

Role of malondialdehyde in the pathogenesis of preeclampsia

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Abstract

Background: The exact cause of preeclampsia is unclear but one of the hypotheses in this regard is that preeclampsia caused by vascular endothelial dysfunction due to increase in circulating free radicals such as lipid peroxides which are determined by malondialdehyde.

Objective: To evaluate the possible involvement of lipid peroxidation in form of malondialdehyde (MDA) in the pathogenesis of pre-eclampsia.

Methods: The present study conducted on a total of 100 Kurdish women in their 3rd trimester of pregnancy admitted to the Gynecologic and Obstetric hospital in Sulaymania city at period of February to June 2007. Maternal blood was collected for determination of basal and post delivery MDA levels of the studied preeclamptic patients and normotensive pregnant controls. In addition, cord blood was collected immediately after delivery from a 25 preeclamptic patients and a 25 normotensive pregnant women delivered by cesarean section.

Results: Statistical analysis reveals that there is significantly higher levels of MDA both in maternal and cord blood of preeclamptic patients compared to normotensive pregnant

control ($P < 0.0025$, $P < 0.015$) respectively. Furthermore, a significant positive correlation between maternal serum and cord blood MDA was found in preeclamptic pregnancies ($r = 0.59$, $P < 0.0005$). A significant increment of basal serum MDA level was demonstrated in normotensive pregnant women delivered by normal vaginal delivery (NVD) ($P < 0.018$). On the other hand, no statistical significant changes were observed in serum MDA level of normotensive women delivered by cesarean section ($P > 0.77$). Serum MDA in preeclamptic patients rose significantly above the preoperative value within one day postoperatively (1.48 ± 0.55 ; $P < 0.01$) then tend to fall significantly (0.9 ± 0.46 ; $P < 0.02$) toward the normal basal level (0.89 ± 0.6) after two days post operatively.

Conclusions: High levels of MDA in the serum of preeclamptic patients and their placenta may play a role in the pathogenesis of preeclampsia.

Key words: Lipid peroxide, Malondialdehyde, Preeclampsia

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Introduction

Pregnancy-induced hypertension (PIH) is a major pregnancy complication appears after 20 weeks of gestation, causing premature delivery, fetal growth retardation, abruptio placentae, and fetal death⁽¹⁾.

Various theories have been proposed to explain the pathophysiology of preeclampsia.

However, it has been proposed that an unknown factor excreted from the placenta play a central role; including placental debris, apoptotic fragments, lipid peroxidation products or other reactive oxygen species, all of which are able to induce maternal oxidative stress⁽²⁾.

Researchers hypothesized that, in women at risk of preeclampsia, the placenta produce an excess of reactive oxygen species (ROS)⁽³⁾. These species are also capable of abstracting hydrogen from adjacent fatty acid side chains and so propagating the chain reaction of lipid peroxidation⁽⁴⁾. Lipid peroxides are formed and bind to the lipoproteins and are then transported to distant sites in the body. This

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transportation causes dissemination of the lipid peroxides, thereby resulting in damage at distant sites⁽⁵⁾.

The role of oxidative stress-related molecules in preeclamptic pregnancies has been investigated^(6,7). Furthermore, it has been reported that the level of malondialdehyde (MDA), an indicator of lipid peroxides, is higher in the mitochondrial fraction of preeclamptic placental tissues than in those obtained from normal placentae⁽⁸⁾, and that vascular endothelial damage might be caused by free radical-mediated lipid peroxidation⁽⁹⁾. Therefore, the aim of the present study is to evaluate the possible involvement of lipid peroxidation in form of malondialdehyde (MDA) in the pathogenesis of pre-eclampsia.

Materials and methods

The present study included a total of 100 Kurdish women (50 pre-eclamptic women and 50 apparently healthy pregnant controls) in their 3rd trimester of pregnancy admitted to the Gynecologic and Obstetric hospital in Sulaimani city at period of February to June 2007. The study was approved by the Medical College Ethical Committee and the aim was explained to the patients who gave their informed consent.

Maternal blood samples collected before delivery (Basal level) and at 1st and 2nd days post delivery. In addition, cord blood was collected immediately after delivery. The level of serum malondialdehyde, as a parameter of lipid peroxidation, was determined by a modified procedure described by Guidet and Shah⁽¹⁰⁾.

Sample collection:

Samples of blood had been collected in plain tubes in the absence of any anticoagulants, and serum had been harvested by allowing the sample to clot within 30 minutes then centrifugation for 10 minutes at 5000 rpm, the sera were stored as aliquots at

-20 °C and assayed within one week, repeated thawing freezing was avoided.

Statistical analysis:

Significance for statistical differences was calculated using Mann-Whitney test and Wilcoxon signed rank. Pearson's test was used to assess the correlation coefficient among the studied parameters. P value less than 0.05 was regarded as significant.

Results

As shown in table 2, the statistical analysis reveals that there is significantly higher levels of MDA in both maternal and cord blood of preeclamptic patients compared to normotensive pregnant control ($P<0.0025$, $P<0.015$) respectively. A significant positive correlation between maternal serum and cord blood MDA was found in preeclamptic pregnancies ($r=0.59$, $P<0.0005$) (Figure 1).

Table 3 shows the serum MDA levels of normotensive pregnant women before and after delivery according to mode of delivery (the mode of delivery was not applied to preeclamptic patients as all were delivered by cesarean section). A significant increment of basal serum MDA level was demonstrated in women delivered by normal vaginal delivery (NVD) ($P<0.018$). On the other hand, no statistical significant difference was observed in serum MDA level of normotensive women delivered by cesarean section ($P>0.77$).

Table 4 represents the serum MDA levels in sera of preeclamptic patients before and at 1st and 2nd days postoperatively. Their serum MDA rose significantly above the preoperative value within one day postoperatively (1.48 ± 0.55 ; $P<0.01$) then tend to fall significantly (0.9 ± 0.46 ; $P<0.02$) toward the normal basal level (0.89 ± 0.6) after two days post operatively.

Table 1: Clinical characteristics of the study groups.

Variables	Normotensive control n= 50		Preeclamptic patients n= 50	
	Mean $\pm$ SD	Range	Mean $\pm$ SD	Range
Age (year)	26 $\pm$ 5.3	19-41	29.5 $\pm$ 4.3	21-38
DBP (mmHg)	75.4 $\pm$ 5.7	60-85	109.9 $\pm$ 9.5*	90-120
Weight (kg)	69 $\pm$ 2.8	55-91	78 $\pm$ 3*	62-101
GA (wks)	36.2 $\pm$ 4.2	35-41	37.5 $\pm$ 2.3	32-42

*refer to the significant difference from the control group ($P < 0.05$), n= sample size,

SD= standard deviation. DBP = Diastolic blood pressure. GA; Gestational age

Table 2: Serum malondialdehyde (MDA) level of normotensive pregnant women and preeclamptic patients before delivery (basal level).

Basal S.MDA (μ mole/L)	Normotensive control (N=50)	Preeclamptic patients (N=50)	P value
Venous blood Mean $\pm$ SD (95% CI)	0.89 $\pm$ 0.69 (0.7-1.09)	1.17 $\pm$ 0.49 (1.03-1.31)	$P < 0.0025$
Cord blood Mean $\pm$ SD (95% CI)	1.49 $\pm$ 0.79 (1.16 - 1.82)	2.09 $\pm$ 0.94 (1.71 - 2.48)	$P < 0.05$

S.MDA: serum malondialdehyde; CI: confidence interval; SD: standard deviation

Table 3: Serum malondialdehyde (MDA) levels of normotensive pregnant women by different modes of delivery.

Delivery mode	Serum MDA levels [μ mole/L]		P value
	Basal mean $\pm$ SD (Range)	Post delivery (Day 1) mean $\pm$ SD (Range)	
NVD n=25	0.86 $\pm$ 0.4 (0.21-1.72)	1.22 $\pm$ 0.48 (0.34-2.06)	P< 0.018
C.S n=25	0.92 $\pm$ 0.9 (0.08-3.87)	0.89 $\pm$ 0.53 (0.09-1.85)	P > 0.77

n: sample size, SD: standard deviation, C.S= cesarean section, NVD= normal vaginal delivery

Table 4: Malondialdehyde (MDA) level in the serum of preeclamptic patients before and after cesarean section “Day I and Day II”.

S.MDA preeclampsia	Pre delivery (n=25)	Post delivery	
		Day I (n=25)	Day II (n=10)
Mean (μ mole/L)	1.03 $\pm$ 0.52	1.48* $\pm$ 0.55	0.90* $\pm$ 0.46
(95% CI)	(0.82-1.25)	(1.25-1.71)	(0.57-1.23)

S.MDA: serum malondialdehyde, CI: confidence interval, SD: standard deviation, n: sample size *: refer to the significant difference from the predelivery level P < 0.05.

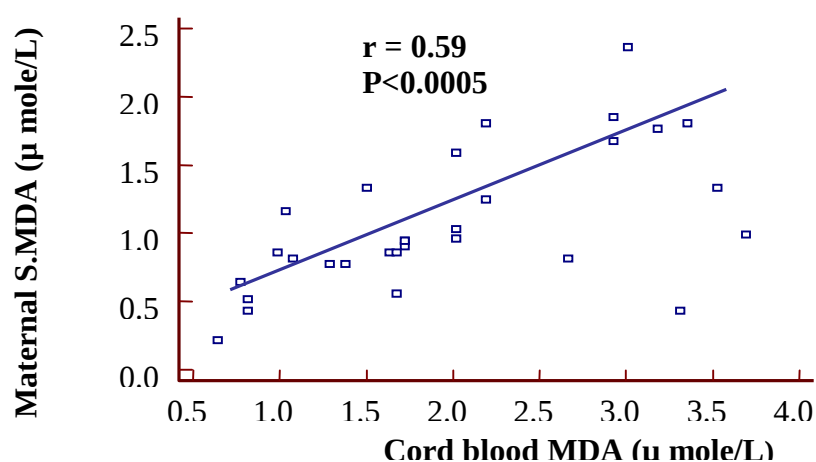


Figure 1: Correlation between serum and cord blood malondialdehyde (MDA) levels of preeclamptic patients.

Discussion

Serum MDA in preeclamptic patients

The results of current study reveal that there is significant higher levels of maternal and cord blood MDA in preeclamptic patients compared to normotensive pregnant control ($P<0.0025$; $P<0.015$). These results are in agreement with and extend the results of previous observations^(3, 7, 11, 12). In contrast, other studies reported no significant difference in MDA level between patients with pre-eclampsia and controls^(13, 14). This disagreement may be due to the lack of comparative methods used to measure the oxidative stress and lack of sensitivity and specificity of different oxidative stress biomarkers. In addition, ethnic factor reported to be associated with variation in lipid peroxidation products⁽¹⁵⁾. In the current study, only Kurdish women were included while Morris et al⁽¹³⁾ and Al-Shawi N⁽¹⁴⁾ perform their studies in different ethnic distribution. Moreover, the presence of major health problems, other than preeclampsia, or the occurrence of in vitro autooxidation, which known to be causative factors of lipid peroxidation⁽¹⁶⁾, have been excluded in the present study. Therefore, the presence of high MDA in sera of the current study patients most likely related to preeclampsia rather than other conditions.

The finding of high level of MDA in preeclamptic group can be explained by the fact that poorly perfused placental tissue may evoke the free radical process and the free radicals released from the poorly perfused fetoplacental unit initiate lipid peroxidation by attacking polyunsaturated fatty acids in cell membranes and converting them to lipid peroxides. This suggestion may be supported by other investigators, such as Hung et al whom showed that oxidative stress occurs when hypoxic

placental tissues are reoxygenated in vitro, which is consistent with an ischemia reperfusion insult⁽¹⁷⁾.

Moreover, in the present study, a significant positive correlation ($r=0.59$, $P>0.0005$) between maternal serum MDA and cord blood MDA was found in preeclamptic pregnancies, which further confirms the suggestion that the placenta may be the main source of the current patient's MDA, and lipid peroxidation products shifted from placenta to the maternal serum.

Follow up study

Normotensive pregnant control

The current study is also evaluating the effect of different modes of delivery on serum MDA levels in normotensive pregnant women.

A significant elevation ($P<0.018$) of basal serum MDA level was demonstrated in normotensive women delivered by NVD. This is in agreement with that of other investigators⁽¹⁸⁻²⁰⁾. On the other hand, the present study shows no statistical significant difference in serum MDA level of normotensive women delivered by cesarean section. To the best of our knowledge no study have been dealt with the level of MDA in normotensive pregnant delivered by cesarean section.

The finding of elevated post partum MDA in sera of NVD women, that is not observed in those delivered by cesarean section, makes it likely that uncontrolled lipid peroxidation caused by reactive oxygen species, which are produced in consequence of tissue reoxygenation, as during labor with NVD (in contrast to those delivered by cesarean section) oxygenation of both maternal and fetal tissue oscillates frequently. This may be due to 1st) periods of apnea and/or shallow respiration between contractions⁽²¹⁾, or 2nd) due to maternal response to pain

and stress, which are more severe in NVD women, in form of release of stress hormones such as epinephrine and nor epinephrine that are causing reduction in uterine blood flow and therefore trigger the production of more lipid peroxidation^(22, 23)

Preeclamptic patients

The time course required for serum MDA to return to base line is also evaluated in the present study. Serum MDA rose significantly ($P<0.01$) above the preoperative value within one day postoperatively then tend to fall significantly ($P<0.02$) toward the normal basal level after two days post operatively. This is in agreement with previous reports^(12, 20).

This increase in the level of MDA in preeclamptic patient may result from squeezing of already high MDA content of placenta due to its stimulation and manipulation, into maternal circulation which further support the suggestion that the placenta is a source of maternal lipid peroxides⁽²⁴⁻²⁷⁾. This idea can be applied to the results for other biochemical parameters such as AST and ALT in preeclamptic women after cesarean section⁽²⁸⁾. Tissue trauma of uterine smooth muscle due to cesarean section is assumed to cause the release of more ALT and AST from injured cells into circulation⁽²⁹⁾.

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