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Effect of L-arginine on nitric oxide levels of maternal and neonatal umbilical blood in intrauterine growth retardation

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Abstract: Objective It has been reported that nitric oxide (NO) might play an important role in the development of intrauterine growth retardation (IUGR). This paper aims at investigating the effect of L-arginine (L-Arg) on NO levels of maternal and neonatal umbilical blood in IUGR. **Methods** Sixty-six pregnant women with IUGR were recruited. Thirty-six cases were given routine therapy (Routine therapy group), and the other 30 cases were given L-Arg combined with routine therapy (L-Arg group). Another 30 cases with normal pregnancy were used as Normal control group. The NO levels of maternal and neonatal umbilical blood were monitored before and after treatment. **Results** After the treatment, the maternal serum NO level in the L-Arg group was significantly higher than that of the Routine therapy group (58.42 ±23.12 μmol/L vs 43.49 ±20.27 μmol/L) ($P < 0.01$). The umbilical blood NO level in the L-Arg group was alao significantly higher than that of the Routine therapy group (25.23 ±12.05 μmol/L vs 16.95 ±11.19 μmol/L) ($P < 0.01$). **Conclusion** L-Arg can increase serum NO levels of both maternal and umbilical blood in IUGR.

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Key words: Intrauterine growth retardation; Nitric oxide; L-arginine

L-精氨酸对胎儿宫内发育迟缓患者母血及脐血一氧化氮水平的影响

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[**摘　要**] **目的**　有研究表明一氧化氮(NO)减少可能在胎儿宫内发育迟缓(IUGR)的发生发展中起重要作用,该文探讨L-精氨酸(L-Arg)对IUGR孕妇外周血及新生儿脐血中NO水平的影响。**方法**　选择IUGR孕妇66例,其中常规治疗组36例,予以常规治疗;L-Arg组30例,在常规治疗的基础上加用L-Arg治疗。选择正常初产妇30例作为正常对照组。监测治疗前后孕妇血清NO水平变化及脐静脉血清NO水平。**结果**　治疗后,L-Arg组孕妇血清NO水平显著高于常规治疗组(58.42 ±23.12 μmol/L vs 43.49 ±20.27 μmol/L)($P < 0.01$);L-Arg组胎儿脐静脉血清NO水平显著高于常规治疗组(25.23 ±12.05 μmol/L vs 16.95 ±11.19 μmol/L)($P < 0.01$)。**结论**　L-Arg能显著提高IUGR孕妇外周血及脐血中NO水平。　[**中国当代儿科杂志,2004, 6(1): 4-6**]

[**关　键　词**]　宫内发育迟缓;一氧化氮;L-精氨酸

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Intrauterine growth retardation (IUGR) is associated with elevated perinatal mortality and morbidity[1]. So far, the exact mechanism of IUGR has not been fully elucidated. However, an abundance of evidence is now available supporting the notion that a deficiency of nitric oxide (NO) may play an important role in the development of IUGR[2,3]. L-arginine (L-Arg) the precursor of NO, was administered to pregnant women with IUGR and the effects of L-Arg on serum NO levels of maternal and umbilical blood

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were investigated in this study.

Materials and methods

Subjects

Sixty-six pregnant women, who were normotensive, nonsmoking, non-alcohol or drug consuming with 26 to 36 weeks of gestation complicated by IUGR from Sept, 2002 to Mar, 2003, were enrolled in this study. Intrauterine infection, pre-eclampsia, diabetes, fetal malformation or any pregnancy combined diseases were not found among them. All pregnancies were singleton and head presentation. Gestational age was confirmed by the first trimester ultrasound scan. Asymmetrical IUGR was diagnosed when the ratio of fetal head circumference (HC) to abdominal circumference (AC) was above the 95th centile[4] or when the ratio of femoral length (FL) to AC was more than 0.24[4]. These women were randomly divided into 2 groups: the L-Arg group (n = 30) and the Routine therapy group (n = 36). In addition, 30 normal pregnancies with 26 to 36 weeks of gestation were used as the Normal control group. Differences in age, height, weight index, systolic blood pressure, diastolic blood pressure, gestational age at the first scan, gestational age at delivery and the interval between the first scan and delivery among these 3 groups were not statistically significant.

Treatments

The Routine therapy group was given a series of medications and remedies during the 7 days course of treatment[5]: (1) left leaning position; (2) oxygen therapy 30 min (tid); (3) 10% glucose 500 ml + ATP 40 mg + CoA 100 u by vein drip (qd); (4) amino acids injection 500 ml by vein drip (qd); (5) dextran 500 ml + danshen injection 8 ml by vein drip (qd); (6) oral salbutamol 2.4 mg (q8h); (7) 5% glucose 500 ml by vein drip (qd). Besides the above treatments, the L-Arg group was given L-Arg (Chinese Xin Yi Drug Factory, Shanghai) 20 g per day that deluted in the injection of 5% glucose via intravenous drip.

Detection of NO levels

As for the pregnants with IUGR, 2 ml blood samples were collected 2 hours prior to the treatments and 24 hours after the treatments. As for all subjects, 2 ml umbilical venous blood samples were collected right after the delivery of placentas. These samples were centrifuged at 3 000 revolutions/min for 10 minutes and the supernatants were stored at -20 ℃ for later analysis of NO levels. The NO levels were assayed via a commercial kit (Jiancheng Biological Engineering Institution, Nanjing, China) strictly according to the instructions.

Statistical analysis

All the data were expressed as mean ± standard deviation. One-way ANOVA, Stundent's *t* test and χ^2 test were used to analyze the differences of the results with SPSS 10.0 soft ware.

Results

The NO levels in maternal serum

Before treatments, there was no statistical difference of maternal serum NO levels between the L-Arg group and the Routine therapy group, but both were lower than that of the Normal control group ($P < 0.01$). After one course of treatment, the maternal serum NO level of the L-Arg group was significantly higher than that of the Routine therapy group ($P < 0.01$) (Table 1).

Table 1 Comparison of maternal serum NO levels among 3 groups ($\bar{x} \pm s$, μmol/L)

Groups	NO	
	Before treatment	After treatment
Normal control group	75.03 ± 11.12	
Routine therapy group	19.17 ± 5.15[a]	43.49 ± 20.27
L-Arg group	20.25 ± 5.50[a]	58.42 ± 23.12[b]

Note: a vs the Normal control group $P < 0.01$; b vs the Routine therapy group $P < 0.01$

The NO levels in neonatal umbilical blood

The NO level of neonatal umbilical blood in the L-Arg group (25.23 ± 12.05 μmol/L) was markedly higher than that of the Routine Therapy group (16.95 ± 11.19 μmol/L) and lower than that of the Normal control group (41.01 ± 12.49 μmol/L), and the differences were significant; respectively ($P < 0.01$).

Discussion

The endogenetic NO is synthesized from L-Arg through nitric oxide synthase (NOS). Yallampalli et al[2] have reported that there was a L-Arg-NO-cGMP system in the utero-placental tissues in pregnant rats which played a key role in maintaining adequate feto-placental perfusion and was crucial for fetal growth and health. As an important intercellular messenger, NO can inhibit platelets adhesion and congragation[2]. It was demonstrated that prolonged blockade of NO synthesis caused by L-nitro-arginine methyl ester (L-NAME) (a NO inhibitor) in gravid rats can lead to IUGR and the severity of IUGR may be associated with the dosage of L-NAME[6]. Another study[7] has also showed that the NO levels of peripheral blood and placental tissue in gravid rats complicated by IUGR were dramatically lower than those in normal controls. The NO levels of maternal and umbilical blood in pregnancies with IUGR were markedly lower than those in normal pregnancies in this study. It suggested that increasing the production of NO in vivo may be crucial in treating IUGR.

It has been proved that the level of L-Arg was pivotal in modulating the activation of NOS in vascular endothelial cells and vascular smooth muscle cells, and the release of NO could be induced by increasing L-Arg concentration in blood[8]. Wu HY, et al[9] have discovered that the endothelin (ET) level reduced in pregnant rats with IUGR after L-Arg therapy, while the fetal weight, the NO level and the ratio of NO to ET increased, which suggested that L-Arg took effects by altering the concentrations of vasoactive substances. Neri et al[10] have reported that L-Arg can notably improve feto-placental circulation and increase NO and growth hormone levels in maternal blood of the IUGR pregnancies with increased resistance in utero-placental circulation.

The NO levels of maternal serum and umbilical vein blood in the L-Arg group were significantly higher than those in the Routine therapy group in this study. It was speculated that inadequate NO production might exists in pregnancies with IUGR, and that L-Arg can promote fetal growth by raising production and/or release of NO and improve feto-placental circulation. Moreover, any apparent side effects of L-Arg were not found. L-Arg may be a promising drug in the treatment of IUGR.

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