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THE ROLE OF OXIDATIVE STRESS MARKERS IN PREGNANCY INDUCED HYPERTENSION

ZNAČAJ MARKERA OKSIDATIVNOG STRESA KOD HIPERTENZIJE U TRUDNOĆI

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Summary

Introduction. This article investigated the role of oxidative stress in the etiology of pregnancy induced hypertension. The aim of this study was to determine the degree of oxidative stress, and the level of thiobarbituric acid reactive substance in the blood of pregnant women with and without pregnancy induced hypertension and to correlate these parameters with clinical parameters during pregnancy and delivery. **Material and Methods.** This prospective study was performed at the *University Clinical Centre of the Republic of Srpska*. It included 200 pregnant women - 100 with pregnancy induced hypertension, and 100 healthy normotensive pregnant women between 28 to 40 weeks of gestation. **Results.** Pregnant women with pregnancy induced hypertension had significantly higher median levels of oxidative stress marker: thiobarbituric acid reactive substance of 36.7 μmol compared to the control group of 13.2 μmol . Pregnant women with pregnancy induced hypertension presenting with complications had significantly higher thiobarbituric acid reactive substance mean levels of 41.6 μmol compared with pregnant women without complications. The highest thiobarbituric acid reactive substance level of 43.9 μmol was found in pregnant women with Hemolysis, Elevated, Liver Enzymes, Low Platelets syndrome. **Conclusion.** The study showed that thiobarbituric acid reactive substance, as an oxidative stress marker, may be used in clinical practice in the assessment of the severity of complications and as an indicator for timely delivery in women with pregnancy induced hypertension. Further studies and a larger study sample of pregnant women with severe hypertension are necessary to confirm this conclusion.

Key words: Oxidative Stress; Hypertension, Pregnancy-Induced; Biomarkers; Pregnancy Complications; Pregnancy Outcome; Thiobarbituric Acid Reactive Substances

Introduction

Pregnancy induced hypertension (PIH) is one of the most common and serious conditions in obstetrics. It puts in danger both the mother and the fetus [1–11]. Up to now, the etiology and pathogenesis of PIH are still unclear. Even today, the most significant

Sažetak

Uvod. Ispitivana je uloga oksidativnog stresa u etiologiji hipertenzije u trudnoći. Cilj ovog istraživanja bio je da se utvrdi stepen oksidativnog stresa, nivo tiobarbituricne kiseline - nivo reaktivnih supstancija tiobarbituricne kiseline u krvi trudnica sa hipertenzijom u trudnoći i korelacija tih parametara sa kliničkim parametrima toka trudnoće i poroda. **Materijal i metode.** Istraživanje je sprovedeno kao prospektivna studija u Univerzitetskoj bolnici Kliničkog centra Banja Luka. Obuhvatilo je 200 trudnica, od kojih je bilo 100 trudnica ispitivane grupe, trudnice sa hipertenzijom, i 100 zdravih trudnica od 28. do 40. gestacijske nedelje. **Rezultati.** Trudnice sa hipertenzijom imale su znatno više srednje vrednosti markera oksidativnog stresa, vrednosti reaktivnih supstancija tiobarbituricne kiseline od 36,7 μmol u odnosu na trudnice kontrolne grupe od 13,2 μmol . Trudnice sa hipertenzijom izazvanom trudnoćom, koje su imale komplikacije, imale su znatno više srednje vrednosti reaktivnih supstancija tiobarbituricne kiseline od 41,6 μmol u odnosu na trudnice bez komplikacija. Najvišu vrednost od 43,9 μmol imale su trudnice sa sindromom hemolize povećanim jetrenim enzimima, niskim trombocitima. **Zaključak.** Ovo istraživanje pokazuje da bi se nivo reaktivnih supstancija tiobarbituricne kiseline, kao marker oksidativnog stresa, mogao primenjivati u kliničkom radu za procenu težine kliničke slike i vremena prekida trudnoća sa hipertenzijom, ali bi to svakako zahtevalo dodatno istraživanje sa većim brojem trudnica pre svega sa teškom hipertenzijom.

Glavne reči: oksidativni stres; trudnoćom indukovana hipertenzija; biomarkeri; komplikacije u trudnoći; ishod trudnoće; TBARS

cause of maternal death, apart from hemorrhages and infections, is pregnancy induced hypertension. According to many authors, PIH accounts for about 12% of total maternal mortality [11–13], whereas according to Shapiro it is about 11% [14]. The highest mortality is associated with the most severe complications such as Hemolysis, Elevated, Liver Enzymes, Low Pla-

Abbreviations

PIH	– pregnancy induced hypertension
TBARS	– thiobarbituric acid reactive substance
CGO	– <i>Clinic of Gynecology and Obstetrics</i>
CCBL	– <i>Clinical Centre of Banja Luka</i>
DIC	– disseminated intravascular coagulation
MDA	– malondialdehyde

teles (HELLP) syndrome, placental abruption, eclampsia, edema and pulmonary embolism, kidneys failure, disseminated intravascular coagulation (DIC), and brain hemorrhages [15–17]. High maternal mortality and morbidity is followed by high fetal mortality and morbidity. Perinatal mortality is mostly associated with iatrogenic preterm birth, intrauterine growth retardation, as well as acute or chronic fetal stress [18, 19].

Nowadays, the role of oxidative stress in the etiology of PIH is being researched, and the results show that it may have a significant role in the development of preeclampsia, since it damages the endothelium of placenta, its vascularization and immune response [20–23]. In normal pregnancy, oxidative stress increases a bit, but there is no increase in free radicals. Recently, a great attention is being paid to lipid peroxidation, which actually is oxidative damage of lipids and increased formation of lipid peroxides, and its final product is malondialdehyde. Nowadays, malondialdehyde (MDA) is used in many expert researches as an oxidative stress marker, i.e. in the assessment of lipid peroxidation [24–27]. In accordance with the current literature findings, it is presumed that PIH is a condition of extremely increased oxidative stress [34]. This study was conducted to analyze the existence and degree of oxidative stress, i.e. lipid peroxidation, correlation of these parameters with clinical parameters of maternal and fetal outcomes in patients with pregnancy induced hypertension. Current medical literature does not contain a comprehensive analysis of all these parameters together.

The aim of this research was to determine levels of thiobarbituric acid reactive substance (TBARS) in blood of pregnant women with pregnancy induced hypertension and to analyze the correlation of TBARS parameters with clinical parameters during pregnancy and delivery in pregnancies with pregnancy induced hypertension.

Material and Methods

The study was performed at the Clinic of Gynecology and Obstetrics (CGO), of the University Hospital, Clinical Centre of Banja Luka (CCBL), according to current standards and regulations of the Ethics Committee. It included 200 pregnant women, 28 - 40 weeks of gestation, who were admitted to the Department of Perinatology of the CGO in Banja Luka. All pregnant women gave birth at the Maternity Ward of the CGO in accordance with medical indications. These were single pregnancies, accurately dated, with no other pathology. Test results were performed at the Institute of Laboratory Diagnosis and the Pediatric Clinic, of the University Hospital, CCBL in Banja Luka.

The pregnant women were divided into two groups: the study group of 100 pregnant women with

the diagnosis of pregnancy induced hypertension based on clinical, laboratory and ultrasound evidence; the control group of 100 pregnant women without clinical, laboratory and ultrasound evidence of pregnancy induced hypertension.

During hospital stay, all the pregnant women were treated in the same way: they were advised to reduce salt intake by half, eat protein-rich food, have strict rest and oxygenation, blood pressure and respiratory rate were measured every 4 hours, unless unregulated blood pressure required more frequent measurement, filled in a blood pressure chart for each patient. PIH is classified as mild hypertension if it equals or is higher than 140/90 mmHg, and severe hypertension if it equals or is higher than 160/110 mmHg. Selection of pregnant women of the control group was performed after collection of data for the study group, and the groups were matched in terms of maternal age and gestational age as much as possible.

The 4 most common complications associated with PIH were analyzed in all patients: HELLP syndrome, eclampsia, placental abruption and hemorrhages. After delivery, the most common maternal complications were: hemorrhages, infections, kidney damages, central nervous system damage, etc.

Fetal outcome was assessed based on the Apgar score at the first and fifth minute (0 to 7 is considered low - dead fetus, severe and mild asphyxia, and 8 to 10 is excellent).

Thiobarbituric acid reactive substance (TBARS) is an oxidative stress marker, which quickly and strongly reacts to malondialdehyde. Due to the simplicity of this oxidative stress marker, i.e. being a lipid peroxidation marker, it was used in this research. Blood tests were performed in all pregnant women, with PIH and the control group, for biomarkers of oxidative stress, TBARS levels, using the spectrophotometric method based on the concentration of MDA, product of lipid peroxidation, at the Institute of Laboratory Diagnosis and Pediatric Clinic, of the University Hospital, Clinical Centre of Banja Luka. TBARS is a very sensitive method for quantitative determination of lipid peroxidation. The principle of this screening method is that two molecules of thiobarbituric acid reactive substance react with one molecule of malondialdehyde, creating a compound, which is determined by spectrophotometry. Five milliliters of venous blood were collected from the cubital vein of each patient and put into a sterile tubes. TBARS levels were determined as an equivalent of MDA standard, in accordance with recommendations of the producer (Oxi Select TBARS Analisa Kit (MDA quantification), and results were acquired by spectrophotometry at 532 nm. In accordance with the recommendations, and minimal and maximal values, the results were divided into intervals for detailed analysis and comparison: low level interval up to 20 μ mol, medium level interval from 20 to 40 μ mol, and high level interval of TBARS over 40 μ mol.

Results were analyzed and presented through descriptive statistics and adequate statistical tests using the SPSS analytic-statistical software kit. In normal division, t-test of independent samples was used, and in cases where the basic group significantly deviated

Table 1. Complications in the group with PIH and in the control group**Tabela 1.** Prisustvo komplikacija kod trudnica sa TIH* i kontrolne grupe

		Complications/Komplikacije			
		Placental abruption <i>Abrupcija placente</i>	Eclampsia <i>Eklamsija</i>	HELLP	Hemorrhage <i>Hemoragija</i>
Group with PIH/ <i>Trudnice sa TIH</i>	No/ <i>Ne</i>	92	98	96	96
	Yes/ <i>Da</i>	8	2	4	4
Control group/ <i>Kontrolna grupa</i>	No/ <i>Ne</i>	100	100	100	100

*TIH = *Trudnoćom indukovana hipertenzija*

from the normal division, we applied the Mann-Whitney U-test. We used Hi-square (χ^2) and Fisher test, and contingency 2 x 2 table, and *Yates' correction* was made for continuity of smaller samples [28].

Results

All the gathered results of pregnant women with PIH and the control group of healthy pregnant women, were analyzed in detail in accordance with anthropometric parameters of pregnancy and delivery.

The mean gestational age at delivery in pregnant women with PIH was 261.9 days, whereas in the control group it was 273.9 days. The Mann-Whitney U test showed a high statistical significance $p=0.00$; a significantly lower gestational age was found in pregnant women with PIH in comparison to the control group. In regard to age distribution, hypertensive pregnant women were statistically significantly older compared to the control group, $p=0.005$; the mean age of hypertensive pregnant women was 31.2 years, whereas in the control group it was 28.9 years. In regard to parity, there was no statistically significant difference between the two groups: there was an equal number of primiparas and multiparas. Regarding the number of abortions, there was no statistically significant difference between the two groups: there was an equal number of pregnant women without abortions and pregnant women with one or more abortions in both groups. The fetal outcomes and Apgar scores at the first minute showed a high statistical significant difference, $p=0.002$; pregnant women with PIH delivered children of significantly lower Apgar score (0 - 7) in comparison to healthy pregnant women. The analysis of arterial tension, showed that the mean systolic pressure of pregnant women with PIH was 160 mmHg, and, in the control group it was 120 mmHg, whereas the mean diastolic pressure of pregnant women with PIH was 110 mmHg, and 70 mmHg in the

control group. The percentage of pregnant women with severe PIH was 59%, whereas 49% had mild PIH.

Complications during pregnancy and delivery in pregnant women with PIH and the control group

Table 1 shows the most common complications during pregnancy and delivery. In pregnant women with PIH, there was a total of 18 complications present in 14 women. Four women had 2 complications each. In pregnant women with PIH, there were 8 with placental abruption, 4 with hemorrhages, 2 with eclampsia and 4 with HELLP syndrome. In the control group, on the other hand, there were no complications whatsoever.

We analyzed the presence of complications during pregnancy and delivery related to the height of blood pressure. Out of 100 women with PIH, 59 women had severe PIH, and 41 had mild PIH.

Table 2 shows complications in patients with mild and severe PIH. There were four pregnant women having two complications each. The Fisher test showed a high statistically significant difference ($p = 0.007$) related to the presence of complications in pregnant women with PIH, those with mild and severe PIH. Pregnant women with severe PIH, presented with a significantly larger number of complications.

The analysis of the maternal outcome showed that there were no lethal outcomes in either group, being the worst complication after delivery. There were no complications after delivery in the control group, whereas there were 5 women with PIH with complications.

TBARS – an oxidative stress marker in pregnant women with PIH and in the control group

We compared the levels of oxidative stress marker - TBARS, byproduct of lipid peroxidation in pregnant women with PIH, and in the control group. The Mann-

Table 2. Complications in the group with PIH**Tabela 2.** Prisustvo komplikacija kod pacijentkinja sa TIH*

Complications <i>Komplikacije</i>	Group with PIH/ <i>Trudnice sa TIH</i>		Total <i>Ukupno</i>
	Mild/ <i>Blaga</i>	Severe/ <i>Teška</i>	
No/ <i>Ne</i>	40	46	86
Yes/ <i>Da</i>	1	13	14
Total/ <i>Ukupno</i>	41	59	100

*TIH - *trudnoćom indukovana hipertenzija*

Table 3. TBARS levels in the group with PIH and in the control group**Tabela 3.** Vrednosti TBARS* kod trudnica sa TIH** i kontrolne grupe

Study group/Ispitivane grupe	N	Min.	Max.	Range	Median	Mean	SD
Group with PIH/Trudnice sa TIH	100	21.70	61.70	40.00	36.7500	36.6860	8.29359
Control group/Kontrolna grupa	100	9.10	25.80	16.70	13.2000	13.4220	2.74493
Total/Ukupno	200	9.10	61.70	52.60	21.7500	25.0540	13.18904

*TBARS – reaktivne supstancije tiobarbiturne kiseline; **TIH - trudnoćom indukovana hipertenzija

Table 4. TBARS levels in the group with PIH in regard to the height of blood pressure**Tabela 4.** Vrednosti TBARS* kod trudnica sa TIH** prema visini krvnog pritiska

Group with PIH/Trudnice sa TIH	N	TBARS ($\bar{x}$)	p
Mild PIH/Blaga TIH	41	30.3000	0.000
Severe PIH/Teška TIH	59	41.1237	
Total/Ukupno	100	36.6860	

*TBARS – reaktivne supstancije tiobarbiturne kiseline; **TIH - trudnoćom indukovana hipertenzija

Table 5. TBARS levels in the group with PIH in comparison to pregnancy and delivery complications**Tabela 5.** Vrednosti TBARS* kod trudnica sa TIH** u odnosu na komplikacije trudnoće i porođaja

Complications/Komplikacije	N	TBARS ($\bar{x}$)	p
No/Ne	86	35.8826	0.008
Yes/Da	14	41.6214	
Total/Ukupno	100	36.6860	

*TBARS – reaktivne supstancije tiobarbiturne kiseline; TIH - trudnoćom indukovana hipertenzija

Whitney U test showed a high statistically significant difference in levels of TBARS in pregnant women with PIH (Md = 36.75, n = 100) in comparison to the control group (Md = 13.20, n = 100), U = 6.000, z = -12.203, p = 0.000 with r = 0.863. Pregnant women with PIH had significantly higher levels of TBARS oxidative stress marker. The mean value was 36.7 μmol in PIH group, in comparison to 13.2 μmol in the control group. The highest TBARS level was found in women with PIH and it was 61.7 μmol , whereas in the group of healthy pregnant women, it was 25.8 μmol . The lowest level of TBARS in women with PIH was 21.7 μmol , and 9.10 μmol in the control group, which is highly statistically significant (**Table 3**).

We also analyzed the levels of TBARS related to the height of blood pressure in women with mild and severe PIH. The Mann-Whitney U test showed a high statistically significant difference in TBARS levels in women with mild PIH (Md = 29.20, n = 41) and women with severe PIH (Md = 41.80, n = 59), U = 272.000, z = -6.571, p = 0.000 with r = 0.657. The pregnant women with severe PIH had significantly higher levels of TBARS in comparison to pregnant women with mild PIH: TBARS in mild PIH - 30.30 μmol , and in severe PIH – 41.12 μmol (**Table 4**).

TBARS - an oxidative stress marker in pregnant women with PIH and in the control group related with complications during pregnancy and delivery

The Mann-Whitney U test revealed a high statistically significant difference in TBARS levels in

women with PIH presenting with complications (Md = 35.95, n = 86) and women with PIH without complications (Md = 43.35, n = 14), U = 334.000, z = -2.663, p = 0.008 with r = 0.266. The pregnant women with PIH accompanied with complications, had significantly higher levels of TBARS; the mean TBARS level was 41.6 μmol , i.e. in high level interval of TBARS, in comparison to pregnant women without complications (**Table 5**).

The analysis of the most common complications in pregnant women with PIH and their comparison with the mean levels of TBARS showed the highest level of 43.9 μmol in pregnant women with HELLP syndrome. All pregnant women with complications had mean level of TBARS in the high level interval, i.e. over 40 μmol (**Table 6**). We got positive correlation of these pregnancy and delivery parameters with levels of TBARS.

Discussion

Former studies dealing with oxidative stress indicate that pregnancy is a state of physiological, slightly increased oxidative stress in comparison to healthy non-pregnant women [20, 21, 29, 30]. Oxidative stress may have a significant role in the development of preeclampsia since it starts damaging the endothelium of placenta, vascularization, and immune response [24–27].

Complications associated with PIH are very difficult and severe; they can put at risk the maternal and the fetal life. The gathered results show that there were no complications during pregnancy and delivery in the

Table 6. TBARS mean levels in the group with PIH in comparison to complications
Tabela 6. Srednje vrijednosti TBARS* kod trudnica sa TIH** u odnosu na komplikacije

Complication/Komplikacije	N	TBARS ($\bar{x}$)
Placental abruption/Abrupcija placente	8	40.8125
Eclampsia/Eklamsija	2	40.9500
HELLP	4	43.9250
Hemorrhage/Hemoragija	4	42.1500
Total/Ukupno	18	36.6860

*TBARS – reaktivne supstancije tiobarbiturne kiseline; **TIH – trudnoćom indukovana hipertenzija

control group. On the other hand, in the group of pregnant women with PIH, including a total of 100 pregnant women, there were 18 complications in 14 women, 4 women had 2 complications each. Most complications referred to placental abruption - 8, hemorrhages - 4, HELLP-syndrome - 2, and eclampsia - 2. Our results are in agreement with literature data [31–33]. The latest findings on the pathogenesis and etiology of PIH [34], indicate that there are different views on the beginning of the disease, severity of symptoms and complications. The analysis of the occurrence of complications in regard to the height of blood pressure showed a high statistically significant difference in the group of pregnant women with mild or severe PIH. The pregnant women with severe PIH had significantly higher number of complications – a total of 17 in 14 pregnant women, while 4 women with severe PIH had 2 complications each. Only 1 pregnant woman with mild PIH presented with 1 complication. These results are also in agreement with literature data [34–37].

The analysis of maternal outcome in women with PIH and in the control group shows that there was no statistically significant difference between the examined groups. In the group of women with PIH, 5 had complications, whereas in the control group there were no complications whatsoever. It is important to say that there were no cases of maternal lethal outcome, which is the worst complication after delivery. Although the difference was not statistically significant, the Fisher test, $p=0.059$, value was at the limit of statistical significance between women with PIH and the control group. The obtained results indicate that the patients were provided with good prenatal diagnosis, pregnancy and delivery management, as well as timely delivery.

In the control group, the mean systolic pressure was 120 mmHg, and diastolic 70 mmHg. In the group of women with PIH, the mean systolic pressure was 160 mmHg, and diastolic 110 mmHg. The highest systolic pressure was measured in women with PIH - 220 mmHg, and diastolic 160 mmHg.

In regard to the levels of TBARS, as an oxidative stress marker, there was a high statistical difference of $p < 0.01$. Pregnant women with PIH had a significantly higher mean value of TBARS in comparison to the control group. The highest level of TBARS in the group with PIH was 61.7 μmol , whereas in the control group it was 25.8 μmol . The lowest level of TBARS in women with PIH was 21.7 μmol , and in the control group it was 9.10 μmol . The mean level of TBARS in the control group was 13.2 μmol , whereas

in women with PIH, it was 36.7 μmol . The obtained results of this research clearly indicate to extremely increased oxidative stress in PIH, i.e. we proved increased level of lipid peroxidation and hence the possibility of its prevention in pregnancy.

We also analyzed the mean levels of TBARS, which proved to be extremely high in hypertensive pregnant women, especially in women with the most severe PIH. Previous analyses showed that the most severe complications and the highest number of complications were found in women with severe preeclampsia (PIH). TBARS may be used as a pre-clinical parameter in hypertensive pregnant women for the purpose of timely diagnosis and in the best maternal and fetal interests.

The analysis of TBARS and complications in the examined groups shows a high statistically significant difference ($p=0.008$) of TBARS levels in pregnant women with PIH with complications, and in pregnant women with PIH without complications. The mean level of TBARS in pregnant women with PIH with complications was 41.62 μmol . The pregnant women with PIH and accompanied complications had significantly higher levels of TBARS in comparison to pregnant women with PIH without complications. Our results show that the highest level of TBARS of 43.92 μmol was found in pregnant women with HELLP syndrome, which is one of the most severe complications of PIH, whereas women with hemorrhages come next with 42.15 μmol .

Conclusion

In conclusion, our research shows that pregnant women with pregnancy induced hypertension have extremely high levels of oxidative stress and lipid peroxidation. Pregnant women with pregnancy induced hypertension and the most severe complications during pregnancy and delivery had extremely high levels of thiobarbituric acid reactive substance, and the highest levels were found in pregnant women with Hemolysis, Elevated, Liver Enzymes, Low Platelets syndrome.

This study shows that thiobarbituric acid reactive substance, as an oxidative stress marker, may be used in clinical practice in the assessment of the severity of complications and as an indicator for timely delivery in women with pregnancy induced hypertension. Surely, further studies with larger study samples of pregnant women with severe hypertension are needed to confirm this conclusion.

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