers PlGF, sFlt1 and the ratio sFlt1/PlGF – prognostic tool in patiente with preeclampsia, Rev. Chim.(Bucharest), **67**, no. 11, 2016, p. 2365
7.PETRE I, FOLESCU R, BACEAN O, ET AL (2014). The macroscopic examination of the placental vasculature with a corrosive agent, Rom J Morphol Embryol, 2 suppl, 613-617, ISSN: 1220-0522.
8.BERNAD, E, PETRE, I, BERNAD, S, ILINA, R,Fetoplacental Network Hemodynamics Investigations, Using Vascular Casting Model, Mat. Plast.,**52**, no. 4,2015, p. 582
9.*** https:/ /en.wikipedia. org/wiki/Trombophylia.
10.NICE Guidelines. Hypertension in pregnancy: the management of hypertensive disorders during pregnancy. 2010.
11.OUZOUNIAN JG, ELKAYAM U, 2012 Physiologic changes during normal pregnancy and delivery. Cardiol Clin 30: 317-329. 8. Hall, J. E., & Guyton, A. C. (2011).
12.*** The American College of Obstetricians and Gynecologists.Task Force on Hypertension in Pregnancy Hypertension in Pregnancy. Hypertension, Pregnancy Induced –Practice Guideline wq244 2013 17.
13.EVANGELIA KINTIRAKI, SOPHIA PAPAKATSIKA, GEORGE KOTRONIS ET AL. Hormones 2015, 14(2): Pregnancy-induced hypertension 211-22.
14.DAVID O. BATES. An unexpected tail of VEGF and PlGF in pre-eclampsia. Biochem Soc Trans. 2011 Dec; 39(6): 1576–1582.
15 BONTE, D.C., BOGLUT,A., DUTA, C., PETRE,I., BERNAD, E., VLAD DALIBORCA, C.,. IACOB, R.E., DIMA, M., IACOB, D., The Harmful Effects of Smoking during Pregnancy and Correlating Lead and Selenium Levels in Mothers and Premature Fetuses, Rev. Chim. (Bucharest), **67**, no. 1, 2016, p, 116
16.DIMA, M., IACOB, D., DUTA, C., PANTEA, S., MARGINEAN, O., BERNAD,E., CRAINA, M., BOGLUT,A., PETRE, I., Association Between Mannose - binding Lectin and Serum Parameters of Neonatal Sepsis, Rev. Chim. (Bucharest), **67**, no. 3, 2016, p.557
17.IONITA, I., GRIGORITA, L., BACEAN MILOICOV, C., PETRE, I., BERNAD,E., CRAINA, M.,DIACONU, M., CITU, C., RADU,F., OROS, D., BOGLUT, A., FURAU,Gh., ENATESCU, V., The role of thrombophilia in pregnancy, Rev Chim. (Bucharest), **67**, no. 12, 2016, 2016, p.2643
18. MOCAN HOGNOGI, L.D., MOCAN HOGNOGI, R.F., MALUTAN, A., FARCAS, A.M., VIDASMITI, L., Rev. Chim. (Bucharest), **68**, no. 9, 2017, p. 2108