

# Correlation of Oxidative Stress Markers with Ultrasound and Cardiotocography Parameters with Hypertension Induced Pregnancy

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## ABSTRACT

**Introduction:** Pregnancy induced hypertension (PIH), especially preeclampsia, is a state of extremely increased oxidative stress (OS), due to decrease of antioxidant capacity in comparison to normotensive pregnant women. The consequences of increased state of oxidative stress with hypertension disorder in pregnancy are disorder of placental blood flow, intrauterine hypoxia of the fetus and disturbance in transfer of O<sub>2</sub> manifested as pathological ultrasound (US) parameters (amount of amniotic fluid and biophysical profile of fetus) and cardiotocography parameters (CTG). **Aim:** The aim of this research is to analyze correlation of TBARS oxidative stress markers with ultrasound parameters of pregnancy course and cardiotocography parameters in pregnant women with PIH. **Patients and methods:** Research has been performed at the Clinic of Gynecology and Obstetrics, University Clinical Centre of the Republic of Srpska. It covered 200 pregnant women, 100 of them with PIH and 100 healthy pregnant women, at gestational age from 28 to 40 weeks. All pregnant women were analyzed for US parameters of pregnancy course and CTG records as well as oxidative stress biomarker, values of Thiobarbituric Acid (TBARS). **Results:** Pregnant women with PIH had high statistical significant (pre)pathological CTG records and US- biophysical profile, less amount of amniotic fluid and delivered in lower gestation compared to healthy pregnant women. TBARS high values are statistical high significant frequent with pregnant women with PIH, who had pathological and pre-pathological biophysical profile and CTG records, as well as with US less amount of amniotic fluid ( $p < 0.01$ ). The highest TBARS values were presented with PIH pregnant women and US of less amount of amniotic fluid 42.3  $\mu\text{mol}$ . **Conclusion:** There is statistical strong connection between TBARS values, being used as oxidative stress markers, and diagnostic methods used in PIH diagnostics, ultrasound (amount of amniotic fluid, fetus biophysical profile) and cardiotocography recording. TBARS could also be significant in clinical application for assessment of pregnant women with PIH in order to make decisions on pregnancy termination period.

**Keywords:** PIH, TBARS, oxidative stress, US parameters, CTG record.

## 1. INTRODUCTION

One of the most common and potential life threatening complications of pregnancy is Pregnancy Induced Hypertension (PIH) (1). Frequency is 5% to 15% in general population of pregnant women (2-4). Preeclampsia is dominant form of PIH. The most common indication for cesarean section is PIH syndrome with 33.7% participation in all cesarean sections (5). It is a cause even in the best developed world countries for over 15% of preterm births and about 18% of maternal deaths (6-8). Role of oxidative stress in pregnancy hypertension etiology is being researched, and it could have an important role in occurrence of preeclampsia (9, 10). In accordance with current findings, pregnancy

hypertension, especially preeclampsia, PIH is a state of extremely increased oxidative stress and increased lipid peroxidation due to decrease of antioxidant capacity in comparison to normotensive pregnant women. Low-molecular aldehyde, malondialdehyde (MDA) is the final product of lipid peroxidation being released. Nowadays, malondialdehyde (MDA) is used in many scientific researches as oxidative stress marker, i.e. to evaluate lipid peroxidation. Oxidative stress marker, which bonds to malondialdehyde fast and strongly is Thiobarbituric Acid Reactive Substance (TBARS) (11-13). It is assumed that, being the consequence of increased state of oxidative stress with hypertension disorder in pregnancy,

disorder of placental blood flow occurs, which leads to intrauterine hypoxia of the fetus and disturbance in transfer of  $O_2$ . So many ultrasound parameters can be analyzed in order to determine the consequence of increased state of oxidative stress in PIH too: amount of amniotic fluid in line with Manning grading, Placenta maturity in line with Grannum grading (I, II, III maturity grade), Placenta localization in line with Koffinas (medial and lateral), biophysical profile (BPP) of fetus (Manning scoring), as well as Cardiotocography parameters (CTG record), which can be modified as CTG score in line with Kuvačić and Dražančić (14-18). This research is analyses of oxidative stress existence, i.e. lipid peroxidation in pregnancy hypertension and correlations of ultrasound (US) and cardiotocography (CTG) parameters of pregnancy course. The current literature does not contain comprehensive analyses of these parameters.

## 2. AIM

The aim of this research is to analyze correlation of TBARS oxidative stress markers with ultrasound parameters of pregnancy course and cardiotocography parameters in pregnant women with pregnancy induced hypertension.

## 3. PATIENTS AND METHODS

Research has been performed at the Clinic of Gynecology and Obstetrics, University Clinical Centre of the Republic of Srpska. It covered 200 pregnant women, gestation from 28 to 40 weeks. All pregnancies were single, accurately termed pregnancies with no other pathology. In this research, the tested pregnant women were divided into two groups based on clinical, laboratory and ultrasound findings. Test group has 100 pregnant women, who are proven to have hypertension pregnancy. Control group has 100 pregnant women, who are proven to have pregnancy free from hypertension.

All pregnant women were regularly measured and accurately recorded blood pressure (TA). Blood pressure was measured by indirect, auscultator method with mercury sphygmomanometer. Mild hypertension (PIH) is considered to be the level of TA equal or higher than 140/90 mmHg, and difficult hypertension (PIH) is considered to be the level of TA equal or higher than 160/110 mmHg. In pregnant women with hypertension, we applied the same therapy treatment. Selection of pregnant women of control group was performed after collection of data for test group, trying to acquire gestation and age of both groups as similar as possible.

With all 200 pregnant women, ultrasound parameters were tested and these were not older than 7 days in relation to delivery. US examination was performed on US device GENERAL ELECTRIC GE LOGIQ Book XP, by 3.5 MHz convex sonde. With all 200 pregnant women, control and test group, the following anthropometric parameters of pregnancy and delivery course were analyzed: gestation period, newborn weight at birth and Apgar score in the first minute after birth. Following ultrasound parameters were analyzed: amount of amniotic fluid in line with Manning grading: decreased amount of amniotic fluid (the largest vertical pocket of amniotic fluid from 0 to 2 cm), normal (the largest vertical pocket of amniotic fluid from 3 to 8 cm), increased (pocket over 8 cm); Placenta maturity in line with Grannum grading (I, II, III maturity grade); Placenta local-

ization in line with Koffinas (medial and lateral); biophysical profile (BPP) of fetus (Manning scoring) and it is grade as: normal 8-10 points, pre-pathological 4-8, pathological from 0 to 4 points. Cardiotocography parameters, CTG record, lasting for 30 minutes, analyzed as well. CTG records were not older than 7 days in relation to delivery, and they were analyzed in line with modified CTG score in line with Kuvačić and Dražančić. According to these authors, CTG is normal from 0 to 2 points, pre-pathological from 3 to 4 points and pathological 5 and more points. All researched pregnant women of test and control group were blood tested for values of Thiobarbituric Acid (TBARS), spectrophotometric method based on concentration of malondialdehyde, product of lipid peroxidation. TBARS level was defined as equivalent of malondialdehyde standard, in line with producer's recommendation (Oxi Select TBARS Analisa Kit (MDA quantification). TBARS level was sorted into interval of low values up to 20  $\mu\text{mol}$ , medium values from 20 to 40  $\mu\text{mol}$  and interval of high values of TBARS over 40  $\mu\text{mol}$ .

In data analyses, SPSS statistic software package was used. Data were analyzed by using descriptive statistic methods. In normal sorting, t-test of independent samples was used, and Mann-Whitney's U-test was used in cases where basic set was significantly deviating from normal division. Chi-squared ( $\chi^2$ ) test was used; correction in line with Yates was applied. Likewise, Fisher's test with certain significance level of  $p < 0.05$  was used.

## 4. RESULTS

Mean value of systolic pressure of test group amounted to 160 mmHg and for control group it amounted to 120 mmHg. As for diastolic pressure, in test group it amounted to 110 mmHg, and for control group it amounted to 70 mmHg. Difficult PIH was recorded in 59% pregnant women, whereas mild PIH was recorded in 41% pregnant women of test group.

In order to see possibility of clinical application of TBARS as oxidative stress marker in hypertension in pregnancy, we compared achieved TBARS mean values with clinical US parameters: amount of amniotic fluid, fetus biophysical profile, placenta maturity in line with Grannum grading, placenta localization, of test and control group of pregnant women.

By applying Mann-Whitney's U test, we discovered a highly significant statistical difference in TBARS values with pregnant women of test group having the following US findings: less amniotic fluid ( $Md = 34.10$ ,  $n = 79$ ) compared with pregnant women with the following US findings: enough and more amniotic fluid ( $Md = 42.10$ ,  $n = 21$ ),  $U = 435.000$ ,  $z = -3.339$ ,  $p = 0.001$  with  $r = 0.334$ . Pregnant women with PIH with US findings: less amniotic fluid had a significantly higher TBARS values compared with pregnant women with PIH with US findings: enough amniotic fluid. By applying Mann-Whitney's U test, no statistical different values were discovered in TBARS value in control group (Table 1).

By applying Mann-Whitney's U test, we discovered significantly higher statistical difference in TBARS values of pregnant women of test group with normal BP of fetus ( $Md = 34.10$ ,  $n = 79$ ) compared to (pre) pathological BP ( $Md = 43.50$ ,  $n = 21$ ),  $U = 465.000$ ,  $z = -3.081$ ,  $p = 0.002$  with  $r = 0.308$ . However, pregnant women of test group with (pre) pathological BP of fetus has significantly higher TBARS values

Groups	Amount of amniotic fluid	n	TBARS ( $\mu\text{mol}$ )	p
Test	Enough or more	79	35.17	0.001
	Less	21	42.37	
Control	Enough or more	96	13.41	0.610
	Less	4	13.72	

Table 1. TBARS values of test and control group of pregnant women in relation to US – amount of amniotic fluid

(41.88  $\mu\text{mol}$ ) compared with pregnant women with normal BP (Table 2).

In analyses of US placenta maturity in line with Grannum

Groups	Fetus biophysical profile	n	TBARS ( $\mu\text{mol}$ )	p
Test	Normal	79	35.31	0.002
	Pre-pathological and pathological	21	41.88	
Control	Normal	99	13.40	0.000
	Pre-pathological and pathological	1	15.40	

Table 2. TBARS values of test and control group of pregnant women in relation to fetus biophysical profile (BP).

grading, there was no statistical significant difference found in TBARS values with pregnant women of test group with US placenta maturity in line with Grannum grade I and II (Md = 36.10, n = 18) and Grannum grade III (Md = 37.00, n = 82), U = 729.500, z = -0.076, p = 0.939 with r = 0.008. Likewise, there was no statistical significant difference found in TBARS values with pregnant women of control group with US placenta maturity in line with Grannum grade I and II (Md = 14.10, n = 49) and US and Grannum grading III (Md = 12.80, n = 51), U = 1041.000, z = -1.438, p = 0.150 with r = 0.144 (Table 3).

With pregnant woman of test group (p=0.153) and control

Groups	US Placenta maturity in line with Grannum grading	n	TBARS ( $\mu\text{mol}$ )	p
Test	Grannum grade I and II	18	36.77	0.939
	Grannum grade III	82	36.67	
Control	Grannum grade I and II	49	13.88	0.150
	Grannum grade III	51	12.98	

Table 3. TBARS values of test and control group of pregnant woman in relation to US- Placenta maturity in line with Grannum grading / groups/

group (p=0.768), having lateral and medial US placenta localization, there was no statistical significant difference found in TBARS values (Table 4).

Analyzing prepartal CTG record of pregnant women of

Groups	US placenta localization	n	TBARS ( $\mu\text{mol}$ )	p
Test	Lateral	2	45.40	0.153
	Medial	98	36.51	
Control	Lateral	2	12.80	0.768
	Medial	98	12.43	

Table 4. TBARS values of test and control group of pregnant women in relation to US – placenta localization

test group, there was statistical significant difference found in TBARS values with pregnant women of test group, whose prepartal CTG record was normal (Md = 33.10, n = 73) and with pregnant women of test group, whose prepartal CTG record was (pre) pathological (Md = 43.20, n = 26), U = 546.500, z = -3.409, p = 0.001 with r = 0.341. TBARS values of test group, pregnant women with PIH, having (pre)

pathological prepartal CTG record, are significantly higher compared to pregnant women of test group having normal prepartal CTG record. Total number of pregnant women in test group having prepartal CTG record was 99 -one pregnant woman experienced missed abortion due to premature placental abruption. All pregnant women in control group had normal prepartal CTG record, and TBARS mean value was 13.42 (Table 5).

Group	Prepartal CTG record	n	TBARS ( $\mu\text{mol}$ )	p
Test	Normal	73	35.03	0.001
	(Pre)pathological	26	41.17	

Table 5. TBARS values of test group in relation to prepartal CTG record

## 5. DISCUSSION

Current studies on oxidative stress (OS) indicate that pregnancy is a state of physiological, slightly increased OS in comparison to healthy and not pregnant women, whereas pregnancy with hypertension is a state of increased OS (19-21). Our research was focused on US parameters of pregnancy course, which are used on daily basis in routine work for assessment of intrauterine situation of fetus and TBARS values being OS markers. In analysis of TBARS mean values with the amount of amniotic fluid, assessed by US, we got results that test group of pregnant women with PIH has high statistical significant difference in TBARS value, whereas pregnant women with PIH and US findings: enough and more amniotic fluid and pregnant women with PIH with US findings: less amniotic fluid, p=0.001. TBARS values of pregnant women with PIH having US findings: less amniotic fluid amount, were in interval of high values and amounted to 42.37  $\mu\text{mol}$ . In control group of pregnant women, there was no statistical significant difference found in TBARS values; pregnant women with PIH with US findings: enough and more amniotic fluid and pregnant women with PIH with US findings: less amniotic fluid, and TBARS mean value in control group of pregnant women with US findings: less amniotic fluid amounted 13.72  $\mu\text{mol}$ , low values interval. Similar results are presented by Bhale DV et al. in their study (22).

We analyzed TBARS mean values and US parameter -fetus biophysical profile (BP), according to which we got high statistical significant difference of test and control group, and showed that this parameter is very important for intrauterine monitoring of fetus situation especially with high-risks pregnancies, such as PIH. In analyzing test group, we got a high statistical significant difference of TBARS values with pregnant women with PIH having US findings: normal - normal fetus biophysical profile (BP) and pregnant women with PIH with US findings: pathological and pre-pathological BP. Pregnant women with PIH having US findings: pathological and pre-pathological BP, had significantly higher TBARS values in comparison to pregnant women having US findings: normal BP. TBARS values of pregnant women with PIH having US findings: pathological and pre-pathological BP, were in interval from high values to and amounted to 41.88  $\mu\text{mol}$ . Analyses of control group did not give any statistical difference in values of TBARS and US-BP.

In our study, we analyzed TBARS and US mean values for parameter placenta maturity in line with Grannum grading

and we got high statistical significant difference of test and control group. This parameter is also important for intra-uterine monitoring of fetus situation, especially of premature placenta maturity up to 34 gestation week in high-risk pregnancies such as PIH (15). In test group, we did not get statistical significant difference in TBARS values in pregnant women with PIH having US findings: placenta maturity in line with Grannum grade I and II and pregnant women with PIH with US findings: placenta maturity in line with Grannum grade III. Analyzing control group of pregnant women, we saw that there was no statistical significant difference found according to these parameters. We did not get positive correlation of III grade placenta maturity in line with Grannum grading and TBARS values. However, Goswami PR et al. concluded in their study that Pregnancy Induced Hypertension alters the placental histomorphology (23). The histopathological changes among PIH group were statistically significant as compared to Normal (23).

Analysis of TBARS mean values and US parameter - placenta localization did not result in statistical significant difference of test and control group in our study. This parameter, according to researches by Koffinas et al. is important, because side localization of placenta is more frequent with PIH (14). In analysis of TBARS values of pregnant women with PIH having US findings as lateral placenta localization, our study showed that TBARS mean value in test group, with lateral placenta localization, amounted to 45.4  $\mu\text{mol}$  in interval of high values. There was no statistical significant difference found in TBARS values with pregnant women of control group and US parameter-placenta localization,  $p=0.768$ . Our results indicate that lateral location of placenta could have clinical significance in PIH, since we had high TBARS values, but it has to be paid attention to the need for further research since it was a rather small number of patients (placentas).

So far, there is no sufficient data in the literature on relation of TBARS and US parameters of pregnancy course, but in general, published results are similar to ours (24-26).

Analysis of prepartal CTG showed that there was high statistical significant difference in TBARS values of test group, where prepartal CTG record was normal, and pregnant women with PIH, whose prepartal CTG record was (pre) pathological ( $p = 0.001$ ). Pregnant women with PIH having (pre) pathological CTG record, had TBARS values in high values interval 41.17  $\mu\text{mol}$ , which indicates to conclusion of possible clinical change of TBARS as a oxidative stress marker with PIH. Pregnant women in control group, 100 pregnant women in total, had normal prepartal CTG record, and TBARS mean value was 13.42  $\mu\text{mol}$ . Results of this research clearly indicate presence of very increased oxidative stress in pregnancy induced hypertension (PIH). Goyal SG et al. presented data in their study that the highest risk factor for deterioration of CTG was PIH (35%) (27).

TBARS values are in positive correlation with blood pressure values, respectively the highest TBARS value were present in pregnant women with the highest blood pressure values (28). Our study proved a positive correlation between diagnostic methods used nowadays in PIH diagnostics, and these are ultrasound (amount of amniotic fluid, biophysical profile of fetus) and cardiotocography parameters (CTG) as

well as TBARS values being OS markers, i.e. lipid peroxidation markers. Poston L et al. and De Lucca L et al. presented similar data in their studies (29, 30).

## 6. CONCLUSION

Results of our research indicate statistical strong connection and positive correlation between TBARS values, being oxidative stress marker, and diagnostic methods used in PIH diagnostics such as ultrasound (amount of amniotic fluid, fetus biophysical profile) and cardiotocography record. TBARS could also be significant in clinical application for assessment of pregnant women with PIH in order to make decisions on pregnancy termination period, but there will be needed additional researches primarily with a larger number of pregnant women experiencing hypertension.

### Conflict of interest: none declared.

**Author's contributions:** DD is done concept and design studies. DD, DJ, NL collected the data, analyzed them and wrote the text. SM assisted in writing the text including final editing and critical revision of the scientific content. All authors have read the text and approved the final manuscript.

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