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Nitric Oxide Synthesis in Placenta is Increased in Intrauterine Growth Restriction and Fetal Hypoxia

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A B S T R A C T

In order to study the possible role of nitric oxide (NO) in the human placenta, we measured the concentration of its stable metabolite nitrite (NO_2^-) in the placentas of women with normal pregnancies and those from pregnancies complicated by intrauterine growth restriction (IUGR) with or without fetal hypoxia. We have measured nitrites by the Griess reaction in 15 placentas from IUGR pregnancies and 12 controls. Cerebroumbilical ratio (C:U) was recorded by color Doppler ultrasound and values below 1 were considered to be a predictor for fetal hypoxia. NO_2^- levels measured in pathological placentas were increased for at least 93 % as compared to control. Subjects from pregnancies complicated by IUGR and fetal hypoxia had increased NO_2^- as compared to the placentas from pregnancies with IUGR and normal fetal oxygenation. NO production in placenta is increased in pregnancies with IUGR. This effect is more pronounced in those with compromised fetal oxygenation.

Key words: *nitric oxide, IUGR, fetal hypoxia*

Introduction

The sufficient blood supply with oxygen and nutritive substances is essential for the normal growth and development of the fetus. Deprivation of oxygen and nutrients leads to intrauterine growth restriction (IUGR) and fetal hypoxia. Newborns with IUGR are at increased risk to develop a metabolic syndrome later in life, namely obesity, arterial hypertension, hypercholesterolemia and cardiovascular disease and diabetes mellitus type 2[1]. Acute and chronic hypoxic insults are the leading causes of perinatal brain damage, as well as the fetal and neonatal morbidity and mortality[2,3]. Placental insufficiency that is characterized by altered fetoplacental circulation is considered to be the main cause of fetal growth restriction and hypoxia[4]. According to literature, placenta lacks autonomic innervations and placental blood flow is regulated by humoral agents (e.g. endothelin-1, prostaglandins, tromboxane A_2) and certain autocrine-paracrine mechanisms[5–8]. Nitric oxide is thought to be the most important vasodilatator in placenta and uterus[9]. Its function is to regulate vascular tone, to attenuate the effect of vasoconstrictors such as tromboxane A_2[10] and endothelin-1[11,12] and to limit platelet adhesion and aggregation[13]. Nitric oxide is generated from the metabolism of L-arginine by the enzyme nitric syntethase (NOS)[14]. The constitutive isoform of NOS has been found in the endothelial cells of arteries and veins of umbilical cord and chorionic plate[15]. Nitric oxide diffuses from generating cells to underlying vascular smooth muscle cells and activates guanilate--cyclase, thus initiating chain of biochemical reactions, which reduce Ca^{2+} entrance in smooth muscle cells. The results are relaxation of those cells and consequently, vasodilatation[16].

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Nitric oxide production is regulated by various humoral agents and mechanical stimuli such as shear stress[17,18]. Some studies have shown that shear stress, which can be induced by altering arterial blood flow and/or by increased viscosity, can increase NO generation in placenta[18]. Experimental results have indicated that angiogenic peptide vascular endothelial growth factor (VEGF) stimulates the proliferation and NO production in endothelial cells and increases their permeability[19–21]. VEGF shares significant sequence homology (53%) at the amino acid level with placental growth factor (PIGF), which inhibits basal release of NO from trophoblast during the first trimester of gestation[17,22]. Hormones such as cortisol[23], estrogen and progesterone[24], atrial natriuretic peptide (ANP)[25], as well as angiotensin[26] also participate in NO production. Even the certain vascoconstrictors such as endothelin, may mediate a paradoxical vasodilatation. Their interaction with some endothelial receptors results with the release of the relaxation factor such as NO and prostacyclin PGI_2[27–29]. All those humoral factors could be very important during pregnancy as well as during normal menstrual cycle[17].

Some results indicate that in pathological conditions, such as preeclampsia and intrauterine growth restriction, the increased vascular resistance in placental bed might be the result of the impaired production of NO[30]. On the other hand, the higher production of NO might be compensatory response in preeclampsia and IUGR, which leads to vasodilatation and insures the supply of the fetus with oxygen and nutritive substances[31]. In support to these findings, other researchers have reported higher levels of NO metabolites in those pathological conditions[32,33]. Obviously, the reports of the effect of NO in IUGR and preeclampsia are still quite controversial and its real contribution to these conditions remains to be elucidated.

Fetus is able to activate a wide specter of cardiovascular, biophysical, biochemical and endocrinological adaptive mechanisms in reaction to hypoxia. Fetal cardiovascular responses to hypoxia are considered the most important adaptive mechanisms responsible for maintaining fetal homeostasis. They are coordinated to redistribute blood flow to organs important for the survival of the fetus, such as the brain, heart and adrenals[34]. This redistribution of fetal blood flow can easily be detected by Doppler ultrasound. The modifications of placental hemodynamics, responsible for IUGR and hypoxia, can be quantified using the umbilical resistance index (URI), measured on the umbilical arterial velocity waveforms. The cerebrovascular adaptation (vasodilatation) can be assessed using the cerebral resistance index (CRI), measured on the middle cerebral artery velocity waveforms[35]. Many studies have shown that the best indicator of the fetal blood flow redistribution between the placenta and the brain is cerebro-umibilical ratio (C:U ratio=CRI:URI)[35,36]. Namely, in uncomplicated pregnancies, vascular resistance in cerebral arteries remains higher than in umbilical arteries; therefore C:U ratio is always higher than 1[36, 37]. If any blood flow redistribution in favor of the fetal brain occurs, the C:U ratio becomes less than 1. Moreover, it is one of the most sensitive parameters for detection and quantification of fetal hypoxia[38]. It has been shown that the decrease in C:U ratio (below 1) strongly correlates with the reduction in pO_2 in fetal blood during acute[39] as well as chronic hypoxia[40].

The aim of our study was to assess the umbilical hemodynamic changes and the blood flow redistribution towards the fetal brain in growth restricted fetuses and to determine the concentrations of NO metabolites in placentas from pregnancies complicated by growth restriction with or without fetal hypoxia.

Materials and Methods

Patients

The study included pregnant women with normal, term delivery (n=12) and women with pregnancies complicated by IUGR (n=15) from 33 to 42 weeks of gestation. The term intrauterine growth restriction was defined as an estimated fetal weight (calculated on the basis of ultrasound fetal biometry) below the 10^{th} percentile for the local reference values for gestational age and gender, and at the same time growth rate slower than normal along a standardized growth curve[41]. Maternal and fetal clinical characteristics, which were taken into consideration, where age, parity, nicotine abuse and fetal sex. The pregnancy outcome was assessed according to the mode of delivery, gestational age, birth weight, birth length and placental weight. Patients with hypertension (blood pressure in three consecutive measurements over 130/85 mmHg), preeclampsia, diabetes mellitus, chorioamnionitis or any type of maternal infections were excluded from our study. Fetuses with congenital anomalies and suspected intrauterine infections were also excluded from the study. The study was conducted in the Clinical Hospital Sestre Milosrdnice Zagreb, Croatia and was approved by the local ethical committee.

Placental tissue collection and preparation of villous homogenate

Placental tissue samples were taken immediately upon delivery. Three tissue blocks (20 × 20 mm), one in close proximity to the umbilical cord insertion and two from randomly chosen spots at the periphery, were cut from each placenta and used for determination of NO metabolites. Three different samples were taken from each placenta assuming that blood flow perfusion varies in different parts of placenta. Placental samples were washed in PBS and 1.5 grams of wet tissue weight were taken from each sample. The samples were manually homogenized and then centrifuged for 10 minutes at 3000 RPM. The supernatants were deproteinized with $ZnSO_4$ and after centrifugation prepared for determination of NO metabolites.

Determination of NO metabolites

NO_2^- concentration was determined using the classical Griess reaction[42]. Briefly, 0.1 ml of placental homogenates was pipetted into the wells of flat-bottomed 96-well microtitration plates, followed by addition of 0.1 ml of Griess solution. The plate was shaken for 10 min at room temperature, after which purple color developed in positive plates. The plates were read in a microplate reader at optical density of 550 nm.

Chemicals

The following chemicals were used for sample preparation and determination of NO metabolites: PBS, zinc--sulfate ($ZnSO_4$) and Griess solution. Griess reagent was formed of 2% sulfanilamide in N-1-naphthylethylenediamine and 0.2% sulfanilamide in distillated water. Griess solutions were purchased by Sigma, St Louise, USA and zinc-sulfate was purchased by Kemika, Zagreb, Croatia.

Doppler indices

Intrauterine growth restriction (n=15), detected by ultrasound biometry, was an indication for color Doppler assessment. Examinations were carried out using the Aloka 2000 (Aloka, Japan) ultrasonic device with transabdominal probe, with a frequency of 3.5 and 5 MHz (maximum emission energy of the device is below the limits approved for use in fetal medicine, SPTA <80 mW/cm^2 for B mode). Blood flow velocity waveforms were recorded from the umbilical artery and middle cerebral artery by serial measurements with an interval of at least one week in the period from 33 weeks of gestation until delivery. Changes in the placental hemodynamics were quantified by using the umbilical artery resistance index (URI) and cerebrovascular adaptation was quantified by using the middle cerebral artery resistance index (CRI). The resistance indices were calculated on the basis of Doppler records of at least 6 sequential heart cycles. The blood flow redistribution between the placenta and the brain was detected and quantified by the C:U ratio expressed as CRI:URI.

TABLE 1
QUALITATIVE CLINICAL PARAMETERS OF PATIENTS WITH NORMAL PREGNANCIES AND PATIENTS WITH INTRAUTERINE GROWTH RESTRICTION (IUGR)

Parameters	Control (n=12)	IUGR (n=15)
Parity (No)		
Primigravid	8	7
Multigravid	4	8
Fetal sex (No)		
Male	6	6
Female	6	9
Mode of delivery (No)		
Vaginal	11	4
Cesarean section	1	11*
Nicotin abuse (No)		
Smokers	2	4
Non-smokers	10	11

Statistically significant differences are indicated by * (P<0.05), No number

Statistics

The Mann-Whitney test was used to compare the concentrations of NO metabolites between control and IUGR group. The same test was used to assess the differences in NO production between two subgroups of IUGR: one with C/U<1 and second with C/U>1. Quality variables such as: parity, mode of delivery, fetal sex and nicotine abuse between pregnant women with uncomplicated, in term delivery and women with fetal growth restriction were compared by using Fisher's Exact test. Quantitative variables such as: maternal age, gestational age, birth weight, birth length and placental weight between women with complicated, in term delivery and women with IUGR were compared by using Mann-Whitney test. To assess if there were differences between concentrations of NO metabolites from three samples (one insertion and two from periphery) Friedman test was used. In all tests, differences were considered to be significant if $P<0.05$.

Results

Patient characteristics of our interest were divided into qualitative and quantitative variables. Qualitative clinical characteristics: parity (primigravid or multigravid), mode of delivery (vaginal or Cesarean section), fetal sex (male of female) and nicotine abuse (smokers or non--smokers) are shown in Table 1. Quantitative characteristics: maternal age, gestational age, birth weight, birth length and placental weight are shown in Table 2. There were no significant differences in parity, fetal sex and nicotine abuse between uncomplicated pregnancies and pregnancies with lUGR. Those findings allowed us to make comparisons between these two groups. Regarding the nicotine abuse, the number of cigarettes smoked per day was not recorded. Also, the majority of our patients (Table 1) were non-smokers. Potential influence of nicotine abuse on NO production has to be investigated on a larger population.

The pregnancy outcome was worse in the IUGR group. We found significant differences in mode of delivery (vaginal or Caesarean section) between IUGR and control group. Namely, the number of Caesarean sections for fetal distress was significantly higher in IUGR group (Table 1). Furthermore, the gestational age was shorter and the newborn and placental weight was decreased in the pregnancies complicated by IUGR. Birth length was significantly shorter in IUGR than in the control group ($P<0.05$, Table 2). The mean maternal age was significantly higher in the IUGR group ($P<0.05$, Table 2).

The mean total concentration of nitrites measured in the placental supernatants was about 15 times higher in the IUGR group than in the control group (Figure 1). The results showed that there were no significant differ-

TABLE 2
QUANTITATIVE CLINICAL PARAMETERS OF PATIENTS WITH NORMAL PREGNANCIES AND PATIENTS WITH INTRAUTERINE GROWTH RESTRICTION (IUGR)

Parameters	Mean	Stanard Error	Median	Range	Minimum	Maximum
Maternal age (years)						
Control	25.7	1.4	25	19	19	38,8
IUGR	29.7*	1	29	15	23	38
Gestational age (weeks)						
Control	39.9	0.3	40.3	3	38.5	41.5
IUGR	36.7*	0.5	36.5	6	33.5	39.5
Birth weight (g)						
Control	3416.7	92.1	3340	920	2980	3900
IUGR	2191.3*	103.8	2220	1300	1400	2700
Birth length (cm)						
Control	50.3	0.6	50	8	47	55
IUGR	44.8*	0.6	46	8	40	48
Placental weight (g)						
Control	547.5	16.5	510	150	500	650
IUGR	407.3*	21.8	440	290	210	500

Statistically significant differences are indicated by * ($P<0.05$)

ences in concentration of NO metabolites between center and periphery of placentas (Figure 1).

All patients with pregnancies complicated with IUGR had increased values of URI (Figure 2), which lead us to conclusion that their placental perfusion was compromised and pathological. The IUGR group was subdivided according to the value of C:U ratio into two subgroups: one with the C:U<1 (n=7) and the other with C:U ≥ 1 (n=8). Cerebral-umbilical ratio less then 1 indicated the fetal blood flow redistribution towards the brain as a response to fetal hypoxia.

Total nitrites levels were examined separately in each subgroup (Table 3). It was found clearly that NO production was significantly higher in placentas of patients with C:U<1 as compared to the patients with C:U ≥ 1 ($P<0.05$).

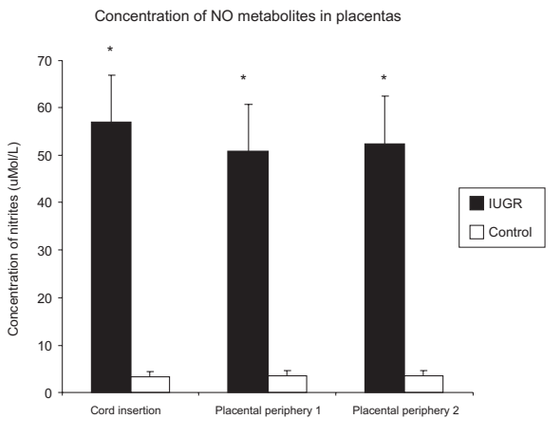

*Fig. 1. Mean total concentrations of nitric oxide (NO) metabolites in three samples of placenta (one from umbilical cord insertion and two from periphery), bars indicate standard error of the mean. Statistically significant differences are indicated by * (P<0.05).*

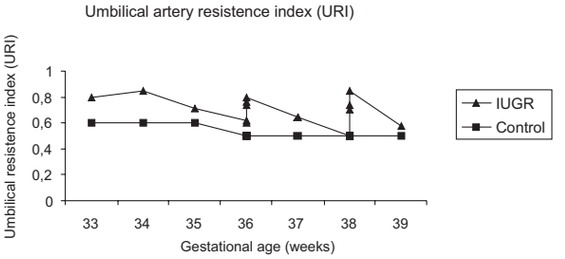

Fig. 2. Changes of umbilical artery resistance index (URI) measured by Doppler assessment through gestation in patients with intrauterine growth restriction (IUGR) as compared to control.

Discussion

Intrauterine growth restriction is a common clinical problem which can lead to long-term metabolic consequences, such as an increased propensity for some of the most common diseases of adult life[43]. Among the many potential underlying processes, placental insufficiency is believed to be the most important cause of intrauterine growth restriction[44,45]. We showed that placentas from pregnancies complicated by IUGR had decreased weight as compared to control (Table 2). Many authors have reported that placentas from pregnancies complicated by IUGR never reach their total growth potential. They are smaller, circulatory compromised and therefore cannot fulfill their nutritional function[44,46]. Furthermore, in pregnancies complicated by lUGR placenta is often rec-

TABLE 3
TOTAL NITRITE LEVELS IN PLACENTAS OF PATIENTS WITH INTRAUTERINE GROWTH RESTRICTION (IUGR)

Cerebro- umbilical ratio (C/U)	C/U<1 (N=7)	C/U ≥1 (N=8)
Placental total nitrites (μMol/L)	69.75 ± 18.85*	39.15 ± 8.83

Patients with IUGR pregnancies are subdivided into two groups according to the cerebro-umbilical ratio (C/U): C/U<1 and C/U≥1. Date are given as mean ± standard error of the mean. Statistically significant difference is indicated by* (P<0.05).

ognized as being in a state of villous immaturity for gestational age and having terminal villi deficiency[47].

The relationship between maternal and fetal circulation in the placenta is crucial for efficient exchanges of oxygen and nutrients[48]. Since placenta lacks nervous autonomic innervations, humoral factors are considered to be the most important blood flow regulators. Different humoral factors are considered to have an affect on NO production in the human organism[17–22]. Since NO has short half-life, we have measured the concentration of its stable metabolites nitrite by the Griess reaction. The Griess reaction was previously shown to be sensitive for determination of these molecules[42]. Our results, rather higher concentrations of NO_2^- in samples of placentas from pregnancies with IUGR and fetal hypoxia (Figure 2), implicate the activation of compensatory blood flow regulation mechanisms on the placental level. It means that the increase in NO production could be one of the compensatory reactions to reduced placental blood flow and hypoxia. Some investigators have shown reduced output of nitric oxide in pregnancies with IUGR[49,50], while in several other studies concentration of NO metabolites was increased as compared to normal[51,52]. Nevertheless, we have to emphasize that in all of these studies, concentration of NO metabolites was measured from maternal serum and umbilical vein. However, none of the investigators used placental tissue for measurements of NO concentration in IUGR pregnancies. Shaamash et al.[31] used placental tissue, but in pregnancies complicated by pre-eclampsia and eclampsia. They also reported higher concentrations of NO metabolites in patients with preeclampsia and eclampsia as compared to normal pregnancies[31].

Normal placental function depends on maintenance of uteroplacental perfusion[48]. Our previous studies have revealed the existence of physiological cardiovascular compensatory mechanisms on the placental level that protect the fetal vital organs, particularly the brain, during hypoxia[4,53]. That results in the blood flow redistribution in favor of the fetal brain which can be detected and quantified using the C:U ratio. That ratio takes into account umbilical vascular resistance and the cerebral response to hypoxia. Values of C:U ratio less than 1 are considered as an indicator of compromised fetal oxygenation. We detected increase of umbilical vascular resistance in our patients with IUGR (Figure 2) which is thought to be the result of the disturbed placental perfusion. Such increase is often detected in color Doppler studies of pregnancies complicated by IUGR[37,39]. Arabin and co-workers found that only 7% of placentas with absent end-diastolic umbilical flow were normal[54]. They noted evidence of chronic placental insufficiency, manifested by small placental villi, fibrosis and microfibrinous deposits in 74% placentas. The remaining 19% showed a reduced perfusion capacity. This increase of impedance to flow in the umbilical artery is associated with hypoxia and a poor perinatal outcome[54].

We found the difference in NO production between the two subgroups of IUGR divided according to the value of C:U ratio (Table 3). Placental NO was released in significantly higher amounts in IUGR pregnancies with disturbed fetal oxygenation (C:U ratio less then 1) as compared to the IUGR control pregnancies (C:U ratio more then 1). Our results suggested that placental NO production depends on the severity of IUGR, as indicated by fetal oxygenation, at least when it is not accompanied with other pathological conditions, such as preeclampsia. To our knowledge, this study is first to assess the NO production in pregnancies with lUGR according to the C:U ratio, as the indicator of fetal oxygenation. Most of the authors assess the placental function according to the umbilical resistance indices[55,56]. However, only the strong disturbances of umbilical resistance, such as absent end diastolic blood flow, have a good sensitivity in the assessment of fetal condition[55]. The fetal oxygenation can be either normal or decreased in case of the somewhat compromised placental function and slightly increased umbilical resistance. The most precise evaluation of fetal pO_2 could be obtained using the C:U ratio. It takes into account the fetal cerebrovascular response to hypoxia, as well as the placental impairment[53,57]. Moreover, C:U ratio is used for calculation of hypoxia index (the sum of daily reductions in C:U ratio over the period of observation) which is suggested to be predictor of a poor neurological outcome in pregnancies complicated by growth restriction and hypoxia[58].

To summarize, our results have shown a significant increase in total placental nitrite production in pregnancies complicated by IUGR, especially when is accompanied with fetal hypoxia. Such increase possibly represents a physiologic adaptive response to overcome the increase placental vascular resistance. Our conclusion is that NO plays an important role in the activation of compensatory blood flow regulation mechanisms on the placental level during IUGR and fetal hypoxia.

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SINTEZA DUŠIKOVOG MONOKSIDA U POSTELJICI JE POVEĆANA KOD INTRAUTERINOG ZASTOJA U RASTU I FETALNE HIPOKSIJE

SAŽETAK

Kako bismo istražili moguću ulogu dušikovog monoksida (NO) u ljudskoj posteljici mjerili smo koncentracije njegovih stabilnih metabolita nitrita (NO_2) u posteljicama žena s normalnim trudnoćama, kao i kod onih s fetalnim zastojem u rastu sa ili bez hipoksije. Koncentraciju nitrita određivali smo pomoću Griessove reakcije kod 12 posteljica iz trudnoća kompliciranih zastojem u rastu, te kod 12 kontrola. Cerebroumbilikalni omjer (C/U) određivan je pomoću ultrazvučnog obojenog Dopplera, a njegove vrijednosti manje od 1 smatrane su dobrim pokazateljima fetalne hipoksije. Vrijednosti NO_2^- mjerene u posteljicama iz patoloških trudnoća su najmanje za 93 % uvećane u usporedbi s kontrolom. Štoviše, posteljice iz trudnoća s fetalnim zastojem u rastu i fetalnom hipoksijom imaju znatno veće koncentracije NO_2^- u usporedbi s posteljicama s fetalnim zastojem u rastu, ali s normalnom fetalnom oksigenacijom. Stvaranje dušikovog monoksida je povećano u posteljicama trudnoća s fetalnim zastojem u rast. Taj je efekt još izraženiji ako je, uz zastoj u rastu, kompromitirana i fetalna oksigenacija.