The Role of Several Angiogenesis Peptides Markers in the Management of Hypertensive Pregnant Women

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The objectives of the research herein are to detect if the modifications of sFlt-1 and PlGF can be correlated with the clinical and biochemical status of the hypertensive pregnant woman and if the sFlt-1/PlGF ratio is a good predictor for preeclampsia in case of the investigated patients. In the study herein, 100 pregnant women were evaluated; they were distributed in the following groups: The group of pregnant women diagnosed with HTN at the time of hospital admission – including 50 pregnant women, of which 16 pregnant women presented medium and severe forms of preeclampsia and 34 pregnant women with pregnancy-induced hypertension and 50 pregnant women with normal pregnancy evolution as control group. We have performed hematological and biochemical tests, using serum samples from all analyzed patients and measured the serum concentrations of sFlt-1 and PlGF angiogenic factors. We found a significant correlation between the value of the arterial blood pressure, the proteinuria, the serum creatinine and the AST, on one hand, and the sFlt-1/PlGF ratio, on the other hand. The ROC curve has emphasized the fact that the proteinuria (AUC = 0.849), the AST (AUC = 0.664), the value of the arterial blood pressure SBP/DBP (AUC = 0.683/ 0.631), the serum creatinine (AUC = 0.674) and the sFlt-1/PlGF ratio, at a cut off value = 200, are effective preeclampsia predictors. Similarly, statistically significant increase (p = 0.001) of the sFlt-1 serum concentration in case of the pregnant women from the PE group (14365±6464 pg/mL) and from the PIH group (9892±8443 pg/mL), compared to the control group (3278±1444 pg/mL) and, respectively, a significant decrease (p = 0.003) of the PlGF pro-angiogenic marker for the group of pregnant women suffering from preeclampsia (119.30±56.63 pg/mL) and from PIH (129.12±21.41 pg/mL), compared to the control group (327.57±59.62 pg/mL). The results obtained within this research show that sFlt-1/PlGF ratio represents an effective preeclampsia predictor, confirming the fact that the study of the angiogenic factors may help to analyze the stratification of the risk degree in HTN pregnant women.

Keywords: soluble fms-like tyrosine kinase-1(sFlt-1), pro-angiogenic placental growth (PlGF), preeclampsia, gestational hypertension

Preeclampsia, a systemic vascular disease, may affect various organs, leading to severe complications of the fetus and of the pregnant mother. Even if precise causes that determine preeclampsia are not yet established, several studies have shown, that placental dysfunctions play an important role in the emergence of this disease, being correlated to the subsequent maternal endothelial disfunctions [1, 2]. The anatomical presentation of placenta in case of pregnant women suffering from severe preeclampsia has frequently shown the presence of infarcts, fibrinoid necrosis of the blood vessels walls, thrombosis and signs of chronic inflammation [1, 3]. In case of preeclampsia, the cytotrophoblast invasion is incomplete, as the cells are present only in the superficial layers of the uterus endometrium [1, 4]. Therefore, the vascular resistance will significantly grow, because the spiral arteries of the endometrium cannot be properly modeled [5]. The anti-angiogenic factors, such as sFlt-1 (soluble fms-like tyrosine kinase-1 receptor), sEng (soluble endoglin) play an important role during the first part of the pregnancy, being related to the physiological vascular neo-formation; also, they are important during the second part of the pregnancy, contributing to the endothelial function and to the physiological vascular remodeling. The soluble Flt-1 is an anti-angiogenic circulating protein related to the receptor of the PlGF (placental growth factor) and VEGF fields (Vascular Endothelial Growth Factor), thus preventing the interaction with the endothelin receptors, causing endothelial dysfunctions. The endoglin is a surface co-receptor protein of TGF (transforming growth factor) β1 and β3 [6]. Its soluble form, the sEng factor, is a new anti-angiogenic that acts in synergy with sFlt-1. During normal pregnancy, a pro-angiogenic status appears, with reduced sFlt-1 levels and increased PlGF levels, until the end of the second trimester; towards the end of pregnancy, these levels reach the normal value. In case of pregnant women suffering from preeclampsia, we may notice abnormalities related to the angiogenic profile, with early changes of the anti-angiogenic status predominance, leading to endothelial dysfunctions. Thus, the PlGF and VEGF levels are lower than the normal value, while the sFlt-1 and sEng levels are high. The sF1t-1 released in a large amount in circulation from the placental level will destroy the homeostasis of the maternal endothelium. The result is the emergence of hypertension, proteinuria and other

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systemic manifestations of preeclampsia and metabolic sindrom [7]. In addition, the sFlt-1 factor is an antagonist of VEGF on the endothelial cells in renal, cerebral and hepatic vessels. Several researchers confirmed the fact that the increased circulating level of the sFlt-1 factor predicts preeclampsia outbreak, being correlated with a serious level of the disease manifestation [6, 8, 9]. Nevertheless, not all pregnant women suffering from preeclampsia have presented modified levels of sFlt-1(the soluble fms-like tyrosine kinase-1 receptor) and of PlGF. It is not clear yet if patients diagnosed with preeclampsia, presenting low sFlt-1 levels, suffer from an alternative non-angiogenic form of the disease. Alternatively, pregnant women suffering from old vascular diseases can develop signs and symptoms of the disease, even if the sFlt-1 values are low [6, 8, 9]. The rennin-angiotensin-aldosterone system (RAAS) is also affected in case of preeclampsia. Unlike normal pregnant women, whose vascular response is reduced in the presence of vasoactive peptides, such as angiotensin II and epinephrine, in case of pregnant women who develop preeclampsia, the vascular response is much too strong [10, 11]. There are studies that have identified agonist antibodies on the angiotensin II receptors. This type of antibodies was subsequently injected to pregnant female mice; they have developed hypertension, proteinuria and increased sFlt-1 and sEng levels [12-14].

Experimental part

Study groups in this study, we have evaluated a number of 100 pregnant women at the Cuza Voda Obstetrics and Gynecology Hospital, Ia°i, during the period January 2013 - May 2014. For this research, the approval of the Ethics Committee within the hospital was obtained from all subjects. The processing of the biological evidence complies with the norms and legal procedures in force [15-17]. The patients were distributed in the following groups: *The group represented by pregnant women diagnosed with hypertensive (HTN)* – including 50 pregnant women who were diagnosed with HTN at hospital admission; this group included 16 pregnant women suffering from medium and severe forms of preeclampsia (*PE group*), aged between 19 and 41 years old, (table 1) and 34 pregnant women diagnosed with non-complicated PIH (*PIH group*), aged between 22 and 44 years old (table 1). *The Control group* – including a number of 50 normal pregnant women, aged between 16 and 41 years old (tabel 1).

Baseline characteristics: The age of the pregnant women varied from 16 to 44 years old, registering a significantly higher average value ($p = 0.001$) in case of pregnant women diagnosed with PIH (31.35 y vs. 28.88 y in the group with patients diagnosed with PE and 26.50 in the Control Group). The height ($p < 0.008$) and the weight ($p = 0.001$) at the beginning of the research were significantly higher in case of patients suffering from PIH. The gestational age at moment of diagnosis varied between 22 and 42 weeks, being significantly lower in case of patients suffering from PE (32.13 week) and PIH (33.74 week), compared to the Control Group (37.48 week) ($p = 0.001$). We notice that the blood pressure values varied in the PE group from 100/55 to 180/120 mmHg, the group average being the highest 153.44/92.5 mmHg, compared to the group of patients suffering from PIH (158.65/88.50 mmHg) or to normal pregnant women (120.40/72.56 mmHg) ($p = 0.001$). Gestity and parity did not register significant discrepancies between the analyzed groups ($p > 0.05$).

Laboratory evaluations: For the hematologic investigations, we have used whole blood collected on K_3EDTA anticoagulant, as well as an automated hematology analyzer (Celltac MEK- 6318 K). For the biochemical investigations, we have resorted to serum obtained after the blood was collected in clot *activator* test tubes and centrifuged at 4000 rpm, during 10 min. In order to determine the biochemical parameters, we used a Clinical Chemistry automated analyzer, RX Imola type, with calibrators and control serums. For the immunological investigations, the serum was frozen at - 80°C. The tests were performed for the C-reactive protein, through the chemiluminescence technique, using an IMMULITE 1000 automated device; for the sFlt-1 and PlGF markers, we have resorted to the electroluminescence technique, using a COBAS E 411 automated device. The proteinuria was determined through the analysis of the urine samples collected at hospital admission, using the VITROS 950 dry chemistry automated analyzer, the samples being diluted accordingly.

Statistical methods

The data were uploaded and processed with the help of the SPSS 17 statistic functions. The ANOVA tests have been applied-using descriptive indicators of the monitored parameters with confidence intervals of 95%; also the F test (ANOVA) was applied -a quantitative test, whose aim is to analyze the significant discrepancy between three averages, as well as the χ^2 test -a qualitative test, through which we have compared 2 or more frequency distributions coming from the same population.

Results and discussions

Clinical and laboratory markers

The C-reactive protein (CRP) was calculated in case of 56,3% of patients suffering from preeclampsia and of 73.5% of patients suffering from PIH; it has registered low values,

Characteristics (mean values ± SD)	Study groups			p values
	PE group (n = 50)	PIH group (n = 50)	Control group (n = 50)	
Age, years	28.60±5.85	29.78±5.64	26.50±5.61	0.016 [a)]
Height, cm	165.10±6.37	168.88±6.24	163.73±6.24	0.001 [a)]
Weight, kg	82.54±17.68	91.17±20.99	72.19±12.43	0.001 [a)]
Pregnancy week	32.24±4.45	34.00±4.45	37.48±3.03	0.001 [a)]
Diastolic BP, mmHg	92.00±14.57	88.26±14.06	72.56±11.09	0.001 [a)]
Systolic BP, mmHg	153.00±18.30	148.06±21.44	120.40±11.99	0.001 [a)]
Parity, median(min-max)	1 (1-4)	1 (1-5)	1 (1-10)	0.096 [b)]
Pregnancies, median(min-max)	1 (1-4)	2 (1-6)	2 (1-10)	0.219 [b)]

[a)] p values for F (ANOVA) Test [b)] p values for Kruskal Wallis Test

Tabel 1
BASELINE CHARACTERISTICS OF THE STUDY POPULATION

from 6 mg/L to 48 mg/L. The CRP average value was significantly higher (p = 0.002) in case of patients suffering from PE (12 vs. 6.72 mg/L) (table 2). The individual hemoglobin values varied from 7.5 to 14.9 mg/dL, registering significantly higher average values in case of patients diagnosed with PE (p = 0.038). The hematocrit registered values ranging from 21.7 to 53.4%, the average values being slightly higher in case of the group of patients suffering from PE (p = 0.102) (table 2). Proteins from urine, in case of the group of patients diagnosed with preeclampsia, varied from traces to more than 300 mg/dL, registering a significantly higher average value (195.63±126.12 mg/dL) compared to the other analyzed groups (p = 0.001) (table 2). Even if, in case of the group of pregnant women suffering from PE, we have noticed that the uric acid (p = 0.001) and the serum urea (p = 0.005) have significantly higher average values of the serum concentration compared to the Control group, these average values did not exceed the reference interval. The average values of the serum creatinine, according to the analyzed groups, do not show significant discrepancies (p = 0.312). The average values of the enzymatic markers (AST, ALT and LDH) corresponding to the analyzed groups did not show significant discrepancies (p > 0.05). In case of patients suffering from preeclampsia, we did not notice significant correlations between the hepatic markers and the sFlt-1/PlGF ratio: AST (r = -0.031; p = 0.909), ALT (r = -0.026; p = 0.925), LDH (r = -0.167; p = 0.537), but 35.3% of the patients suffering from HTN have shown increased values of the sFlt-1/PlGF ratio, which were statistically correlated with the increased values of the AST (r = 0.353; p = 0.044); also, 32% have shown increased ALT values (r = 0.320; p = 0.049). In case of patients suffering from PE, we have noticed as well a poor direct linkage between the uric acid and the sFlt-1/PlGF ratio (r = 0.297; p = 0.283); this phenomenon was not noticed in case of the PIH group (r = 0.050; p = 0.785). The average values of the number of thrombocytes, evaluated for each analyzed group, did not show significant discrepancies (p = 0.584) (table 2). We have evaluated the sFlt-1 and PlGF markers as angiogenesis factors with an important role for preeclampsia diagnosis. We have noticed that sFlt-1 has varied from 1152 to 32708 pg/mL, registering a variation of over 92%; in case of the PE group, it has reached the highest average value (14365±6464 pg/mL), which is significantly higher compared to the other analyzed groups (p = 0.001). The PlGF average values in case of the PE group (119.30±56.63 pg/mL) were significantly lower.

Correlations of clinical and laboratory markers with the sFlt-1/PlGF ratio: the statistical analysis has emphasized significant variations (p = 0.001) of the sFlt-1/PlGF ratio, which, according to the investigated group, had the following values (table 3, fig. 1):

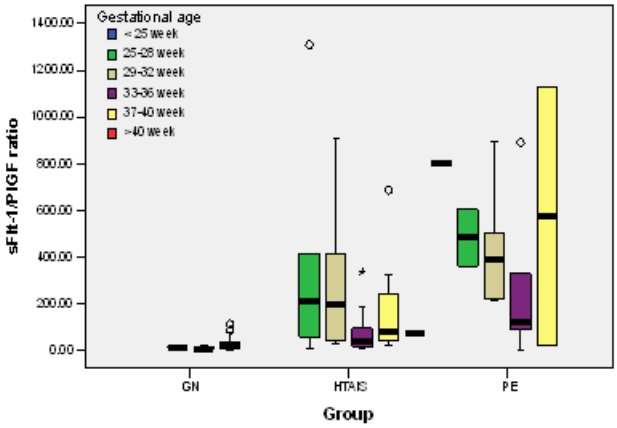

Fig. 1. Average sFLT-1/PlGF ratio in study groups between gestional ages on diagnosis

-In case of the PE group, the series of values varied between 1.92 and 1124.56 and registered the highest average value (417.62±350.73 pg/mL), in particular at a gestational age of 37-40 weeks (about 600±200);

-In case of the group of patients diagnosed with PIH, the ratio varied from 2.87 to 1309.18, with an average group value of 199.09±186.14;

-in case of the witness group, the sFLT-1/PlGF ratio varied from 0.88 to 110.64; the lowest average value (23.70±17.02) was registered.

In case of patients suffering from preeclampsia, we have noticed a direct and moderated correlation between the systolic arterial pressure (SBP) and the sFlt-1/PlGF ratio (r = 0.555; p = 0.026); nevertheless, the increased values corresponding to the diastolic arterial pressure (DBP) have been correlated to increased values of the sFlt-1/PlGF ratio only in case of 18.5% of patients (r = 0.185; p = 0.493) (fig.

Table 2

COMPARISON OF CLINICAL AND LABORATORY MARKERS BETWEEN STUDY GROUPS

Markers (mean values ± SD)	Study groups			p values
	PE (n = 50)	PIH (n = 50)	Control (n = 50)	
CRP, mg/L	12.00±4.58	6.72±1.99	-	0.037[b3)]
Hemoglobin, mg/dL	12.49±0.98	12.42±1.16	11.75±1.37	0.004[a)]
Hematocrit, %	37.24±2.57	37.00±3.21	35.18±5.02	0.013[a)]
Proteinuria, mg/dL	195.63±126.12	98.68±23.00	5.63±4.29	0.001[b1)] 0.001[b2)] 0.001[b3)]
Creatinine, mg/dL	0.85±0.20	0.92±0.59	0.73±0.13	0.166[a)]
Urea, mg/dL	31.67±12.00	31.46±20.62	18.09±4.42	0.001[a)]
Uric acid, mg/dL	6.04±1.35	6.02±2.01	3.89±1.19	0.001[a)]
ALT, UI/L	81.75±54.39	36.48±8.22	55.96±36.50	0.001[b1)] 0.056[b2)] 0.014[b3)]
AST, UI/L	76.50±40.29	35.88±33.32	49.46±27.25	0.107[b1)] 0.332[b2)] 0.457[b3)]
LDH, UI/L	479.41±130.90	398.71±146.92	353.44±161.68	0.005[a)]
sFlt-1(pg/mL)	14365±6464	9892±8443	3278±1444	0.001[b1)] 0.001[b2)] 0.011[b3)]
PlGF (pg/mL)	119.30±56.63	129.12±21.41	327.57±59.62	0.001[b1)] 0.001[b2)] 0.004[b3)]
sFlt-1/PlGF ratio	405.80±341.76	195.21±167.47	23.70±17.02	0.001[b1)] 0.001[b2)] 0.001[b3)]
Thrombocytes, $x10^3/mm^3$	216.50±64.32	206.72±79.66	222.39±58.79	0.584[a)]

[a)] p values for Test F (ANOVA)

[b1)] p values for Mann-Whitney U test – PE *vs* Control

[b2)] p values for Mann-Whitney U test – PIH *vs* Control

[b3)] p values for Mann-Whitney U test – PE*vs* PIH

Table 3
DESCRIPTIVE INDICATOR OF THE sFlt-1/PlGF RATIO

Study groups	N	Average	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Min	Max
					Lower Bound	Upper Bound		
PE	16	417.62	350.73	87.68	230.73	604.51	1.92	1124.56
PIH	34	199.09	186.14	49.07	99.25	298.93	2.87	1309.18
Control	35	23.70	17.02	4.57	14.41	32.98	0.83	110.64
Total	**85**	**168.01**	**174.52**	**29.78**	**108.79**	**227.22**	**0.83**	**1309.18**

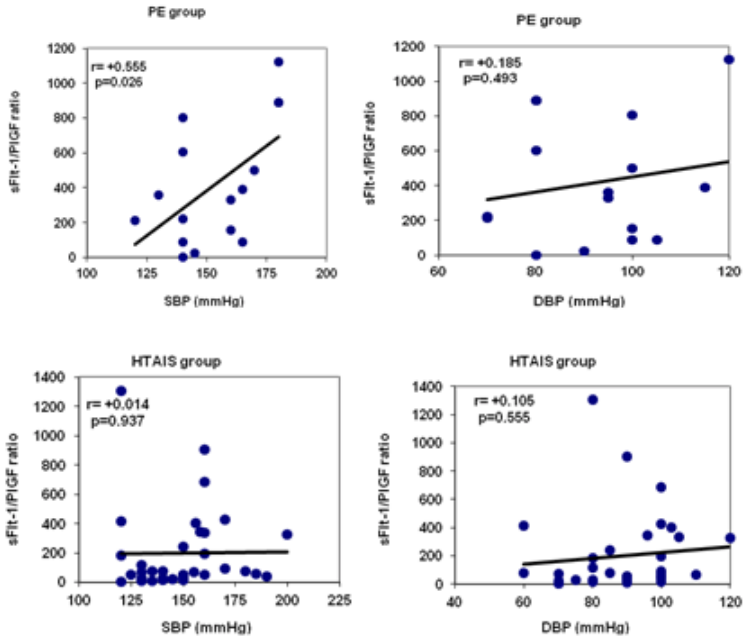

Fig. 2. sFlt-1/PlGF ratio in correlation with hypertensive disorders by PE and HTAIS groups

2). In case of patients suffering from PIH, the correlations between SBP (r = 0.014; p = 0.937) and DBP (r = 0.105; p = 0.555), on one hand, and the sFlt-1/PlGF ratio, on the other hand, were not significant from a statistical perspective (fig. 2).

The increased values of proteinuria were correlated to increased values of the sFlt-1/PlGF ratio in case of 44.8% of patients diagnosed with PE (r = 0.448; p = 0.049) and in case of 32.5% of patients diagnosed with PIH (r = 0.325; p = 0.060). In case of patients from the PE group, we have noticed a weak direct correlation between the creatinine and the sFlt-1/PlGF ratio (r = +0.279; p = 0.296), while in case of patients diagnosed with PIH, these parameters are independent from a statistical perspective (r = -0.058; p = 0.750). The statistic analysis of these data did not emphasize, in case of pregnant women diagnosed with preeclampsia, significant correlations between the values obtained for the hepatic function markers and the sFlt-1/PlGF ratio: AST (r = -0.031; p = 0.909), ALT (r = -0.026; p = 0.925); nevertheless, 35.3% of the pregnant women diagnosed with PIH have shown increased values of the sFlt-1/PlGF ratio, correlated to increased AST values (r = +0.353; p = 0.044), while 32% have shown increased ALT values (r = +0.320; p = 0.049). In case of patients suffering from preeclampsia (PE), we have noticed a weak direct correlation, which is insignificant, between the number of thrombocytes and the sFlt-1/PlGF ratio (r = 0.264; p = 0.324); in case of patients diagnosed with PIH, these parameters show an indirect correlation (r = -0.312; p = 0.072), which is also insignificant from a statistic perspective.

Within this research, the following parameters were evaluated as markers for preeclampsia diagnosis: the systolic arterial pressure/the diastolic arterial pressure (SBP/DBP), the proteinuria, the creatinine, the urea and the uric acid at the serum level, the number of thrombocytes, the AST, ALT, LDH enzyme markers, as well as the sFlt-1 and PlGF angiogenic proteins. The ROC curve has shown that proteinuria (AUC = 0.849), AST (AUC = 0.664), the increased SBP/DBP values (AUC = 0.683/0.631), the serum creatinine (AUC = 0.674) and the sFlt-1/PlGF ratio, at a cut off value = 200, are effective preeclampsia predictors (fig. 3).

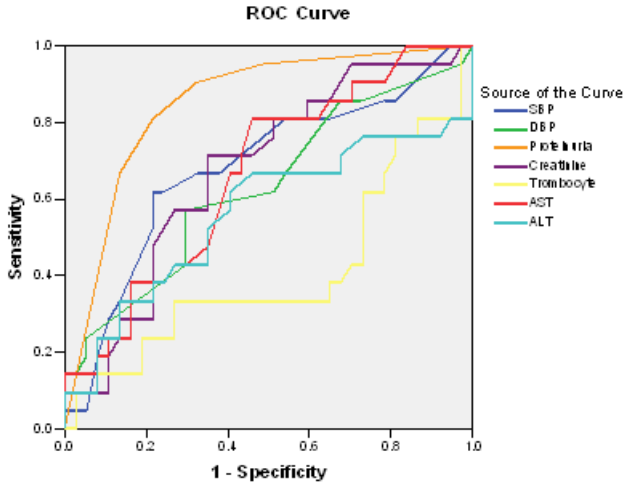

Fig. 3. The variation of markers such as: blood pressure (SBP/DBP), proteinuria, serum creatinine, number of thrombocytes, AST, ALT, as predictors of preeclampsia in case of pregnant women
Obs.: The test result variable(s): SBP, DBP, Proteinuria, Creatinine, Thrombocytes, AST, ALT has at least one link between the positive actual state group and the negative actual state group. Statistics may be biased. a Under the nonparametric assumption; b Null hypothesis: true area = 0.5

Proteinuria is evaluated at hospital admission; it refers to the excretion of whole proteins. The renal modifications that may be noticed in case of preeclampsia are generated by a glomerular particular lesion, characterized by the endothelial proliferation of capillary vessels. These lesions, associated to the decrease of the renal plasma flow (RPF), because of vasoconstriction, lead to the decrease of the glomerular filtration (GFR) by about 25% compared to normal pregnancy. Thus, in case of preeclampsia, the values corresponding to urea and creatinine can be approximately equal or slightly higher compared to the valued registered in normal pregnancy [1, 6]; nevertheless, the proteinuria degree largely varies, being situated between minimal values and nephritic range proteinuria values [18, 19]. Within this research, in order to analyze proteinuria and serum creatinine, we have resorted to tests whose sensitivity value (Se) is higher than the specificity value (Sp), in case of proteinuria values of 15.50mg/dL (Se = 0.875, Sp = 0.646) and of serum creatinine values of 0.77mg/dL (Se = 0.750, Sp = 0.521).

Rarely, preeclampsia may lead to acute renal lesions during pregnancy. After giving birth, the glomerular changes tend to reach relatively fast the normal level, once hypertension and proteinuria are stabilized [1, 6].The hepatic damage in case of preeclampsia depends on the disease severity; in general, the values corresponding to transaminases and to the lactate dehydrogenase are moderately increased, except for the outbreak of the HELLP syndrome, when their values are significantly higher [20, 21]. Indeed, the increased transaminases levels represent a severity clinical marker. Hepatic microscopic exam may reveal periportal hemorrhage, ischemic lesions and fibrin depositions [19]. Within this research, in order to analyze the AST level, we resorted to a test whose sensitivity value (Se) is higher than its specificity value (Sp), for AST values of 27.5 UI/L (Se = 0.816, Sp = 0.646).In what concerns the long-term systemic complications, about 20% of pregnant women diagnosed with preeclampsia develop, after 7 years, high blood pressure or microalbuminuria, compared to 2% of the healthy pregnant women. In case of pregnant women suffering from preeclampsia, the risk of death caused by cardiovascular factors is also high; in case of pregnant women who experience an early manifestation of the disease, the risk is extremely high [22, 23]. Preeclampsia and cardiovascular diseases have surely in common physiopathological mechanisms and risk factors, such as obesity or diabetes mellitus; they may lead to preeclampsia, as well as to cardiovascular diseases during life [19, 23-26]. Even if the acute manifestation of the disease is more dangerous for the mother, preeclampsia may also affect the fetus, leading to an increased risk of spontaneous preterm birth, fetal growth retardation, oligohydramnios, as well as to an increased risk of perinatal death. The use of ultrasonography helps to evaluate the fetus condition, in particular growth retardation, as well as the extent to which fetal circulation is affected [9]. Certain studies have demonstrated that, in case of children exposed to preeclampsia during pregnancy, high values of blood pressure were registered during childhood, as well as strokes during adulthood [19, 23]. Certain pregnant women are diagnosed with the so-called *atypical preeclampsia* (which does not involve hypertension or proteinuria) and their condition worsens unexpectedly [27]. The evaluation of the ratio of circulating angiogenic protein - sFlt-1/PlGF may contribute to differentiate preeclampsia manifested by hypertension or proteinuria from other conditions (systemic lupus erythematosus) [19, 28, 29]. The results obtained within this study have indicated a significant increase of the serum concentration corresponding to the sFLT-1 anti-angiogenic factor of more than 4 times for the PE group and of more than three times for the HTN group, compared to the control group. The average values obtained for the PlGF parameter have shown a decrease of more than 2.5 times in case of the PE group, as well as in case of the HTN group, compared to the control group. On the other hand, the results obtained for the analyzed groups have shown that the sFlt-1/PlGF ratio represents an effective preeclampsia predictor, characterized by a high specificity level.

Conclusions

Preeclampsia is a serious multisystemic syndrome, which represents one of the major causes of maternal, fetal and neonatal mortality and morbidity. Angiogenic factors contribute to preeclampsia molecular mechanisms, leading to hypertension and proteinuria. According to the specialized literature, molecular markers, such as the soluble fms-like tyrosine kinase-1 (sFlt-1) and the pro-angiogenic placental growth protein (PlGF), have significantly modified values, preceding by several weeks the emergence of preeclampsia signs and symptoms. In this respect, these markers can be successfully used in order to identify patients presenting a high risk of early preeclampsia manifestations (< 34 weeks). The results of our study confirm the importance of the analysis of these markers for the diagnosis and monitoring of hypertensive pregnant women; at the same time, they emphasize the fact that the sFlt-1/PlGF ratio represents an effective predictor of preeclampsia and of its severity. Thus, this angiogenic protein ratio may contribute, together with the well-known clinical and biological factors, to the stratification of the risk presented by hypertensive pregnant women; also, it could play an important role in what concerns the decision taken by the obstetrician related to the management of these pregnant women. Therefore, the obstetrician could have the possibility to promptly direct pregnant women from the increased risk group to the competent specialized health care facilities, to allot to this pregnant women group the appropriate medical resources and to rapidly take the necessary measures for the ultimate treatment- termination of pregnancy. Taking all these steps, the obstetrician will be more effective in what concerns preeclampsia treatment. Decisions based on data supported by evidence will contribute to reduce the risk for the mother, as well as for the newborn baby.

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