Determining Markers PlGF, sFlt1 and the Ratio sFlt1/PlGF - Prognostic Tool in Patients with Preeclampsia

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Preeclampsia represents a pregnancy complication characterized by high blood pressure and proteinuria, after the 20th week of gestation. It appears in 3-5% of pregnant women, having a substantial maternal, foetal and neo-natal mortality and morbidity rate. In a normal pregnancy: the PlGF (package factor) serum level increases in the first two trimesters of pregnancy and decreases as the pregnancy comes to term; the serum level of sFlt-1 remains stable in the first two trimesters of pregnancy, and then increases as the pregnancy comes to term. In the cases of women who develop preeclampsia, the level of sFlt-1 is higher and that of PlGF is lower, than in normal pregnancies. The ration of sFlt-1/PlGF is a better indicator of preeclampsia than any other of the two individually evaluated factors. The results of our study come to confirm the importance of determining these markers for the diagnosis and monitoring of pregnant women and at the same time to highlight the fact that the ratio of sFlt- 1/PlGF represents a good predictor of preeclampsia.

Keywords: gestational age, PlGF, preeclamsia, pregnancy, sFlt1.

Preeclampsia and its complications, eclampsia and HELLP syndrome (Haemolysis, Elevated Liver enzymes, Low Platelet count), are the most frequent causes of maternal and foetal morbidity in the world. Despite all of the presented complications, preeclampsia can have a favourable diagnosis if the pregnant woman is hospitalized in time and is monitored by a medical team (obstetrician, anaesthesiologist, and neonatologist) [1-6]. Despite numerous researches, preeclampsia ethiopatogeny is not clearly known, there are numerous studies which favour a number of theories, but no final theory has been established, accepted by everyone. Recent theories maintain that at the base of preeclampsia ethiology a significant contribution is attributed to the imbalance between of angiogenic factors – the endothelial vascular growth factor (VEGF) and the placenta growth factor (PlGF) and those antiangiogenic factors – soluble tyrosine-kinase 1 fms-like (sFlt1) and soluble endoglin (sEng). PlGF and sFlt-1 can differentiate a normal pregnancy from a preeclampsia one, even before the clinical symptoms are shown [7-12].

Experimental part

The study took place between 2014 and 2015, at the Obstetrics and Gynaecology I and II wards of the Timisoara County Emergency Clinical Hospital Pius Brinzei – the only third party unit from the West Region, in collaboration with all profile units in the area and it tried to establish the level of the sFlt-1/PlGF ratio, as a diagnosis instrument in preeclampsia patients depending on the influence of cumulative risk factors.

The study had a number of 50 pregnant women which have given freely their consent to become part of the study, for which the PlGF and sFlt-1 biomarkers have been determined and the sFlt-1/ PlGF ratio has been calculated.

Results and discussions

Statistics referring to group characteristics ® numeric variables

The results synthesis of the 50 cases (tables 1 and 2).

	N	Minimum	Maximum	Average	Deviation Std.
Age [years]	50	22	41	31.40	4.768
Height [cm]	50	147	196	164.50	7.332
W before pregnancy [kg]	50	50	116	67.88	13.247

Table 1
STATISTICS REFERRING TO GROUP CHARACTERISTICS

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Environment	Number of cases (total 50 cases)	Percentage of the total, %
rural	21	42
urban	29	58

Table 2
STATISTICS REFERRING TO GROUP CHARACTERISTICS

Gestation	Number of cases (total 50 cases)	Percentage of the total, %
0	6	12
1	16	32
2	20	40
3	6	12
4	2	4

Table 3
STATISTICS REGARDING TO GESTATION

Parity	Number of cases (total 50 cases)	Percentage of the total, %
0	19	38
1	27	54
2	4	8

Table 4
STATISTICS REGARDING TO PARITY

Births before the study	Number of cases (total 50 cases)	Percentage of the total, %
0	26	52
1	22	44
2	2	4

Table 5
STATISTICS REGARDING TO BIRTHS

Education level	Number of cases (total 50 cases)	Percentage of the total, %
High school	23	46
Primary	4	8
Higher education	23	46

Table 6
STATISTICS REGARDING TO EDUCATION LEVEL

Table 7
STATISTICS REGARDING TO GESTATIONAL WEEKS

Gestational age, weeks	Number of cases (total 50 cases)	Percentage of the total, %
14	1	2
15	15	30
16	20	40
17	7	16
18	4	8
19	2	4

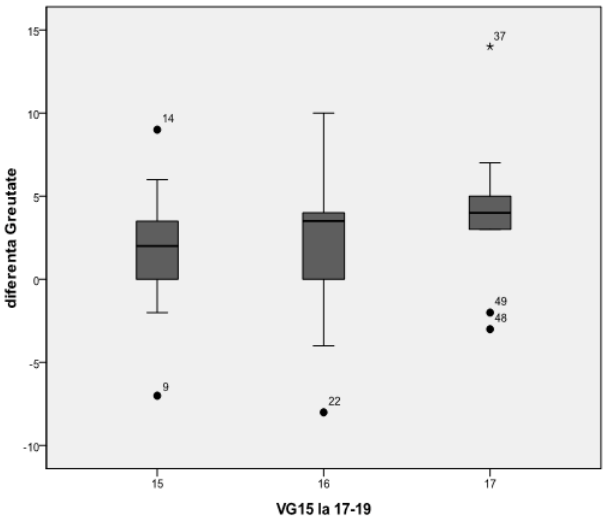

Fig. 1. Statistics referring to wight difference

Table 8
STATISTICS REFERRING TO BIOLOGICAL VALUES

	N	Minimum	Maximum	Average	Deviation Std.
sFlt-1	50	486.90	2898.00	1526.57	598.19
PIGF	50	36.00	684.80	174.75	120.82
Ratio	50	2.48	33.11	11.93	7.77
Wight difference	50	-8	14	2.55	3.99

Statistics regarding to group characteristics → category variables

The results synthesis of the 50 cases (tables 3-7).

- Statistics reffering to biological values
- The results synthesis of the 50 cases:

Is the ratio of biological values in between normal limits?

sFlt-1 « PIGF ratio analysis: is there a difference between biological values or between their ratios for the three gestational ages of the lot? [13-15].

- 15w, 16w, 17w ← we eliminated everything that was below 15w (one case) or higher than 17w (6 cases)

Test variant homogeneity: p=0.001** → the variants are not homogenous → the post-hoc test will be Tamhane.

Gestational age, weeks	ratio OK		Total
	NO	YES	
14	0	1	1
15	3	12	15
16	0	20	20
17	0	8	8
18	0	4	4
19	0	2	2
Total	3	47	50

Table 9
STATISTICS REFERRING TO GESTATIONAL AGE

sFlt-1	N	Min	Max	Average	StdErr	95% CI	Test post-hoc
15	15	876.00	2719.00	1562.53	147.29	(1246.63 – 878.44)	-
16	20	486.90	2898.00	1516.08	157.16	(1187.16 – 1845.01)	-
17	8	1047.00	1994.00	1525.88	118.77	(1245.02 – 1806.73)	-
Total	43	486.90	2898.00	1534.11	90.37	(1351.73 – 1716.49)	-
Test variant homogeneity: p=0.14 → the variants are homogenous							
Test ANOVA → p=0.974 → values sFlt-1 does not present significant statistical differences between the three groups							

Table 10
STATISTICS REFERRING TO BIOLOGICAL VALUES - sFlt-1

Variant analysis for biological values for the three groups of gestational age (43 cases)

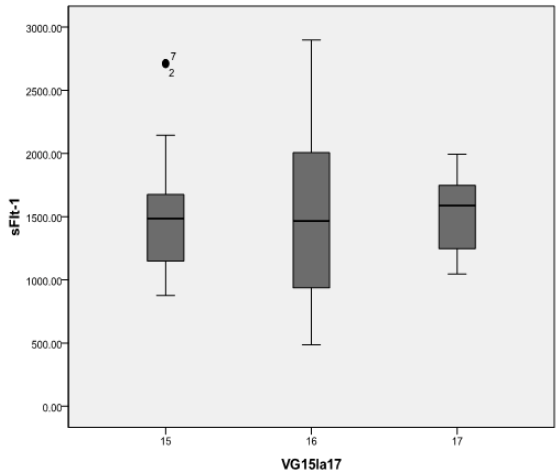

Fig. 2. Variant analysis for biological values - sFlt-1

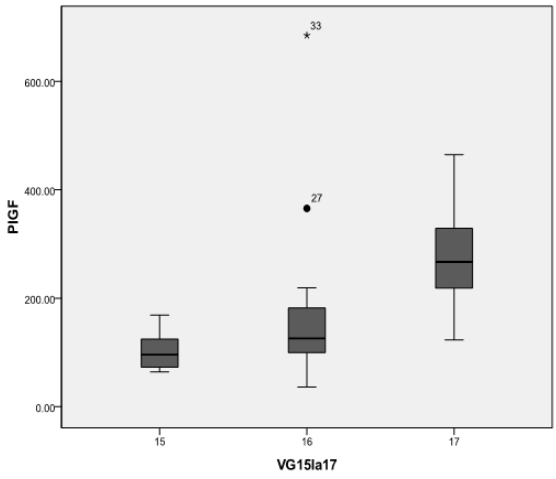

Fig. 3. Variant analysis for biological values – PIGF

PIGF	N	Min	Max	Average	StdErr	95% CI	Test post-hoc
15	15	64.00	168.80	99.91	8.2	(82.33 – 117.49)	15vs16 → p=0.076 15vs17 → p=0.001**
16	20	36.00	684.80	167.06	31.43	(101.27 – 232.86)	16vs17 → p=0.019*
17	8	123.00	465.00	277.16	36.89	(189.92 – 364.41)	-
Total	43	36.00	684.80	164.12	18.68	(126.43 – 201.82)	-
Test variant homogeneity: p=0.123 → the variants are homogenous → the post-hoc test will be LSD							
Test ANOVA → p=0.002** → PIGF values present very significant statistical differences, i.e. there is at least one different group → a post-hoc test will be applied for the comparison of two groups [16].							

Table 11
STATISTICS REFERRING TO BIOLOGICAL VALUES - PIGF

Table 12
STATISTICS REFERRING TO RATIO

Ratio	N	Min	Max	Average	StdErr	95% CI	Test post-hoc
15	15	5.97	33.11	17.41	2.2	(12.68 – 22.14)	15vs16 → p=0.165 15vs17 → p=0.001**
16	20	2.48	23.04	12.09	1.54	(8.87 – 15.30)	16vs17 → p=0.003**
17	8	3.87	8.51	5.94	0.56	(4.62 – 7.26)	-
Total	43	2.48	33.11	12.80	1.21	(10.36 – 15.24)	-
Test ANOVA → p=0.002** → the reports values show very significant statistical differences, there is at least one different group → the post-hoc test will be applied for comparison of two groups							

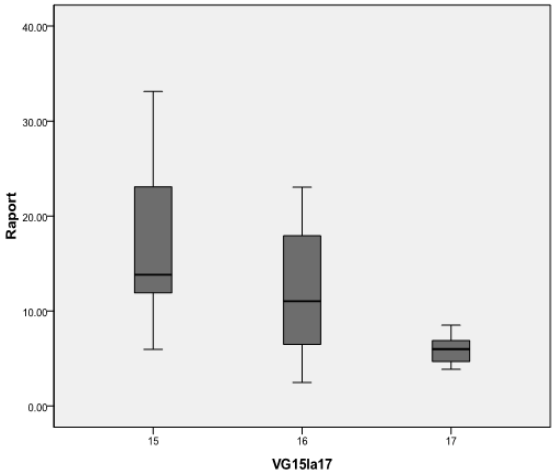

Fig. 4. Variant analysis for ratio

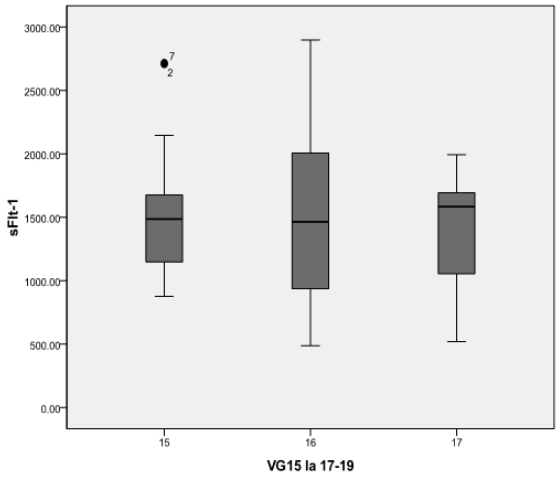

Fig. 5. Variants analysis for biological values - sFlt-1

sFlt-1	N	Min	Max	Average	StdErr	95% CI	Test post-hoc
15	15	876.00	2719.00	1562.53	147.29	(1246.63 – 878.44)	-
16	20	486.90	2898.00	1516.08	157.16	(1187.16 – 1845.01)	-
17	14	519.30	1994.00	1427.76	113.027	(1183.59 – 1671.93)	-
Total	49	486.90	2898.00	1505.07	83.51	(1337.17 – 1672.97)	-
Test variant homogeneity: p=0.185 → the variants are homogenous							
Test ANOVA → p=0.826 → the sFlt-1 values does not present significant statistical difference between the three groups							

Table 13
VARIANTS ANALYSIS FOR BIOLOGICAL VALUES IN THE THREE GESTATIONAL AGE GROUPS (49 CASES)

PIGF	N	Min	Max	Average	StdErr	95% CI	Test post-hoc
15	15	64.00	168.80	99.91	8.2	(82.33 – 117.49)	15vs16 → p=0.07 15vs17 → p<0.001**
16	20	36.00	684.80	167.06	31.43	(101.27 – 232.86)	16vs17 → p=0.011*
17	14	123.00	465.00	264.81	26.38	(207.82 – 321.81)	-
Total	49	36.00	684.80	174.43	17.46	(139.38 – 209.49)	-
Test variant homogeneity: p=0.081 → the variants are homogenous, at the border of statistical significance → the post-hoc test will be LSD							
Test ANOVA → p=0.001** → the PIGF values show very significant statistical differences, i.e. there is at least one different group → the post-hoc test will be applied for comparison of two groups							

Table 14
VARIANT ANALYSIS FOR BIOLOGICAL VALUES - PIGF

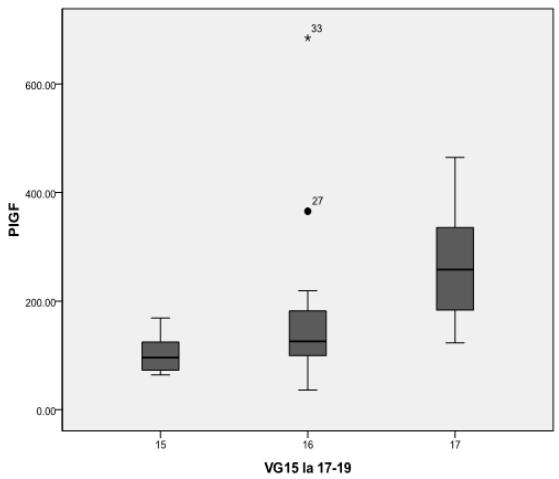

Fig. 6. Variants analysis for biological values - PIGF

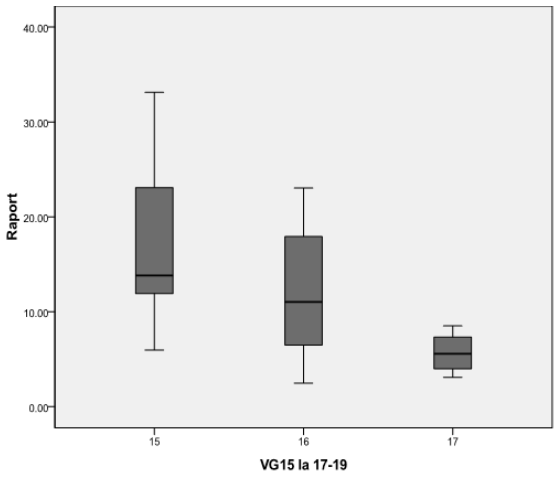

Fig. 7. Variants analysis for raport

Table 15

STATISTICS REFERRING TO RATIO

Ratio	N	Min	Max	Average	StdErr	95% CI	Test post-hoc
15	15	5.97	33.11	17.41	2.2	(12.68 – 22.14)	15vs16 → p=0.165 15vs17 → p<0.001**
16	20	2.48	23.04	12.09	1.54	(8.87 – 15.30)	16vs17 → p=0.002**
17	14	3.09	8.51	5.690	0.450	(4.7 – 6.67)	-
Total	49	2.48	33.11	11.89	1.120	(9.64 – 14.14)	-
Test variant homogeneity: p<0.001** → the variants are not homogeneous → the post-hoc test will be Tamhane							
Test ANOVA → p<0.001** → the values of the report show very significant statistical difference, i.e. there is at least one different group → the post-hoc test will be applied for comparison of two groups							

Conclusions

The results of our study come to confirm the importance of determining these markers for the diagnosis and monitoring of pregnant women and at the same time to highlight the fact that the sFlt-1/PlGF ratio represents a good predictor of preeclampsia.

Together with the evaluation of the general state, the sFlt-1/PlGF ratio is an objective factor in the evaluation of suspicions in preeclampsia. Recent research has shown the the value of the sFlt-1/PlGF ratio can be associated with the severity of preeclampsia, offering a short term prediction in regards to the duration of the pregnancy, which helps in identifying women at immediate birth risk. For the measurement of the PIGF and sFlt-1 levels, there are standardized and automatic tests available at global level, for ensuring the correct diagnosis and monitoring of preeclampsia at a large scale.

In conclusion, similar to other medical domains, the usage of new technology in preeclampsia looks rather promising. Additional studies are necessary, some are already on-going, in order to clarify the role of PIGF and sFlt-1 in the diagnosis and algorithm of preeclampsia management.

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