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OXIDATIVE -ANTI-OXIDATIVE SYSTEM IN PERIPARTUM ACUTE RENAL FAILURE AND PREECLAMPSIA -ECLAMPSIA

PERİPORTUM AKUT BÖBREK YETMEZLİĞİ VE PREEKLAMPSİ—EKLAMPSİDE OKSİDATİF SİSTEM

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SUMMARY

*In this study we aimed to evaluate the oxidative -anti-oxidative systems in peripartum acute renal failure, preeclampsia -eclampsia. The study groups consisted of 17 patients with periparthum acute renal failure (8/17+HELLP Syndrome) (GI), 11 preeclamptic pregnant(GII), 11 pregnant (<30 weeks) (Gill) and 11 healthy women (GIV) with aged 18-38 years. Superoxide dismutase (SOD), glutathione peroxidase (GSHPx) in erythrocytes and plasma malondialdehide (MDA) levels were measured in all groups. SOD, GSHPx and MDA levels were also measured at the beginning (GIA), regression of renal dysfunction (GIB) and recovery of renal functions (GIC). MDA levels were 11.95 ±4.25, 9.22±3.62, 5.10 ±3.65, 3.40 ± 1.27, 4.91 ± 2.06, 4.24 ± 1.67 mmol/ml in GIA, GIB, GIC, Gil, GUI and GIV respectively. SOD activitiy in erythrocyte were 3269.23+1437.83, 2641.35 ± 1411.13, 2056.35±l 143.11, 924.±160.04, 1057.91 ±257.03, 861.63+243.28 Ug/Hb in GIA, GIB, GIC, **Gil,** Gill and GIV respectively. GSHPx activity in erythrocyte were 70.17 ± 23.52, 58.27+23.75, 45.44+17.60, 24.48 + 6.77, 26.28 + 7.27, 32.95 ± 8.24 Ug/Hb in GIA, GIB, GIC, Gil, GUI and GIV respectively. MDA levels and activities of SOD, GSHPx in erythrocytes on the begining, improvement and recovery of acute renal failure (GIA, GIB and GIC) were significantly different from each other and their values decreased while regaining of renal functions. Preeclampsia-eclampsia or normal pregnancy did not cause elevation of plasma MDA levels and GSHPx, SOD in erythrocyte. Although SOD and GSHPx in erythrocytes and plasma MDA level were found similar in healthy women, pregnant women and preeclamptic women. In patients with peripartum acute renal failure SOD, GSHPx and MDA increased at the begining and decreased during recovery of renal functions.*

Key Words: Glutathione peroxidase, Malondialdehide, Periphartum acute renal failure, Superoxide dismutase

ÖZET

Bu çalışmada, preeklampsi-eklampsi ve peripartum akut böbrek yetmezliğinde oxidatif sistemi değerlendirmeyi amaçladık.

Çalışma grubu 18-38 yaş grubundaki ,17 peripartum akut böbrek yetmezlikli (Gl), 11 preeklampsi-eklampsili (GII), 11 sağlıklı gebe (GUI) ve 11 sağlıklı kadın (G1V) dan oluşturuldu.Bütün gruplarda plasma malondialdehid(MDA) ve eritrositlerde glutatyon peroksidaz (GSHPx)- superoxid dismutaz(SOD) düzeylerine bakıldı.GI de MDA, GSHPx ve SOD düzeyleri başlangıç (GIA), toparlanma(GlB) ve düzelme (GIC) dönemlerinde olmak üzere üç kez bakıldı. MDA düzeyleri GIA, GIB, GIC, GII, GUI ve GIV de sırası ile 11.95+4.25, 9.22+3.62, 5.10+3.65, 3.40±1.27, 4.91+2.06, 4.24+1.67 olarak bulundu. Eritrosit SOD aktivitesi GIA, GIB, GIC, GII, GUI ve GIV de sırası ile 3269.23±1437.83, 2641.35±1411.13, 2056.35+1143.11, 924.00+160.04, 1057.91+257.03, 861.63+243.28 Ug/Hb olarak bulundu.Eritrosit GSHPx aktivitesi ise GIA, GIB, GIC.GII, GUI ve GIV de sırası ile 70.17±23.52, 58.27±23.75, 45.44±17.60, 24.48±6.77, 26.28+7.27, 32.95+S.24 Ug/Hb olarak bulundu. GI de başlangıç, toparlanma ve düzelme (GIA,G1B,G1C) dönemlerindeki MDA, SOD ve GSHPx değerleri birbirlerinden istatiksel olarak farklı idi ve böbrek fonksiyonlarının düzelmesine paralel olarak düşüş gösterdi. G II,III ve IV de MDA, SOD ve GSHPx düzeylerinde faklılık yoktu. Preeklampsi, sağlıklı gebe ve sağlıklı kadın gruplarında MDA, SOD ve GSHPx için farklılık olmamasına rağmen, peripartum akut böbrek yetmezliği olan grupta bu değerler yüksekti ve böbrek fonksiyonlanndaki düzelmeye paralel olarak azaldı.

Anahtar Kelimeler : Peripartum akut böbrek yetmezliği, Superoxid dismutaz, glutatyon peroksidaz, malondialdehid

INTRODUCTION

Pregnancy related some physyological changes such as systemic vasodilatation, high cardiac output and glomerular filtration rate and increased synthesis of nitric oxide, oxidative -anti-oxidative balance and ratio of prostoglandin I_2 to tromboxane A_2 reversed in preeclampsia and releated disorders. Increased free oxygen radicals secondary to ischemia and hypoxia can promote the occurence of peripartum acute renal failure. Free oxygen radicals combining with lipids, carbonhydrates and DNA, destroy their consruction. If this reaction can not be neutralized, a serial reactions which result cell lysis, are began (1). In this study we evaluated oxidative system in periparthum acute renal failure by measuring intracellular activities of superoxide dismutase (SOD), glutathione peroxidase (GSHPx) and plasma malondialdehide (MDA) levels and comparing that of pregnant with preeclampsia-eclampsia and healthy pregnant, and nonpregnant women.

SUBJECT AND METHODS

Seventeen patients with peripartum acute renal failure(ARF) [8/17 had also HELLP (haemolysis, elevated liver enzyme levels and low platelet) syndrome] [Group (G) I], 11 patients with preeclampsia without renal failure (blood pressure > 140/90 mmHg, proteinuria >300 mg/day, edema) (Gil), 11 healthy pregnant (>30 weeks), (GUI) and 11 healthy non pregnant women (GIV) enrolled into this study. All subjects were nonsmoker and nondiabetic In addition to history and physical examination we measured haemotocrit, white blood cell, thrombocyte, BUN, creatinine, uric acid, AST, ALT and daily proteinuria in all groups. The activities of SOD, GSHPx enzymes in erythrocyte and plasma MDA levels in plasma measured only one time in all subjects except GI. In GI SOD, GSHPx and MDA were measured 3 times on the begining (G IA,), improvement (G IB) and recovery (G 1C) of ARF. In Gil and GUI blood samples for SOD GSHPx and MDA were taken before delivery.

The blood samples were collected in to Ethylene diaminetetra-acetate (EDTA) tubes. After then blood centrifuged at 3000 x g for 10 min at 4°C to separete plasma and erythrocytes. The erythrocyte pellet was washed three times with cold isotonic saline. Antioxidant enzymes such as SOD and GSHPx were assayed according to the methods of McCord et al. and Beutler respectively (2, 3).

MDA levels in plasma was assessed by spectrophotometrical methods based on measuring the concentration of pink chromogen compound, which forms when MDA couples to thiobarbituric acid (4). The lipid peroxidation was expressed as nanomoles MDA formed per milliliter plasma.All chemicals were used in highest purity commercially.

The statisticaly analysis was performed by using Mann-Whitney-U

RESULTS

Mean ages and standart deviations were 27.35 ± 5.74 years, 27.54 ± 5.80 years, 25.09 ± 4.92 years and 24.54 ±2.29 years in GI, Gil, GUI, GIV respectively. In GI, there were patients with 9 preeclampsia, 5 eclampsia, 2 HELLP syndrome and 1 sepsis syndrome. Four patients had preeclampsia-HELLP syndrome and 2 had eclampsia-HELLP syndrome.The causes of ARF were ischemic acute tubular necrosis (14) and prerenal azotemia (3) Activities of SOD and GSHPx erythrocyte, MDA levels and some biochemical results of G I and Gil were shown on tables 1 and 2.

In G III and IV blood pressure, renal functions and biochemical tests were normal and the levels of SOD, GSHPX and MDA were shown on table 3.

The mean values and statistically differences of SOD, GSHPx and MDA in all groups were shown on table 4 and figure I,II,III.

In GI, SOD levels were significantly different from each other (SODGIA,GIB, GIC) and there were no differences between control groups. When compared SODGIA and SODGIB with Gil, III, IV significant differences were found. Also SODGIC was significantly different from SOD levels in Gil and GIV but the differences was not significant from GUI (Figure I).

GSHPx values were significantly different from each other in GI and there were no differences between Gil -GUI and GUI -GIV for GSPHx. But the differences between Gil and GIV for GSHPx was statistically significant. The comparision of GSHPxGIA and GSHPxGIB with control groups showed that significant differences. Also GSHPxGIC was significantly different from Gil and GUI for GSHPx but not different from GIV for GSHPx (figure II).

MDA levels of GIA, GIB and GIC was significantly different from each other. There were no differences at control groups for MDA. MDAGIA and MDAGIB were significantly different from control groups but MDAGIC was not different from control groups (figure III).

MDA levels were only statistically significant but not for activities of SOD, GSHPx when the patients with peripartum acute renal failure (GI) were divided as oliguric and nonoliguric ($P<0.05$) (figure IV).

The corelation of SODGIA and GSHPxGIA was shown on figure V.

Table I: Some biochemical, haematological parameters and the activities of SOD, GSHPx and level of MDA in Group I

		SOD ug/ Hb	GSH Px ug/Hb	MDA nmol/ml	BUN mg/dl	Creatinin mg/dl	PLT/mm³	AST U/L	ALT U/L
SÖ	A	4130	93	10	54	5.3	801.000	67	35
	B	3850	80	8.8	42	2.2	377.000	41	32
	C	3267	61	3.8	23	1.1	321.000	19	29
HA	A	3440	78	7.2	39	2.1	41.000	2778	804
	B	2620	62.4	4.8	75	7.3	105.000	356	178
	C	2150	52.8	2.9	21	1.7	333.000	41	33
FK	A	2426	32.7	14.7	73	3.8	42.000	1000	615
	B	1914	27	11	63	4.3	98.000	346	393
	C	1649	25.8	2.5	19	1.3	220.000	19	13
RD	A	2884	47	16	29	1.3	48.000	775	368
	B	2581	34	12	20	1.6	110.000	117	147
	C	1593	25.8	1.8	7	0.7	302.000	27	22
ZK	A	2985	47.96	16.3	70	5.8	137.000	286	139
	B	1530	38.6	11.7	40	3.6	256.000	167	124
	C	1380	28.65	3.4	22	1.2	309.000	40	38
OC	A	2116	50.8	10	35	3.2	94.000	400	265
	B	1700	45.6	5.1	44	4.1	114.000	122	98
	C	855	34	2.1	12	1	260.000	49	57
OP	A	4360	77	10.2	61	5.2	98.000	2180	1630
	B	4155	58.8	9	65	3.2	102.000	433	505
	C	3740	45	8.8	25	1.5	160.000	54	43
LT	A	5019	81	14.2	77	4.6	23.000	501	229
	B	4217	68	5.8	40	3.8	193.000	70	44
	C	3760	60	4	16	1.5	330.000	20	15
NŞ	A	5231	120.8	20	100	2.9	5.000	463	62
	B	4963	120	18	32	1.3	101.000	196	76
	C	3540	82.9	15	8	0.7	413.000	29	41
HÖ	A	4758	93	19.8	46	3.1	26.000	596	1211
	B	3965	87	15	26	2.3	135.000	109	118
	C	3227	63	10.3	18	1.3	324.000	40	37
ZC	A	1150	54	9.7	80	4.7	120.000	67	86
	B	950	47	8.1	57	3.1	165.000	58	77
	C	860	51	5.6	25	1.8	258.000	48	41
HS	A	1560	73	10	79	1.3	7.000	143	119
	B	1650	71	12	58	1.2	85.000	105	89
	C	1220	68	9.1	25	1	160.000	47	38
EY	A	2796	86	11.3	95	7.5	65.000	1360	769
	B	1260	55	7.8	67	4.8	112.000	358	277
	C	840	32	3.2	22	1.3	190.000	48	37
İD	A	950	45	7	91	10.6	201.000	81	20
	B	785	34.2	8	55	4.8	250.000	63	35
	C	752	22.0	3	24	1.3	258.000	38	25
LE	A	2116	45.6	10	86	7.8	158.000	89	65
	B	855	34	6.7	48	3.9	205.000	78	47
	C	760	28.7	2.1	18	1.2	250.000	48	34
GB	A	5336	90	7.2	78	5.6	128.000	116	75
	B	4390	73	6.2	47	3.4	110.000	76	57
	C	2500	45	3.1	24	0.9	157.000	38	27
EÖ	A	4320	78	9	65	4.8	78.000	258	356
	B	3220	55	6.7	48	3.1	109.000	117	178
	C	2865	47	6	17	0.9	222.000	44	37
Mean ±SD	A	3269.23± 1437.38	70.17± 23.52	11.95± 4.25	68.19± 21.32	4.68± 2.42	121.88± 183.67	656.47± 781.82	402.82± 462.46
	B	2641.35± 1411.13	58.27± 23.75	9.22± 3.62	48.64± 14.85	3.40± 1.50	154.40± 78.70	165.41± 126.04	313.82± 40.77
	C	2056.35± 1143.11	45.44± 17.60	5.10± 3.65	19.06± 5.62	1.20± 0.32	263.00± 72.77	37.76± 11.08	33.29± 10.81

BP: Blood pressure AST: Aspartat amino transferase ALT: Alanin amino transferase BUN: Blood urea nitrogen
SD:Standart deviation

Table II: In group II baseline blood pressure, some bichemical tests and the value of SOD, GSHPx and MDA

Patients	Years	SOD Ug/Hb	GSHPx Ug/Hb	MDA nmol/ml	BUN mg/dl	Cr mg/dl	AST U/L	ALT U/L	PLTx $100/mm^3$	BP mm/Hg
ME	22	1045	33.2	4	18	1.2	38	41	167	180/100
ES	26	985	25.8	3	9	0.9	25	18	164	160/100
FP	20	672	28.9	6	8	0.7	18	12	222	160/100
SK	28	754	36.1	2	9	0.7	30	11	198	150/100
AU	27	1100	23.1	2	15	0.8	28	15	203	200/100
KT	32	976	23.1	2	22	1.4	33	27	158	170/100
AG	24	856	18.8	4	25	1.3	24	10	225	160/100
LO	35	947	26.7	3	18	0.7	17	11	198	170/100
ZZ	23	871	22.1	4.5	12	0.8	28	13	186	150/100
HK	33	758	19.4	2.7	13	9.9	30	25	260	170/100
AP	33	1200	12.1	4.3	18	1.2	33	41	228	170/90
Mean±SD	27.54± 5.8	924.0± 160.04	24.48+ 6.77	3.40± 1.27	14.36± 5.76	0.96± 0.26	27.64± 6.34	20.36± 11.65	200.82± 31.38	167.27± 14.20/ 99.09± 3.015

Table III: The activities of SOD, GSHPx and MDA of subjects in groups **III** and IV

Patients	Gin			GIV		
	SOD Ug/Hb	GSHPx Ug/Hb	MDA nmol/ml	SOD UG/Hb	GSHPx Ug/Hb	MDA nmol/ml
1	1545	33.4	5.0	1009	35.4	5.0
2	1545	21.7	7.0	757	31.4	2.5
3	1220	19.0	8.1	757	31.4	4.8
4	110	20.7	2.0	560	46.7	7.0
5	877	19.1	7.0	650	26.8	7.0
6	920	25.8	7.0	740	17.8	4.0
7	640	40.1	3.0	1200	27.8	2.5
8	895	21.2	4.0	1100	49.4	3.0
9	1040	26.7	4.5	680	25.6	5.4
10	1085	25.0	3.4	570	34.1	2.8
11	905	36.4	3.0	1100	34.9	3.0
Mean	**1057.91+** 257.03	26.28 ± 7.27	4.91 ± 2.06	861.63 ± 243.28	32.95 ± 8.24	4.24 ± 1.67

Table IV: The mean values for MDA and activities of SOD, GSHPx in all groups

		GSHPx(U/g Hb)	MDA (nmol/ml)	
		a,c,d,e.f	a,c,d,e,f	a,c,d,e,f
	A	3269.23+1437.83	70.17 ±23.52	11.95+4.25
		b,g,h,i	b,g,h,i	b,g,h,i
GI	B	2641.35 ± 1411.13	58.27±23.75	9.22± 3.62
		cj,i	c,j,k	
	C	2056.35+1143.11	45.44+ 17.60	5.10 ±3.65
Gil		d,g,h,j	d,g	
		24.48 ± 6.77	3.40 ±1.27	
GUI		e,h,k	e,h	
		26.28 + 7.27	4.91+2.06	
GIV		n,f	f,i	
		32.95 ±8.24	4.24 ±1.67	

a= GIA GI_B d= GI_A Gil g=GI_B Gil j=GI_c Gil m=GII GUI
b= GI_B GI_C e= GI_A GIIIh=GI_B GUI k=GI_c GUI n= Gil GIV
c= GIA GI_C f= GI_A GIVi=GI_B GIV 1=GI_C GIV o= GUI GIV
*all letters show statistically significance ($p<0.005$)

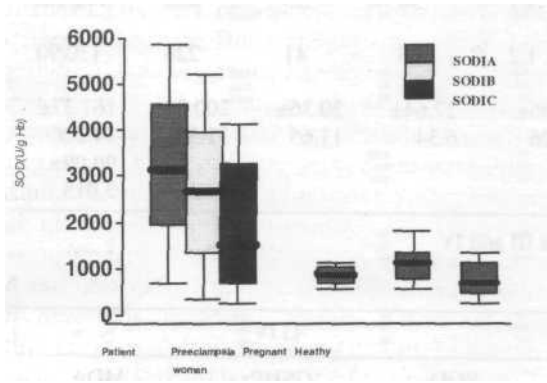

Figure I. The values of SOD in all groups

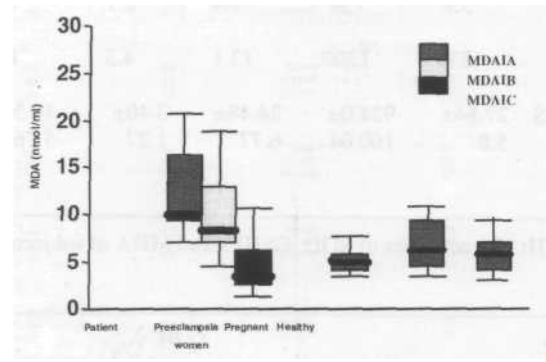

Figure III. The values of MDA in all groups

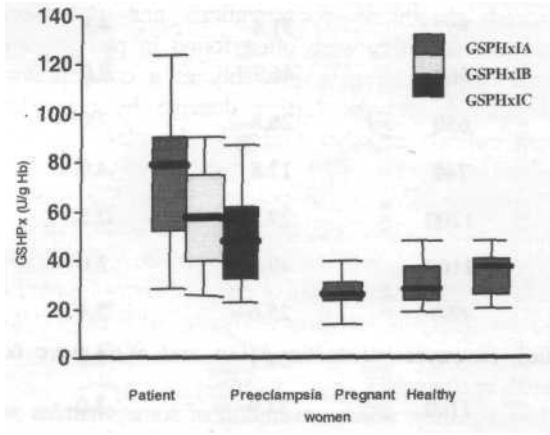

Figure II. The values of GSHPx in all groups

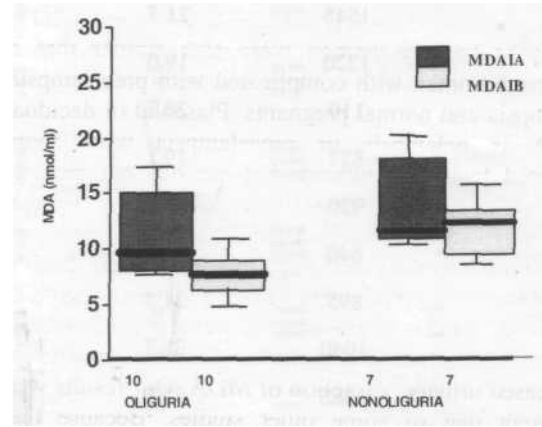

Figure IV. The mean values of MDAIA and MDAIB in GI when the patients divided as oliguria and non oliguria

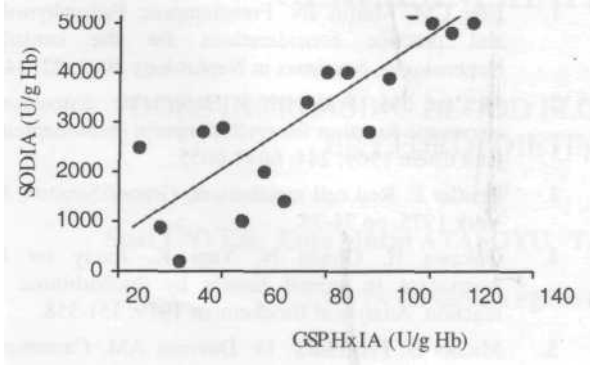

Figure V. The corelation of SODIA and GSHPxIA

DISCUSSION

Preeclampsia-eclampsia, pregnancy related disorders are major problems and can cause morbidity and mortality. In pregnancy, there are many causes and promoter factors for development of acute renal failure. The most common causes of ARF is acute tubular necrosis (5). In our study GI consisted of 14 patients with acute tubular necrosis and 3 patients with prerenal azotemia. MDA levels and activities of SOD, GSHPx in erythrocytes on the begining, improvement and recovery of acute renal failure (GIA, GIB and GIC) were significantly different from each other and their values decreased while regaining of renal functions.

MDA is the last product of lipid peroxidation of cell membrane during the increased oxidative stress condition (6). Because of higher levels of MDA in GI than that of G II, III, IV, we can say that there was activition of oxidative system in patients with peripartum ARF and/or decreased urinary excretion, and preeclampsia-eclampsia or normal pregnancy did not cause elevation of plasma MDA levels. MDA levels of healthy women were also similar that of pregnant women with complicated with preeclampsia-eclampsia and normal pregnants. Plasental or decidual. MDA in eclampsia or preeclampsia were found elevated by some authors, but we did not measure MDA of tissue. In patients with ARF on the recovery phases of renal function MDA values were not different from preeclamptic pregnants, healthy pregnants and nonpregnant healthy women. According to these results, regression of oxidative stress was correlated with recovery of renal functions and /or increased urinary excretion of MDA. Our results were different that of some other studies. Because they reported increased MDA, SOD and GSHPx of placental and decidual tissue ,in preeclampsia-eclampsia.These changes are associated with a reduction in the various placental antioxydants. But we did not measure the SOD, GSHPx and MDA of placental tissue. Lipid peroxidation is also increased in the peripheral blood, as IL-6, IL-8, and TNF alpha. Maternal cell protect themselves with both plasma and intracellular antioxydants(7).

SOD and GSHPx are an important intracellular anti-oxidative enzymes. In patients with peripartum ARF (GI), increased levels of MDA seems to be represent activated oxidative system and increased activities of SOD and GSHPx can be defense mechanism to oxidative stress. In patients with peripartum ARF (during the begining, improvement and recovery) GIA, GIB for SOD and GSHPx were significantly different from each other and control groups. There were no differences for SOD and GSHPx between women with eclamptic pregnants, healthy pregnants and healthy women. In contrast to our findings in another study there was a significant increase in superoxide generation and marked reduction in gluthatione content in preeclamptic women as compared to normotensive pregnant women (8). SODGIC was same with only that of healthy pregnant This may be releated to standart deviation. Because there was significant differences for GSHPx between healthy women and patients with ARF during the recovery period. In another study severe pre-eclampsia is characterised by decreased unstimulated neutrophil oxygen radical production. According to authors this may be the result of an exhausted cellular response due to stimulation by a factor present in the serum of these patients (9). We did not find enhanced free oxygen production in serum and anti-oxidatives in erythrocyte in pre-eclamptic patients and even in patients with HELLP syndrome. But in patients with ARF both plasma MDA and anti-oxidatives (SOD, GSHPx) in erthyrocytes were found increased.

Glutathione and glutathione related enzymes, as one of the major detoxificating and free-radical scavenging systems, may play a role in controlling the disease. Enhanced glutathione concentrations and glutathione peroxydase activities were often found in placenta and decidua in pre-eclampsia, probably as a compensatory mechanism to prevent further damage by peroxides, oxygen radicals or other toxins in the placenta or in fetoplacental interface (10). The higher levels of GSHPx in GI, may be secondary to oxydative stress like as SOD. The activities of GSHPx in eclamptic and healthy women were significantly different. This can be related with imbalance between oxidative-antioxidative system in preeclampsia. This result was similar with some other studies. However values for MDA and SOD were not different in controls.

In pregnancy, urinary excretion of some vitamins are increased so that requirement of these vitamins are higher. Preeclampsia is caused by nutritional, enviromental and genetic factors that lead to creation of an imbalance

between the free radicals nitric oxyde, superoxide and peroxynitrite in the vascular endothelium (11). Preeclampsia and releated disorders are seen especially in women with lower socioeconomic societies. Decreased levels of some vitamins due to increased urinary excretion and inadequate intake may cause defective anti-oxidant system.

The etiology of preeclampsia is still unkown. The 4 hypothesis currently accepted are the placental ischemia hypothesis, genetic hypothesis, the immune maladaption and hypothesis of the imbalance between free oxygen radicals and scavengers in favor of oxydants. At the present the theory of oxydative stres is most popular, that lead to incresased production of lipide peroxides, thromboxane A2 and decreased level of prostacyclin. Scavenging antioxidants have protective effect in this process (1,12).

At the begining and improvement of peripartum ARF, MDA levels were significantly higher in nonoliguric patients compare to oliguric patients but GSHPx and SOD were similar. We can not explain this finding. The higher levels of MDA in nonoliguric patients may be related with other pathologic conditions.

In patients with peripartum ARF and HELLP syndrome the levels of MDA, SOD and GSHPx activities were not different than that of patients without HELLP syndrome.

Increased oxidative stress is important component of pathogenesis of ARF. In patients with peripartum ARF we found that plasma MDA levels was increased and anti-oxidative system also activated as defensive mechanism.

As a result; in peripartum ARF oxidative and antioxidative system were found to be activated and/ or decreased excretion of products of activation of these systems. These activations of oxidative and anti-oxidative system can not be related with pregnancy or preeclampsia-eclampsia and regressed with improvement of ARF. But we did not evaluate oxidative- anti-oxidative activity in non-pregnant patients with ARF in this study. Although there are endothelial dysfunction in eclampsia and preeclampsia, increased products of oxidative -anti-oxidative stress were not found in serum and in erythrocyte in our study. It was suprised that pregnant, nonpregnant and eclamptic women had same values for plasma MDA and SOD and GSHPx in erthyrocyte. So that we can ask that antioxydative vitamins can be useful in eclampcia and related disorders? However we did not measure oxidative-antioxidative products of placental tissue. Increased activities of SOD and GSHPx and levels of MDA in patients with peripartum ARF may be related with ischemia and/or uremia but may not preeclampsia - eclampsia. Due to occurence of imbalance of oxidative-antioxidative activity we want to study that whether anti-oxidantives such as vitamin C, allopurinol for treatment of peripartum ARF can be useful.

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