

## Nitric oxide biosynthesis during normal pregnancy and pregnancy complicated by preeclampsia

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### ABSTRACT

**Aim** To investigate biosynthesis in nitric oxide (NO) during normal pregnancy and in pregnancies complicated by preeclampsia.

**Methods** This prospective cross-sectional study included 80 patients hospitalized at the Department of Women's Health, Neonatology and Perinatology Cantonal Hospital in Zenica. Serum NO concentration in 20 non-pregnant women, 40 healthy pregnant women and 20 pregnant women with preeclampsia aged 17-40 years were measured. The group of healthy pregnant women were divided into 4 subgroups by gestational age. For each woman with preeclampsia, a healthy pregnant control was matched for age, parity and gestational age. Serum NO concentrations were determined after reduction of nitrates to nitrites using the Griess reaction.

**Results** NO concentrations during second trimester of pregnancy ( $37.2 \pm 1.7 \mu\text{M}$ ;  $p < 0.05$ ) and third trimester of pregnancy ( $40.9 \pm 2.8 \mu\text{M}$ ;  $p < 0.05$ ) were significantly higher in healthy pregnant women than in non-pregnant women ( $29.3 \pm 1.7 \mu\text{M}$ ). Serum NO concentrations were lower in preeclamptic women ( $30.7 \pm 1.8 \mu\text{M}$ ) compared to matched healthy pregnant women of the third and the late third trimester ( $35.1 \pm 2.2 \mu\text{M}$ ), without significant differences. Mean NO concentrations in pre-eclamptic women was positively correlated with systolic blood pressure ( $r = 0.58$ ;  $p < 0.01$ ), diastolic blood pressure ( $r = 0.45$ ;  $p < 0.05$ ), creatinine clearance ( $r = 0.48$ ;  $p < 0.05$ ), uric acid ( $r = 0.49$ ;  $p < 0.05$ ), and negatively correlated with platelet count ( $r = -0.57$ ;  $p < 0.05$ ).

**Conclusion** NO production was increased with gestational age during normal pregnancy and slightly decreased in preeclampsia suggesting that NO may modulate the cardiovascular changes during normal pregnancy and pregnancy complicated by preeclampsia.

**Key words:** pathogenesis, vasoconstriction, hypertension, pregnancy complications

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## INTRODUCTION

Normal pregnancy is associated with intensive changes in the maternal cardiovascular system that enables adequate oxygen delivery and nutritive ingredients to the fetus. Physiological vascular adaptation (increased blood volume, increased cardiac minute volume and reduced vascular resistance) is followed by increased endogenous production of nitric oxide (NO) and improved response of smooth muscles on the reaction of NO (1,2). Impaired response of the blood vessels on vasoconstrictor agonists during the pregnancy could be partly regulated by NO (3). Recently, in several *in vitro* studies the role of NO in vascular reactivity in pregnancy and preeclampsia has been estimated (4). Choi et al. and Shaamash et al. (5,6) studies showed that the biosynthesis of NO has increased in normal pregnancy, especially in the second trimester, with its peak in the third trimester of pregnancy. However, Hata et al. (7) obtained the results about reduced production of NO, while Brown et al. and Smarason et al. (8,9) showed that there were no changes in the biosynthesis of NO in normal pregnancy compared with non-pregnant women suggesting that the biosynthesis of NO during normal pregnancy still remains controversial. Preeclampsia is considered to be one of the most significant health problems in pregnancy, complicating 6-10% of all gestation over 20 weeks (10). However, World Health Organisation estimates that frequency of preeclampsia is seven times higher in developing countries than in developed countries (11). This disease is one of the leading causes of fetal growth disorders, fetal morbidity and mortality, premature labour and mother's death. Despite numerous findings and surveys, pathophysiology, treatment and early prediction of preeclampsia, it still represents a major challenge in modern medicine (12). Reliable evidence suggests that general vascular endothelial dysfunction, which occurs during preeclampsia can explain mechanism responsible for its pathogenesis. Endothelial cell dysfunction can cause hypertension with its increased production of vasoconstrictor agents such as plasma endothelin or reduced release of vasodilator agents such as prostacyclin and NO (13). NO biosynthesis data are also controversial in preeclampsia. Therefore, some authors obtained different results and they showed that the biosynthesis of NO in preeclampsia was decreased (14,15), unchanged (16,17) and increased (18,9).

The aim of this research was to examine the biosynthesis of NO during normal pregnancy and pregnancy complicated by preeclampsia, as well as factors that influence its production (foods high in nitrates, consuming cigarettes, anaemia, low serum iron and renal function).

## PATIENTS AND METHODS

### Patient and study design

Eighty females aged 17 to 40 who were hospitalized at the Department of Women's Health, Neonatology and Perinatology, Cantonal Hospital Zenica during the period January 2011 to January 2013, were included in this study. The study was approved by the Ethics Committee of the School of Medicine, University of Sarajevo, and all subjects gave informed, written consents. Investigations were carried out in accordance with the Declaration of Helsinki as revised in 2000.

In order to clarify the biosynthesis of NO in normal pregnancy the two groups of were formed: a control group of non-pregnant women (n=20) and the group of healthy pregnant women (n=40). The group of healthy pregnant women was divided into 4 subgroups according to gestational age: the first trimester (1.0-12.0 weeks, n=10), the second trimester (12.1-24.0 weeks, n=10), the third trimester (24.1-32.0 weeks, n=10) and late third trimester (32.1-40.0 weeks, n=10). In order to clarify the biosynthesis of NO in pregnancy complicated by preeclampsia the two groups were formed: a group of pre-eclamptic women (n=20) and the control group of healthy pregnant women in the third and the late third trimester (n=20). The control group of healthy pregnant women were matched to the pre-eclamptic women by age ( $\pm 4$  years old), parity (0,1,2,3 $\geq 4$ ) and gestational age ( $\pm 13$  days). Patients were allowed to take only these medications: antihypertensive (methyldopa), corticosteroids (dexamethasone) and benzodiazepine (diazepam) for which it has been proven not to affect serum NO concentration (9). The patients suffering from chronic diseases such as renal diseases and diabetes mellitus were not included in the research.

### Methods

Body weight, blood pressure and the haematological and biochemical parameters (complete blood count, creatinine clearance, uric acid

level) were measured in all patients using the standard diagnostic methods. Gestational age was calculated from the first day of the mother's last menstrual period. Diagnosis of preeclampsia was made by strict criteria: appearance of blood pressure >140/90 mmHg on at least two consecutive measurements and proteinuria over 300 mg/24 hours which appeared for the first time after 24 weeks of gestation, and disappeared the six months after labour (19).

Serum was prepared from peripheral vein blood, collected between 7 and 10 AM, 24 hours after prescription of diets low in nitrite and nitrate (no spinach, beetroot, cured meats, fish and cheese) followed by overnight fasts. Blood samples for the determination of NO concentrations were diluted 1:1 (vol/vol) with 0.9% saline, protein-precipitated (30% ZnSO<sub>4</sub>, 0.05 mL per mL of blood), centrifuged at 2000 g for 10 minutes and frozen at -20°C until the determination of NO concentrations.

The measurement of NO concentrations in serum was carried out at the Institute of Physiology and Biochemistry, School of Medicine, University of Sarajevo. Conversion of NO<sub>3</sub><sup>-</sup> into NO<sub>2</sub><sup>-</sup> was done with elementary zinc. NO<sub>2</sub><sup>-</sup> concentrations in serum was determined by classic colorimetric Griess reaction (20). Briefly, equal volumes of samples and Griess reagent (N-(1-Naphthyl) ethylenediamine) were mixed at room temperature. After 5 min, the absorbance was measured at 570 nm using Perkin Elmer 550 S spectrophotometer. The concentrations of nitrite were determined by a standard curve prepared with sodium nitrite (NaNO<sub>2</sub>) (1-200 μM).

**Statistical analysis**

Results were expressed as a mean ± SEM. In order to compare the results between comparative groups, one-way analysis of variants (ANOVA) was carried out, followed by post hoc multiple comparisons with Bonferroni adjustment. To assess correlation between serum NO concentrations in pre-eclampsia and various laboratory and clinical parameters the Pearson's coefficient of correlation was calculated as well as Spearman's rank correlation since some of these parameters may not have a normal distribution. The Student's t-test was used to compare NO concentrations of women with pre-eclampsia and pregnant controls. The value of p<0.05 were taken as significant.

**RESULTS**

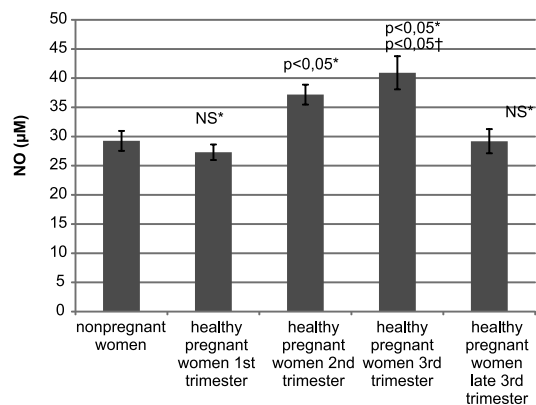
Systolic and diastolic blood pressure of the preeclamptic women showed more values compared with healthy pregnant women in the third and the late third trimester (p<0.05). There was no statistically significant difference in age, body weight and parity between the four studied groups (Table 1).

**Table 1. Clinical characteristics of the women included in the study**

	Clinical characteristics (X±SEM)			
	Non-pregnant women	Healthy pregnant women	Healthy pregnant women in third and late third trimester	Preeclamptic women
Age (years)	36.2±1.2	25.7±0.9	25±1.2	26.6±1.6
Week of gestation	/	23.9±1.9	34±1.3	33.9±1.4
Body weight (kg)	68.3±2.3	70.1±1.6	76.7±1.6	85.6±2.3
Systolic blood pressure (mmHg)	119±1.7	114±1.1	111±1	171±1.8*
Diastolic blood pressure (mmHg)	79.5±1.2	78.6±0.9	77±1.1	107±1*
Parity	1±0.2	1.3±0.1	1.4±0.2	1.6±0.2

\*p<0.05

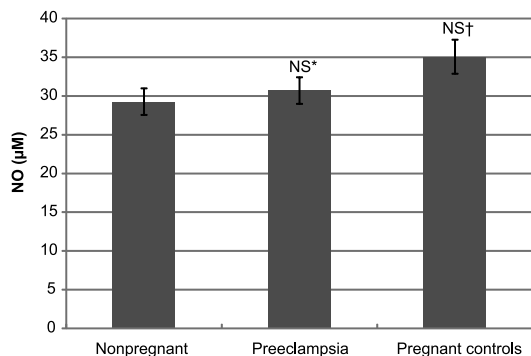
There were no significant differences in serum NO concentration between healthy pregnant women in the first trimester (27.3±1.3μM) and control group of non-pregnant women (29.3±1.7μM). The values of serum NO concentrations in the second trimester (37.2±1.7μM; p<0.05) and the third trimester (40.9±2.8μM; p<0.05) were significantly higher compared to control group of non-pregnant women. In the late third trimester the values of serum NO concentrations in healthy pregnant women (29.2±2.1μM) were not significantly different comparing to control group of



**Figure 1. Serum NO concentrations of nonpregnant (controls) and healthy pregnant women**

\*healthy pregnant women 1<sup>st</sup>, 2<sup>nd</sup>, 3<sup>rd</sup> and late 3<sup>rd</sup> trimester vs non-pregnant women; †healthy pregnant women 3<sup>rd</sup> trimester vs healthy pregnant women 1<sup>st</sup> trimester  
NS, non-significant

nonpregnant women (Figure 1). There was not statistically significant difference in serum NO concentrations between the preeclamptic women ( $30.7 \pm 1.8 \mu\text{M}$ ) and nonpregnant women ( $29.3 \pm 1.7 \mu\text{M}$ ). Serum NO concentrations in the preeclamptic women were lower than in healthy pregnant women of the third and the late third trimester ( $35.1 \pm 2.2 \mu\text{M}$ ). However, this difference was not statistically significant (Figure 2).



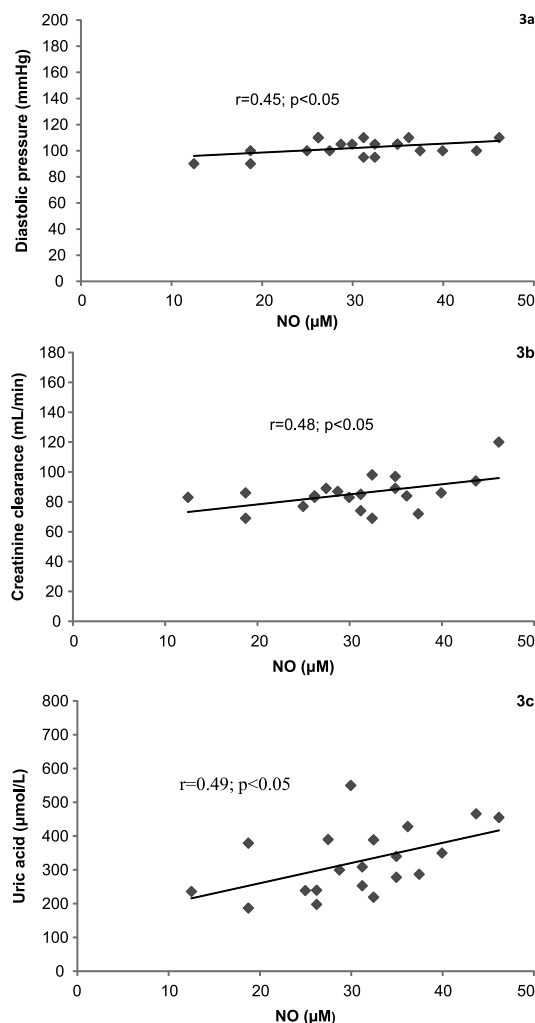
**Figure 2. Serum NO concentration of non-pregnant, preeclamptic and healthy pregnant women in third and late third trimester**

\*preeclamptic vs non-pregnant women; †healthy pregnant women in third and late third trimester vs preeclamptic women  
NS, non-significant

There was a positive correlation between serum NO concentrations and systolic blood pressure ( $r=0.58$ ;  $p<0.01$ ), diastolic blood pressure ( $r=0.45$ ;  $p<0.05$ ), creatinine clearance ( $r=0.48$ ;  $p<0.05$ ), uric acid ( $r=0.49$ ;  $p<0.05$ ), and a negative correlation of platelet count ( $r=0.57$ ;  $p<0.05$ ) of the preeclamptic women (Figure 3). Gestational age, as well as the level of serum iron, were not related to serum NO concentrations.

## DISCUSSION

In our study we found that NO production has increased with gestational age during normal pregnancy and slightly decreased in preeclampsia. These results are in accordance with the results of the authors who also established that the biosynthesis of NO increases in normal pregnancy, especially in the second trimester, with its peak in the third trimester of pregnancy (5,6). However, the results of NO biosynthesis vary in different studies. Hata et al. (7) reported that the level of circulating NO in mother's blood decreases during pregnancy. Brown et al. (8) and Smarason et al. (9) have proved that there is no change in NO production during normal pregnancy com-



**Figure 3. Correlation of NO level with diastolic blood pressure, creatinine clearance, uric acid level and platelet count in serum samples from preeclamptic women. A) positive correlation ( $r=0.45$ ;  $p<0.05$ ) between serum NO concentration and diastolic blood pressure; B) positive correlation ( $r=0.48$ ;  $p<0.05$ ) between serum NO concentration and creatinine clearance; C) positive correlation ( $r=0.49$ ;  $p<0.05$ ) between serum NO concentration and uric acid level; D) negative correlation ( $r=-0.57$ ;  $p<0.05$ ) between serum NO concentration and platelet**

pared to the nonpregnant healthy subjects. From the above examples, we can conclude that the biosynthesis of NO during pregnancy still remains unclear. These discrepancies could be explained by using different methods for the determination of NO in different types of biological tissue (serum, plasma, urine etc.) (21).

Several studies have shown that iron-deficiency anaemia increases production of NO at humans, and that the increased concentrations of NO return to the normal level after supplemental therapy with iron (22). Ni et al. (23) have found that

the level of NO in plasma grows significantly in animal models of iron-deficiency anaemia. Ma-bott et al. (24) have proved that the production of NO correlates directly with development of anaemia and that systemic inhibition of NO synthesis leads to significant increase of haemoglobin concentration in the animal experiments. In order to exclude the effects of iron-deficiency anaemia on the results of serum NO concentrations during normal pregnancy, we analysed serum NO concentrations only in those healthy pregnant women in whom serum iron concentrations did not statistically significantly differ in relation to control group of nonpregnant subjects.

Serum NO concentration of the healthy pregnant women was significantly higher during the second and the third trimester of pregnancy in relation to control nonpregnant subjects, although there was no statistically significant difference in the concentration of serum iron between these groups. Also, there was no statistically significant difference in serum NO concentration between the women with preeclampsia and healthy pregnant women. Our results are in accordance with previous results of Lyall et al. (25) and Davidge et al. (16) who showed no significant difference in serum NO concentrations between the control group of healthy pregnant women and the group of women with preeclampsia. On the other hand, Brennecke et al. (26) and Zeng et al. (15) obtained the results which show the reduced production of NO in the group of women with preeclampsia. Reduced NO serum levels of preeclamptic women could be caused by increased binding and reduced releasing of nitrates from red blood cells (27). However, there are some groups of authors who showed that the biosynthesis of NO became increased at preeclamptic subjects (25), as well as that serum NO concentration in patients with preeclampsia is significantly higher in comparison with the control group of healthy pregnant women (18). These results could be explained in many ways. Food rich in nitrates such as cured meats or vegetables are sources of exogenous nitrates. In these studies, the subjects were not subjected to the long-lasting specific diet which is poor in nitrates, before collecting the serum samples. In our research, all patients with diagnosis of preeclampsia were hospitalized at our department and at a certain time they were at identical

dietary regimen such as the control group of healthy pregnant women of the third and late third trimester. We can ascertain that in our study we were measuring the level of the main metabolite of NO (nitrates and nitrites) in serum, but only at subjects who were subjected to diet poor in nitrates and nitrites.

The severity of preeclampsia is another factor that could explain a disagreement in results of these studies. Cameron et al. (17) found no difference between hypertensive pregnant women and control normotensive groups even though the systolic pressure of hypertensive pregnant women correlated positively with excretion of nitrates and nitrites, similarly as in our study, suggesting that this could be compensatory response in achieving homeostasis. In addition, our research showed a positive correlation between serum NO concentrations and creatine clearance as well as uric acid concentration of the preeclamptic group, which is in accordance with the research of authors who observed the correlation between serum NO concentrations and creatine clearance of patients at intensive care (28). Davidge et al. (16) found no difference in the concentration of nitrates in plasma of healthy and preeclamptic pregnant women, but they proved decreased fractional excretion of nitrates and reduced urinary relation of nitrates and creatine in preeclamptic pregnant women; in non-pregnant healthy women clearance of nitrate was about 20 mL/min suggesting a component of tubular reabsorption. Paşaoğlu et al. (29) showed that serum NO concentrations correlates positively with plasma urate concentration of preeclamptic patients, what is in accordance with our results. Our results showed a negative correlation between serum NO concentrations and platelet count of the preeclamptic group. Beside direct effect on cardiovascular system, NO inhibits the adhesion of monocytes on layers of blood vessels and prevents aggregation of thrombocytes. Under conditions which activate thrombocytes and stimulate the production of thrombin, thrombocytes and endothelial cells release NO, so in that way they restrict thrombus formation and maintain mobility of vascular system. Therefore, NO inhibits mobility and flow of calcium ions in thrombocytes. We can say that our results are in accordance with above-mentioned facts.

In our study, we found that the biosynthesis of NO increases gradually in normal pregnancy and slightly decreases in preeclampsia. Although significant difference of serum NO concentrations between the preeclamptic and healthy pregnant women was not proven, our research shows that NO affects the cardiovascular changes during normal pregnancy and pregnancy complicated by preeclampsia.

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## TRANSPARENCY DECLARATION

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## Biosinteza nitričnog oksida u normalnoj trudnoći i trudnoći kompliciranoj preeklampsijom

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### SAŽETAK

**Cilj** Ispitati biosintezu nitričnog oksida (NO) u normalnoj trudnoći i trudnoći kompliciranoj preeklampsijom.

**Metode** Ovo prospektivno presječno istraživanje obuhvatilo je 80 pacijentica, starosne dobi između 17 i 40 godina, koje su bile hospitalizirane na Službi za ženske bolesti, perinatologiju i neonatologiju Kantonalne bolnice Zenica. Ispitivana je koncentracija NO u serumu 20 negravidnih žena, 40 zdravih trudnica i 20 trudnica s preeklampsijom. Grupa zdravih trudnica bila je podijeljena u 4 podgrupe prema gestacijskoj dobi. Za svaku pacijenticu s preeklampsijom uzeli smo kontrolnu zdravu trudnicu koja je odgovarala po starosnoj dobi, paritetu i gestacijskoj dobi. Nivo NO u serumu određivali smo mjerenjem koncentracije nitrita korištenjem klasične kolorimetrijske Griessove metode.

**Rezultati** Vrijednosti serumske koncentracije NO zdravih trudnica u drugom ( $37.2 \pm 1.7 \mu\text{M}$ ;  $p < 0.05$ ) i trećem trimestru ( $40.9 \pm 2.8 \mu\text{M}$ ;  $p < 0.05$ ) bile su statistički signifikantno više u odnosu na kontrolnu grupu negravidnih ispitanica ( $29.3 \pm 1.7 \mu\text{M}$ ). Serumska koncentracija NO grupe ispitanica s preeklampsijom ( $30.7 \pm 1.8 \mu\text{M}$ ) bila je niža u poređenju s kontrolnom grupom zdravih trudnica trećeg i kasnog trećeg trimestra ( $35.1 \pm 2.2 \mu\text{M}$ ). Međutim, ova razlika nije bila statistički signifikantna. Utvrđena je pozitivna korelacija između serumske koncentracije NO i sistolnog pritiska ( $r = 0.58$ ;  $p < 0.01$ ), dijastolnog pritiska ( $r = 0.45$ ;  $p < 0.05$ ), klirensa kreatinina ( $r = 0.48$ ;  $p < 0.05$ ), urične kiseline ( $r = 0.49$ ;  $p < 0.05$ ), te negativna korelacija nivoa trombocita ( $r = -0.57$ ;  $p < 0.05$ ) grupe ispitanica s preeklampsijom.

**Zaključak** Biosinteza nitričnog oksida se postepeno povećavala u normalnoj trudnoći, a blago smanjivala u preeklampsiji. Rezultati ukazuju da nitrični oksid utječe na kardiovaskularne promjene tokom normalne trudnoće i trudnoće komplicirane preeklampsijom.

**Ključne riječi:** patogeneza, vazokonstrikcija, hipertenzija, komplikacije u trudnoći