

Preeclampsia and the imbalance between reactive oxygen species and antioxidants

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Abstract

The aim of this study was to investigate the plasma level of the degradation products of nitric oxide - which is a potent vasodilator - in relation to the plasma levels of the degradation products of reactive oxygen species and to the plasma levels of antioxidants in preeclampsia. About 240 patients were considered for the study divided into three groups. We determined the plasma levels of lipid peroxides and carbonyl content of proteins, the hydrogen donating ability of plasma and nitrates and nitrites. The results reveal a significant increase of plasma reactive oxygen species and a significant increase of plasma antioxidants and nitric oxide in healthy pregnant women compared with non-pregnant women. Significantly increased plasma levels of reactive oxygen species and significantly decreased antioxidant level and nitric oxide were found in pregnant patients with preeclampsia, compared to healthy pregnant women. Normal pregnancy has a new oxidant/ antioxidant balance compared with non-pregnant status, the increase of oxidants being neutralized by the increase of antioxidants, whereas in preeclampsia the oxidant/ antioxidant balance does not longer exists and oxidative stress occurs. In this manner, decreased level of nitric oxide may contribute to the accentuation of the imbalance of vasoconstrictor and vasodilator factors in preeclampsia that leads to the arterial hypertension that characterises this disease.

Keywords: preeclampsia, reactive oxygen species, antioxidants, nitric oxide.

Introduction

Preeclampsia is a frequent disorder that complicates the second and third trimester of pregnancy, producing increased maternal and foetal morbidity. In spite of this, the mechanisms involved in the pathogenesis of this disorder have not been yet completely understood⁽¹⁾. The cause of inadequate trophoblastic invasion in preeclampsia is still unclear, but is known that this deficient trophoblastic invasion along with the imbalance between vasoconstrictor and vasodilator factors results in preeclampsia⁽²⁾. We evaluated the level of reactive oxygen species, antioxidants and nitric oxide in preeclamptic women in order to establish whether they have a role in the pathogenesis of this disorder.

Methods

The present study included 240 patients admitted to 'Dominic Stanca' Obstetrics and Gynecology Clinic, Cluj-Napoca, Romania, divided in 3 groups, as follows:

■ Group 1: 80 healthy non-pregnant women with age between 22 and 40 years old, that were selected following clinical and usual laboratory examinations that were within normal limits;

■ Group 2: 80 healthy pregnant women with the same age and having gestational age from 29 to 41 weeks that were selected following clinical and usual laboratory examinations that were within normal limits;

■ Group 3: 80 pregnant women with preeclampsia with the same age and gestational age like the women in the second group.

For all groups we have determined the plasma levels of some damage products of reactive oxygen species in organism (lipid peroxides and carbonyl content of proteins), the hydrogen donating ability of plasma (which reflects the level of antioxidants) and nitrates and nitrites (which are the degradation products of nitric oxide in organism). The plasma level of lipid peroxides was established using the thiobarbituric method. The plasma level of carbonyl content of proteins was established using the Reznick method. The plasma level of the hydrogen donating ability of plasma was established using the Hatano method. The plasma level of nitrates and nitrites was established using the Griess reaction after the conversion of nitrate in nitrite by nitrate reductase⁽³⁾.

Statistical analysis

Acquired data were analysed from statistical point of view using t-Student and ANOVA tests.

Results

The results reveal a significant increase ($p < 0.001$) of plasma level of lipid peroxides in healthy pregnant women compared with healthy non-pregnant women (Figure 1).

In addition, we found significantly higher values ($p < 0.001$) of plasma level of carbonyl content of prote-

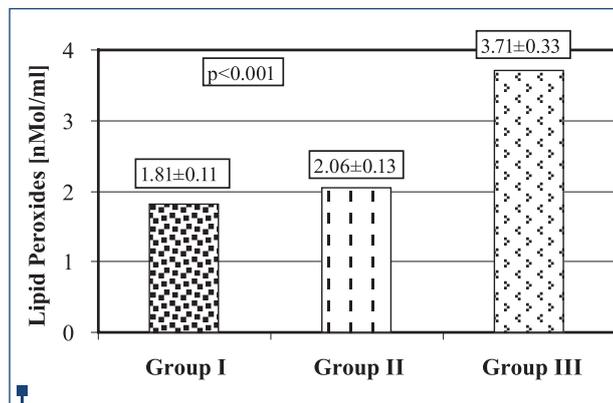


Figure 1. Plasma lipid peroxides in healthy non-pregnant women, healthy pregnant women and patients with preeclampsia

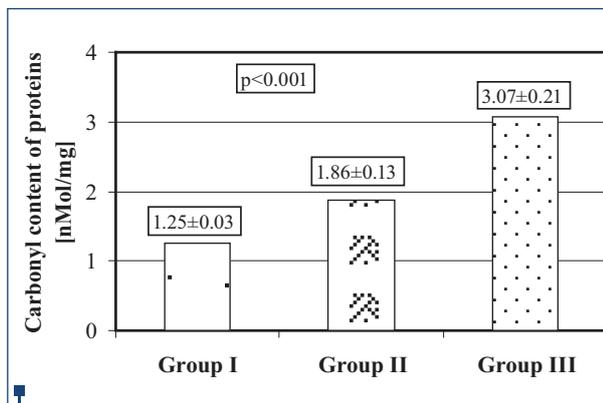


Figure 2. Plasma carbonyl content of proteins in healthy non-pregnant women, healthy pregnant women and patients with preeclampsia

ins in healthy pregnant women compared with healthy non-pregnant women (Figure 2).

Lipid peroxides and carbonyl content of proteins are the degradation products of reactive oxygen species in our body, and because those levels are found increased results that the level of reactive oxygen species is increased in pregnant women compared with non-pregnant women.

We also found that the hydrogen donating ability of plasma was significantly higher ($p < 0.001$) in healthy pregnant women compared with healthy non-pregnant women (Figure 3). So, the antioxidants are also increased in pregnant women compared with non-pregnant women.

Moreover, the plasma level of nitrates and nitrites was significantly higher ($p < 0.001$) in healthy pregnant women compared with healthy non-pregnant women (Figure 4). Because nitrates and nitrites are the degradation products of nitric oxide in our body results that the level of nitric oxide is increased in pregnant women compared with non-pregnant women.

Significantly increased plasma levels of lipid peroxides ($p < 0.001$), were found in patients with preeclampsia, compared to healthy pregnant women (Figure 1).

Likewise, we found significantly higher values ($p < 0.001$) of plasma level of carbonyl content of proteins in patients with preeclampsia, compared to healthy pregnant women (Figure 2).

On the other hand, we found significantly decreased ($p < 0.001$) hydrogen donating ability of plasma in patients with preeclampsia, compared to healthy pregnant women (Figure 3).

The results reveal also significantly decreased ($p < 0.001$) plasma level of nitrates and nitrites in patients with preeclampsia, compared to healthy pregnant women (Figure 4).

Discussion

The production of reactive oxygen species is increased in healthy pregnant women compared with healthy non-pregnant women. Reactive oxygen species are formed in great quantities because there is an increase in basal metabolism and oxygen consumption (15-20%) associated with normal gestation(4). Moreover, one of the endogenous sources of reactive oxygen species is represented by the white blood cells⁽⁵⁾ that rise in number with advancing pregnancy⁽⁶⁾. The more white

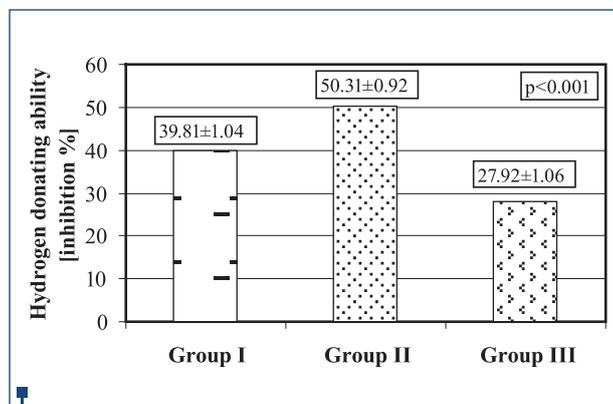


Figure 3. Hydrogen donating ability of plasma in healthy non-pregnant women, healthy pregnant women and patients with preeclampsia

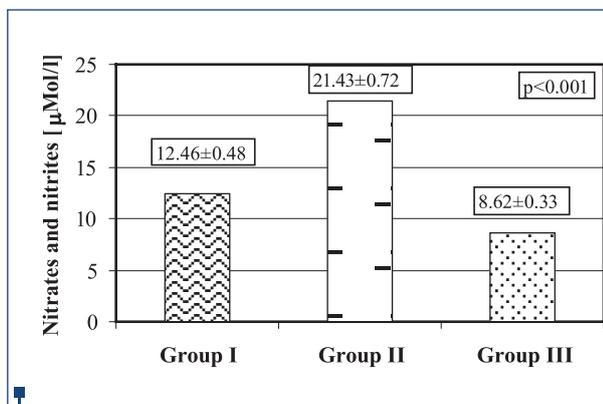


Figure 4. Plasma level of nitrates and nitrites in healthy non-pregnant women, healthy pregnant women and patients with preeclampsia

blood cells, the greater quantities of reactive oxygen species are formed.

In women with normal pregnancy there is also an increased level of antioxidants compared with the non-pregnant women. There is a great production of antioxidants in order to neutralize the increased reactive oxygen species level⁽⁷⁾. Thus, we can affirm that the process that occurs in normal pregnancy is a physiological one because it maintains a perfect balance between the production of reactive oxygen species and that of antioxidants and oxidative stress does not occur⁽⁸⁾.

Regarding the level of nitric oxide our study reveals that it is increased in normal pregnancy compared with the non-pregnant women. Nitric oxide produces the relaxation of smooth muscle, so we can conclude that its level is increased in order to participate to the relaxation of uterus during the pregnancy together with progesterone⁽⁹⁾. The relaxation of uterus during the pregnancy is extremely important for the development of the fetus. Furthermore, nitric oxide produces the relaxation of the vessel smooth muscle⁽¹⁰⁾. Nitric oxide is produced in greater quantities in normal gestation in order to maintain the predominance of vasodilator factors that characterized normal pregnancy^(9,11).

It may be justified to conclude also that nitric oxide is one of the factors that participate at the cardiovascular adaptation in normal pregnancy. In addition, nitric oxide is produced in greater amount in gestation in order to maintain the pregnancy through its effect of relaxation of the uterus.

In normal pregnancy there is a new oxidative status. This is a physiological process that occurs because the sources of reactive oxygen species increase in pregnant women. On the other hand, the organism of the mother has stronger antioxidants mechanisms that neutralize reactive oxygen species produces in great quantities and prevent the injuries that can be produced to the foetus by them⁽¹²⁾. The result is a perfect balance between oxidants and antioxidants in normal pregnancy.

Regarding the patients with preeclampsia, the results illustrate an excess of reactive oxygen species in pregnant women with this disease. The antioxidants are decreased because they were used for the neutralization of reactive

oxygen species produced in excess in pregnant patients with preeclampsia, these antioxidants being consumed in these neutralization reactions. Therefore, we can affirm that oxidative stress occurs in preeclampsia. Oxidative stress occurs when the reactive oxygen species are produced in excess and antioxidants are decreased, because they are consumed in order to neutralize reactive oxygen species⁽¹³⁾.

From the above presented results, nitric oxide is decreased in pregnant women with preeclampsia and this may be due to the fact that nitric oxide produced in organism was consumed in the reaction with superoxide anion, which is the most reactive of reactive oxygen species. The resulted product is peroxy-nitrite, which is known to be involved in the dysfunction of endothelial cells in pregnancies complicated with preeclampsia^(14,15). Nitric oxide consumed in the reaction with superoxide anion can no longer exert its vasodilator effect, accentuating the imbalance of vasoconstrictor and vasodilator factors, already existing in pregnancies complicated by preeclampsia. Therefore, the process worsens. Alteration in vaso-reactivity may be responsible for the abnormal gestational adaptation associated with preeclampsia.

Thus, nitric oxide is no longer found in sufficient amounts to counterbalance the vasoconstrictor factors, but it rather participates in the formation of peroxy-nitrite which is incriminated in the destruction of endothelial cells. We may conclude that oxidative stress may be one of the multiple dysfunctions that can be incriminated in pathogenesis of preeclampsia and nitric oxide has also an important role in this process.

Conclusions

1. In normal pregnancy it appears a new oxidant/antioxidant balance compared with non-pregnant status, the increase of oxidants being neutralized by the increase of antioxidants.

2. In preeclampsia the oxidant/antioxidant balance does not longer exists and oxidative stress occurs.

3. The decreased level of nitric oxide may contribute to the accentuation of the imbalance of vasoconstrictor and vasodilator factors in preeclampsia that leads to the arterial hypertension that characterises this disease. ■

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