THE ASSESSMENT OF BIOLOGICAL MARKERS IN PATIENTS WITH PREECLAMPSIA WHEN AN INFLAMMATORY PROCESS APPEARS

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Abstract. Preeclampsia represents a pathological state that is specific to pregnancy, is characterized by high blood pressure *de novo* and significant proteinuria and appears after 20 weeks of pregnancy. The continuously increasing mortality caused by preeclampsia in our country totally justifies the fact that all efforts are directed towards primary and secondary prevention of the disease and underlines the necessity of urgent intervention at population level, together with the implementation of a screening programme that is able to reduce the impact of this condition on the mother and the baby. The cases were gathered between 2003 and 2014. The patients were selected by studying the observation charts of the pregnant women hospitalized in ”Cuza Vodă” Clinical Hospital of Obstetrics and Gynecology Iaşi, having a pregnancy over 20 weeks, who came for a specialized consult and who were harvested CRP, without an infectious context or prematurely and spontaneously ruptured membranes. The comparison of the lab markers for the pregnant women with severe preeclampsia, depending on the plasmatic level of CRP over 12 mg/l, showed significantly higher values of fibrinogen, LDH, GOT, GPT, serum blood urea nitrogen, creatinine and urine proteins, while the mean number of white cells was significantly reduced ($p<0,05$). The study confirms the change in the inflammatory process markers, the hepatic and kidney function, associated with a high plasmatic level of CRP for pregnant women with severe preeclampsia.

INTRODUCTION

Preeclampsia is characterized by generalized vascular endothelial dysfunction, which appears long before the first clinical signs. Pathophysiological changes in preeclampsia are the result of pathological changes of placenta and induce a generalized alteration of the endothelium, which results in vasoconstriction, hypovolemia and thrombus formation. But systemic endothelial damage manifests itself differently in different organs and tissues: foetus-placenta, brain, liver, kidney or haematological. Endothelial dysfunction in preeclampsia is also associated with an exaggerated systemic inflammatory response from the mother and this is why these phenomena are considered to have a crucial role in the physio-pathological mechanism of preeclampsia (Roberts, 2005).

The inflammatory maternal response in preeclampsia and especially in severe preeclampsia is an exaggerated systemic inflammatory response. There must be noted that some cytokines increase in preeclampsia like: IL 6, TNF alpha, IL 1ß, IL 8 just like in SIRS (Systemic Inflammatory Response Syndrome), but they are differentiated by NO which, unlike SIRS, has low values in preeclampsia. So preeclampsia, at a certain moment in its evolution, borrows a link from the systemic inflammatory response, which gets intricate with the endothelial dysfunction. The following fact has to be remarked: IL 6 and TNF alfa significantly increase in preeclampsia in comparison with normal pregnant women; IL 6 and IL 1ß significantly increase in severe preeclampsia in comparison with the normal pregnant women, but for IL 6, IL 8, IL 1ß, TNF alfa there are no significant differences between mild and severe preeclampsia. The conclusion of these studies is that the increase in the value of IL 6 and TNF alfa can play the role of trigger from mild to severe preeclampsia, but further studies need to be made in order to use these markers in clinical practice (Merih, 2012).

CRP marker is closer to our practice and routinely used and is also a marker belonging to the group of acute phase proteins. It is synthesized by the liver and RHS (reticulo-histiocytic system) and does not cross the placenta. CRP increased levels usually reflect the existence of an inflammatory process, which can be destructive, infectious or non-infectious, but unspecific. The normal plasmatic concentration (<6 mg/l) increases slightly with age and gets to a level that increases progressively from pregnant women, to mild inflammations, viral infections, bacterial infections and severe sepsis.

Thus, the study of different biochemical potential markers for prediction in the first and second trimester of pregnancy and of the detection markers in case of manifested preeclampsia, and also their association with ultrasound exploration, shows that although there are different potential markers for preeclampsia, their validity as predictors appears differently and uncertain in different stages of pregnancy. In the end the conclusion is that preeclampsia, which is a multifaceted

disorder, is not actually a disease, but an association of 'different diseases' and, in order to propose these markers for the routine medical practice, further studies are necessary (Can, 2011; Tjoa et al, 2004).
In Romania, the annual incidence of reported preeclampsia cases varies between 6 and 14%. An early detection of preeclampsia, not only based on the inventory of risk factors, but also with the help of some markers, could indicate more correctly the moment when treatment should start, be in progress or the birth moment as the only effective treatment. Motivated by the fact that these changes appear long before the first clinical signs of the disease, the research in this field has intensified and the recent studies focus on the endothelial dysfunction as a physio-pathological mechanism of preeclampsia.

MATERIAL AND METHODS

The retrospective case-control study focused on studying the clinical-progressive aspects of preeclampsia, by checking the correlation between the inflammatory parameters and arterial blood pressure, and also the relation between the plasmatic level of C reactive protein and other biological markers, on a group of 54 pregnant women with preeclampsia and a pregnancy over 20 weeks, hospitalized in 'Cuza Vodă' Clinical Hospital of Obstetrics and Gynaecology Iași, in the period of time between 2003 and 2014. The data was systematized and centralized in a SPSS 18.0 data base and it was processed with the appropriate statistical functions, with a significance threshold of 95%.

RESULTS AND DISCUSSION

The age over 30 represented a relative risk 2.5 higher of developing a severe form of preeclampsia, as 85,7% of the pregnant women with severe preeclampsia were over 30 years old.
The profile of the pregnant woman with preeclampsia is characterized by values of arterial blood pressure over 160/100 mmHg. These values induce a relative risk about 1,4-1,8 higher towards a severe evolution. The mean arterial blood pressure over 120 mmHg showed, in the present study, a relative risk of severe that is 2,2 higher and this aspect does not have correspondence in other studies.
The cases we studied showed a significant increase of fibrinogen, LDH, GOT, GPT, blood urea nitrogen, urine proteins, but a significantly reduced level of thrombocytes ($p<0,05$) for the patients with preeclampsia.

Table I. Predictive markers of severe preeclampsia

Parameter	Preeclampsia				Statistical significance		RR	IC95%
	severe (n=7)		mild (n=47)					
	N	%	N	%	χ^2	P		
Age ≥ 30 years old	6	85.7	16	34.0	4.74	**0.029**	2.52	1.53÷4.15
Body mass index (kg/m^2)	4	57.1	1	2.1	15.89	**0.001**	6.71	4.47÷9.58
Systolic blood pressure ≥ 160 mmHg	7	100.0	33	70.2	1.48	0.224	1.42	1.18÷1.72
Diastolic blood pressure ≥ 100 mmHg	7	100.0	26	55.3	3.41	**0.024**	1.81	1.40÷2.34
Mean arterial pressure >100 mmHg	7	100.0	21	44.7	5.42	**0.019**	2.24	1.63÷3.08
CRP ↑	7	100.0	45	95.7	0.27	0.605	1.04	0.98÷1.11
Haemoglobin ↓	5	71.4	30	63.8	0.15	0.975	1.12	0.67÷1.87
Haematocrit ↓	7	100.0	42	89.4	0.82	0.836	1.12	1.01÷1.24

Parameter	Preeclampsia				Statistical significance		RR	IC95%
	severe (n=7)		mild (n=47)					
	N	%	N	%	χ^2	P		
Thrombocytes ↓	4	57.1	26	55.3	0.10	0.751	1.03	0.52÷2.06
Fibrinogen ↑	6	85.7	38	80.9	0.05	0.831	1.06	0.76÷1.48
LDH ↑	6	85.7	39	83.0	0.13	0.717	1.03	0.74÷1.44
GOT ↑	6	85.7	20	42.6	4.55	**0.033**	2.01	1.29÷3.16
GPT ↑	6	85.7	19	40.4	5.03	**0.025**	2.12	1.34÷3.36
Uric acid ↑	5	71.4	40	85.1	0.13	0.717	0.89	0.52÷1.36
Serum blood urea nitrogen ↑	5	71.4	35	74.5	0.08	0.771	0.96	0.58÷1.58
Creatinine	5	71.4	34	72.3	0.16	0.688	0.99	0.60÷1.63
Proteinuria	4	57.1	21	44.7	0.04	0.833	1.28	0.62÷2.62
Edema	0	-	6	12.8	0.13	0.720	-	-

In the present study we demonstrated that the plasmatic level of C reactive protein is significantly correlated with systolic, diastolic and mean arterial pressure, and this aspect is in agreement with many studies (Pricop et al, 2001; Carcia, 2007; Eiland et al, 2012).

In his study reported in 2011, Can Murat uses mean arterial pressure as indicator of severity in preeclampsia and proves the direct association with the inflammatory reaction (Can, 2011). This result follows the same trend as the studies that claim that C reactive protein is an efficient marker of preeclampsia and is significantly correlated with the severity of the disease.

Carl A. and collaborators prove in a recent study the fact that a value over 3 mg/l is a good predictor of cardiovascular and inflammatory risk for women with a history of preeclampsia/eclampsia (Carl et al, 2008).

Also, Mihu D. and collaborators, published a work in 2008, where they establish that CRP is a marker for the severity of preeclampsia and low weight of the new-born at birth (Mihu et al, 2008).

A prospective study, initiated by Behboudi G. and collaborators (2012) on a group of 778 pregnant women, establishes a benchmark of 4,5 mg/dl for the C reactive protein in the first trimester of pregnancy as a predictive factor for preeclampsia (Behboudi et al, 2012), while Bita M. (2010), studies a group of 400 pregnant women and establishes the threshold for predicting preeclampsia in the first trimester of pregnancy at over 5 mg/l (Bita, 2010).

With the purpose of establishing CRP benchmarks for the normal pregnant women and also for the ones with preeclampsia, Hwang HS and collab. also prove the possibility of using CRP as a marker of severity in preeclampsia (Hwang, 2007).

Kumru S. highlights the positive correlation between CRP, mean arterial blood pressure and proteinuria. This study also highlights the relations between C reactive protein and the clinical and biochemical parameters in preeclampsia; the increased values of haemoglobin, creatinine, GOT, GPT, LDH, blood urea and proteinuria were associated with increased values of C reactive protein (Kumru, 2006).

C reactive protein is used by Azizia MM and collab. to monitor chorio-amniotitis in the ruptured membranes. Also, preeclampsia and gestational diabetes were related to inflammation (Azizia, 2006).
In the recent research, Stefanovic M. has focused on endothelial dysfunction as anomaly in preeclampsia and has concluded that there is also an increased resistance to insulin in preeclampsia, but regarding CRP as an inflammation marker he concludes that its level is not increased and cannot be associated with the severity of preeclampsia (Stefanovic, 2009).
The close relationship between adiposity and CRP can be a possible explanation for CRP's lack of predictability in the studies that do not consider this variable. An increased CRP is a useful parameter in assessing the severity risk of preeclampsia in pregnant women with an increased body mass index in the third trimester of pregnancy (Ertas, 2010). According to the cases we studied, we noticed a risk 6, 71 times higher of severe preeclampsia in obese patients.
Our study showed that the plasmatic level of C reactive protein is directly correlated with the individual values of haemoglobin and haematocrit and this aspect is also confirmed in Kumru S.'s study (2006), but our result is not significant statistically speaking ($p>0,05$).
According to the cases we studied, we noticed a low level of thrombocytes (55-57%) and an increased level of fibrinogen (81-86%) for the pregnant women with preeclampsia, without significant percentage differences depending on severity ($p>0.05$). This aspect is also underlined by other authors (Kupferminc, 2003; Lin, 2005).
The changing of the hepatic enzymes, especially GOT and GPT, induces a relative risk of severe preeclampsia twice higher ($p<0.05$).
The pathological urinalysis appeared in 57.1% of the pregnant women with severe preeclampsia and in 44.7% of the pregnant women with less severe forms of preeclampsia and also insignificant distributions of frequency from the statistic point of view ($p=0.833$). The parameters of the renal function showed increased levels in over 70% of the pregnant women with preeclampsia, without significant percentage differences depending on severity ($p>0.05$), which aspect was also showed by Gabble SG et al, in Obstetrics, 5th Ed, 2007.
The cases studied did not show oedemas for the patients with severe preeclampsia, but they appeared in 6 patients (12.8%) with mild preeclampsia, without significantly associating the presence of the oedema with the severity of preeclampsia.

CONCLUSIONS

The cases studied showed the association of preeclampsia with a high value of haematocrit, with low thrombocytes and fibrinogen, increased uric acid (an important element in the assessment of renal damage in preeclampsia, the high levels being correlated with the severity of the disease and the foetal prognostic), increased transaminases, low proteinemia, increased creatinine.
In preeclampsia, CRP is correlated with systolic blood pressure, diastolic blood pressure and average blood pressure. The increase in CRP in severe preeclampsia can be attributed to other complications of the disease, too, not only to preeclampsia alone.

CRP is an inflammation marker, but in preeclampsia there is no response of acute phase that can be detected only by CRP that can be used in clinical practice as a singular element.

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