The Role of C-reactive Protein and Interleukin 6 in the Cases of Preeclampsia Associated with Obesity

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In the management of preeclampsia/eclampsia, it would be useful at least at European level, to have clear protocols for early detection and approach of cases with hypertension, as well as to create an algorithm to identify the predisposition to hypertensive pregnancy pathology. The aim has been to identify the favorable factors and the evolution of the pregnancy in the 100 patients admitted to the obstetrics clinic between January 2014 and December 2018, aged between 15-44 years, who have been diagnosed with preeclampsia. In recent years, the management of pregnant women with preeclampsia has improved a lot due to a better understanding of the pathogenesis and a refinement of adequate pregnancy monitoring. Obesity has been shown to be a risk factor in preeclampsia. Several studies have identified preeclampsia as an inflammatory condition. A large number of inflammatory markers, such as C-reactive protein (PCR) and Interleukin 6 (IL-6), have been shown to be elevated in pregnant women with preeclampsia.

Keywords: Preeclampsia, Interleukin 6 (IL-6), body mass index (BMI), C-reactive protein (PCR)

Preeclampsia is a pregnancy-specific syndrome that occurs during the second trimester of gestation and is defined by the occurrence of hypertension (systolic blood pressure> 140 mmHg and diastolic blood pressure> 90 mmHg) in a previously normotensive patient, accompanied by proteinuria (> 0.3g / 24h). Its etiology is unknown, and there are numerous studies, some of them contradictory, regarding the occurrence and risk factors of preeclampsia. Some studies indicate that placenta plays a key role in preeclampsia. The global preeclampsia prevalence is between 2-8%.[1-6].

There are a number of risk factors that predispose to the occurrence of preeclampsia.

Obesity increases the overall risk of preeclampsia by approximately 2- to 3-fold. The risk of preeclampsia increases progressively with increasing BMI (body mass index), even in the normal range. It is important to know that both mild preeclampsia with elevated blood pressure and severe preeclampsia are associated with higher perinatal morbidity and mortality. Given the global obesity epidemic, the obesity is one of the most important risk factors for preeclampsia [7-8].

Some studies suggest that excessive increase maternal body weight is associated with risk of preeclampsia, although they may be confused with increasing fluid retention that contribute to weight gain, especially if there is another pathology (kidney disease, diabetes, hypertension preexisting pregnancy)[9-12].

Inflammation is a common feature of obesity, cardiovascular disease and preeclampsia.

Interleukin 6(IL-6) is a potent pre-inflammatory cytokine being involved in vascular inflammation and leakage, and is associated with obesity, insulin resistance, and subsequent cardiovascular disease.

IL-6 is secreted from adipose tissue into the circulation, and its expression is positively correlated with BMI and total fat tissue mass. Interleukin-6-deficient might develop mature-onset obesity

Adipose tissue generates several inflammatory mediators that can alter endothelial barrier function and are more active in obese people. C-reactive protein (CRP) is an acute inflammatory protein, manufactured by the liver and adipocytes is higher in obese individuals and is associated with cardiovascular morbidity. Circulating CRP is elevated early in pregnancy prior to the development of preeclampsia and appears to have a stronger association with pre-eclampsia in obese women.

Experimental part
Material and method

In this case control study we analyzed 200 patients having the age between 15 years and 44 years. We split the database in two homogeneous groups. The first group contains patients who developed preeclampsia during pregnancy (study group, N1=100 patients) and in the second group we have heathy patients who had a normal development during pregnancy (control group, N2=100 patients). For the statistical analysis we used a Mann – Whitney test, a χ^2 test for proportions, a risk analysis and a

correlation and regression analysis using the SPSS, Microsoft Excel and Epi Info programs.

Results and discussions

The association between the risk of preeclampsia and obesity has also been demonstrated in different populations worldwide [13-15].

IL-6 is a potent pre-inflammatory cytokine being involved in vascular inflammation and leakage, and is associated with obesity, insulin resistance, and subsequent cardiovascular disease. Circulating concentrations are also higher with obesity and with preeclampsia, indicating a potential link [16-22].

In order to prove the main ideas that characterize our study we run a statistical analysis upon our database. For this we took under consideration two equal samples. 100 patients who develop preeclampsia during pregnancy (the study group) and 100 patients who had a normal development during pregnancy (the control group). The two groups have the same main characteristics: age, parity and gestational period, but we registered differences regarding their BMI and the CRP and IL6 values. So, further on we will analyze the database to see if this observed differences can be considered statistical significant.

First of all we run a distribution analysis, we applied a Kolmogorov - Smirnov test and we obtained that for all our variables we don't have a normal distribution. So, based on this result we will use for our analysis only non - parametric tests.

As well we present a descriptive analysis for our data using the central tendency and dispersion indicators. From this tables we seen that beside the age and height variable the other variables register quit major differences (table 1).

After observing the results from the descriptive analysis we tested to see if this differences are statistically significant. For this we applied a Mann - Whitney test for the two studied groups upon all the numerical variables from our study. As we expected, beside the age and the height, where we don't have significant differences, all the other variables register extremely significant differences within the groups (p<0.001) (table 2).The dynamics of the numerical data is plotted as well in figure 1.

After seeing that there are major differences between the two groups we tested to see if a BMI higher than 30 can be considered a risk factor for developing preeclampsia. In our case we have a case control study, so we will calculate the odd ratio value and for the statistical significance we will apply a χ^2 test for proportions and we will compute the 95% confidence interval for the odd ratio values. So based on this criteria we split our data base in four different subgroups: patients with or without preeclampsia and patients who have the BMI higher or less than 30. After running the risk analysis we obtained an extremely significant risk factor in developing preeclampsia if the BMI is higher than 30 (OR > 1, p < 0.001). All the data is presented in table 3 and plotted in figure 2.

In the end of our analysis we run a regression analysis in order to see if there is an association between the BMI and the CRP and IL6. We obtained a positive extremely significant association between the BMI and the CRP values (r=0.676; R^2=0.458; p < 0.001). In the case of BMI and IL6 as well, we obtained a positive extremely significant association (r=0.631; R^2=0.398; p < 0.001).

Table 1

WE CALCULATED THE CENTRAL TENDENCY AND DISPERSION INDICATORS FOR BOTH GROUPS. THE STUDY GROUP IS HIGHLIGHTED WITH GREEN AND THE CONTROL GROUP WITH YELLOW

Statistics	Age	Age	Height [cm]	Height [cm]	Weight [kg]	Weight [kg]	BMI (Kg/m2)	BMI (Kg/m2)	PRC	PRC	IL6	IL6
Mean	27.05	26.48	165.07	162.56	79.46	59.68	29.25	22.66	17.59	5.71	64.82	14.95
Standard Error	0.70	0.58	0.63	0.65	1.21	0.86	0.47	0.35	0.36	0.13	3.74	2.89
Median	24	26	167	163	78.5	58	30.70	22.27	17.24	5.27	81.3	2.9
Mode	24	19	167	160	70	54	30.84	19.53	22.48	5.27	87.4	2.9
Standard Deviation	7.04	5.79	6.33	6.49	12.06	8.63	4.68	3.54	3.57	1.33	37.38	28.87
Sample Variance	49.54	33.50	40.13	42.11	145.34	74.52	21.86	12.50	12.73	1.76	1397.07	833.38
Kurtosis	-0.95	0.25	4.68	0.32	-0.17	3.05	-0.40	1.95	-1.17	1.04	-1.35	6.88
Skewness	0.58	0.75	1.06	-0.40	0.14	1.52	-0.05	1.33	-0.04	1.27	-0.43	2.69
Range	26	29	43	28	67	40	24.54	16.40	13.79	5.69	112.01	144.7
Minimum	15	15	153	147	49	50	18.59	18.37	9.79	3.93	1.99	0.7
Maximum	41	44	196	175	116	90	43.13	34.77	23.58	9.62	114	145.4
Sum	2705	2648	16507	16256	7946	5968	2924.77	2265.65	1758.97	571.3	6482.43	1495.07
Count	100	100	100	100	100	100	100	100	100	100	100	100

Table 2

AFTER APPLYING THE MANN - WHITNEY TEST WE OBTAINED THAT THE WEIGHT, BMI, CRP AND IL6 ARE SIGNIFICANTLY HIGHER IN THE STUDY GROUP . THE SIGNIFICANT RESULTS ARE HIGHLIGHTED WITH GRAY

| Variables	Group	N (volume)	Mean Rank	Sum of Ranks	p - values
Age	study	100	100.38	10037.50	
	control	100	100.63	10062.50	$p = 0.976$
	Total	200			
Height [cm]	study	100	111.59	11158.50	
	control	100	89.42	8941.50	$p = 0.07$
	Total	200			
Weight [kg]	study	100	141.94	14193.50	
	control	100	59.07	5906.50	$p < 0.001$
	Total	200			
BMI (Kg/m2)	study	100	137.11	13710.50	
	control	100	63.90	6389.50	$p < 0.001$
	Total	200			
CRP	study	100	150.50	15050.00	
	control	100	50.50	5050.00	$p < 0.001$
	Total	200			
IL6	study	100	140.32	14032.00	
	control	100	60.68	6068.00	$p < 0.001$
	Total	200			
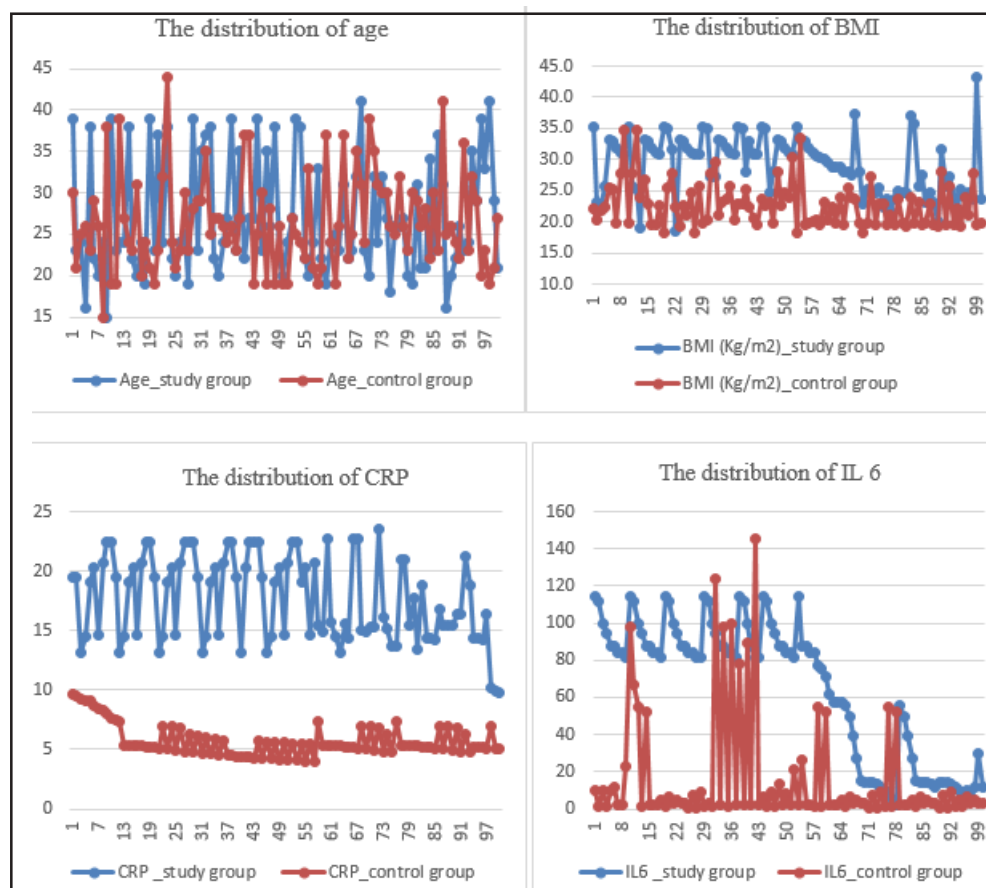
Fig. 1. We plotted the distribution of the most important variables from our study within the two groups

	Preeclampsia+	Preeclampsia-	Total	Statistics
BMI>30	53	4	57	p=0.001
BMI<=30	47	96	143	OR=2.82
Total	100	100	200	OR=(2.21;3.61)

Table 3

WE PRESENTED THE CONTINGENCY TABLE FOR OUR STUDY AND WE APPLIED A χ^2 TEST FOR PROPORTIONS AND WE CALCULATED THE ODD RATIO INDICATOR AND THE ODD RATIO 95% CONFIDENCE INTERVAL

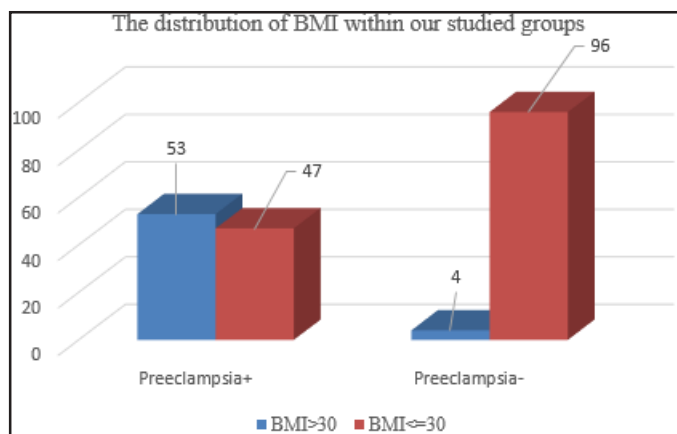The distribution of BMI within our studied groups

Fig. 2.The distribution of BMI in the studied group and in the control group. The threshold value for the BMI is the value of 30

Conclusions

Obesity has been shown to be a risk factor in preeclampsia. Several studies have identified preeclampsia as an inflammatory condition. A large number of inflammatory markers, such as PCR and IL-6, have been shown to be elevated in pregnant women with preeclampsia. More recent studies establish an association between obesity and elevated levels of inflammatory markers, suggesting that obesity is an inflammatory disease or predisposes to a pro-inflammatory state. Although weight loss is discouraged during pregnancy, obesity is a potentially modifiable risk factor for preeclampsia. Along with obesity, maternal plasma concentrations of IL-6 play a significant role in the pathogenesis of preeclampsia

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