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OXIDANT AND ANTIOXIDANT STATUS IN SMOKING MOTHERS AND THEIR NEWBORNS

(Literature review)

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Summary

Environmental tobacco smoking is known to be associated with adverse pregnancy outcomes. Maternal cigarette smoking accompanied with fetal and neonatal growth restriction causes abnormalities in organ development in the postnatal life. Smoking cessation influences the risk of infant death. Placenta tissue may be a major source of lipid peroxidation (LPO) products in pregnancy. Increased lipid peroxidation and reduced antioxidant activity may contribute to the development of complications in pregnancy. Associations between both maternal smoking and infant irritability and later behavioral dysregulation have important implications for early identification and intervention with at-risk offspring.

Rezumat

Statutul oxidant și antioxidant la mamele fumătoare și nou-născuții lor

Este cunoscut faptul că fumatul de tutun este asociat cu modificări adverse în timpul sarcinii. Fumatul matern asociat cu restricțiile de creștere fetală și neonatală provoacă anomalii în dezvoltarea de organe în viața post-natală. Renunțarea la fumat influențează riscul de deces pentru sugari. Țesutul placentar poate fi o sursă majoră de produse de peroxidare a lipidelor în timpul sarcinii. Mărirea peroxidării lipidelor și activitatea antioxidantă redusă poate contribui la dezvoltarea complicațiilor în timpul sarcinii. Asociațiile dintre fumatul matern și iritabilitatea infantilă cu dereglările tardive de comportament au implicații importante pentru identificarea și intervenirea timpurie a urmașilor grupei de risc.

There have been a few studies that examined the oxidative stress effects of nicotine during pregnancy and lactation. The adverse effect of prenatal smoking exposure on human fetal development and growth has been a major public health issue. Active or passive smoking during pregnancy can result in a wide variety of adverse outcomes, including intrauterine growth retardation (IUGR), prematurity, stillbirth, and the sudden infant death syndrome. Smoking in pregnancy has also been associated with an increased risk of attention deficit and learning problems in childhood. Oxidative stress in smoking pregnant women is assumed to be enhanced by oxidants and free radicals of tobacco smoke.

Maternal smoking during pregnancy greatly enhances perinatal morbidity/mortality and is the major risk factor for Sudden Infant Death Syndrome (SIDS). Slotkin T. et al. [24] studies in developing rodents indicate that nicotine is a neuroteratogen that targets monoamine pathways involved in the responses to hypoxia.

Smoking and severe asthma exacerbations in pregnancy are risk factors for low birth weight babies. No studies have assessed the clinical implications of smoking on asthma exacerbations in pregnancy. During pregnancy, asthma exacerbations are more common and more severe in current smokers than never smokers. The risk of effects of maternal asthma on the fetus may be greater among smokers. [16]

Pregnancy places increased demands on the mother to provide adequate nutrition to the growing conceptus. A number of micronutrients function as essential cofactors for or themselves

acting as antioxidants. Oxidative stress is generated during normal placental development; however, when supply of antioxidant micronutrients is limited, exaggerated oxidative stress within both the placenta and maternal circulation occurs, resulting in adverse pregnancy outcomes. Mistry H. and colab. [15] summarized the current understanding of selected micronutrient antioxidants selenium, copper, zinc, manganese, and vitamins C and E in pregnancy. They wrote about antioxidant activity of selenium via its incorporation into the glutathione peroxidase enzymes, levels of which have been shown to be reduced in miscarriage and preeclampsia. Copper, zinc, and manganese are all essential cofactors for superoxide dismutases, which has reduced activity in pathological pregnancy. Larger intervention trials are required to reinforce or refute a beneficial role of micronutrient supplementation in disorders of pregnancies. [15]

In pregnancy decreased vitamin C concentration in blood serum is observed as well. Vitamin C concentration in non-smoking pregnant woman blood serum are higher. These differences should be explained by taking multivitamin supplements widely recommended during pregnancy, by education and promotion of healthy living, by improvement of socioeconomic and environmental conditions. However the fact of harmful influence of cigarette smoking on vitamin C concentration in pregnant woman blood serum is still clear. [12]

Cigarette smoking during pregnancy generates free radicals and has been implicated in oxidative cellular damage. Vitamin E is natural factor protecting cells from damaging influence of free oxygen species. Reduced concentration of vitamin E in blood plasma and erythrocytes during pregnancy suggest that consumption of this antioxidant for neutralization of free radicals present in cigarette smoking is enhanced. [4]

Maternal smoking during pregnancy is known to be associated with not only intrauterine fetal growth retardation or low birth weight but also causes disturbances in postnatal growth and development. The prime role of oxidative stress in the pathogenesis of adverse pregnancy outcomes is almost universally accepted. Chelchowska M. et al. [5] wrote that in group of women smoking during pregnancy concentration of malondialdehyde (MDA) was higher in plasma and in erythrocytes when compared to group of tobacco abstinent. Also in cord blood of newborns of smoking mothers level of MDA was significantly higher in plasma as well as in erythrocytes than in control group. Smoking during pregnancy may be promotes free radical damage in growing fetus and newborns therefore stimulate metabolic disorders dependent on oxidative stress. [5]

Nitric oxide (NO) is a potent vasodilator released by endothelial cells that plays an important role in modulating maternal and fetal vascular tone in normal pregnancy. Lower plasma levels of vitamins may result in hyperhomocysteinemia, a known risk factor in pregnancy. Ozerol E. and colab. [19] investigated whether there are alterations in the serum levels of total homocysteine (tHcys), folate, vitamin B₁₂, and total nitrite, as an index of NO, in smoking as compared with age-matched nonsmoking pregnant women. The serum tHcys concentrations were significantly increased in smoking as compared with nonsmoking pregnant women. The folate and vitamin B₁₂ concentrations were lower in smoking than in nonsmoking pregnant women. The serum total nitrite concentrations were lower in smoking than in nonsmoking pregnant women. The serum nitrite levels in smoking pregnant women had significant negative correlations with tHcys and positive correlations with folate and vitamin B₁₂ levels. [19]

Chelchowska M. and colab. [7] estimated the effect of tobacco smoking on serum nitric oxide (NO) concentration in pregnant women and umbilical cord blood and birth weight. They also examined the relation between serum NO and number of cigarettes consumed by mother. They observed that the mean concentrations of nitric oxide in serum were similar on the beginning and the end of pregnancy. In group of smoking women these values decreased during pregnancy and were lower in I and in III trimester than in tobacco abstinent. In umbilical cord blood of infants born to smoking women level of nitric oxide was slightly lower than in non-smoking ones. In smoking group they observed positive correlation between concentrations of NO in serum of mothers and cord blood of their newborns. Their analysis revealed negative

correlation between number of cigarettes consumed and serum nitric oxide in smoking women as well as in their children. Birth weight in infants born of smoking mothers was lower in average by 260g as compared with non-smoking ones. [7]

A number of genetic studies have been performed to find susceptibility genes for smoking behavior. Recently the polymorphism MspI in CYP1A1 was reported to facilitate quitting of smoking during pregnancy. Hozyasz K. and colab. [13] determined whether polymorphisms of catalase (CAT), superoxide dismutase (MnSOD₂), glutathione peroxidase (GPX₁), the null glutathione-S-transferase (GSTM₁) and (GSTT₁) are associated with smoking behavior in pregnant women. They found no significant differences in genotypes distribution between women who quit smoking in the first trimester of pregnancy and persistent smokers. Analyzed polymorphisms seems to not influence susceptibility to smoking in the investigated group of women. [13]

Delpisheh A. and colab. [9] investigated the role of maternal CYP1A₁, GSTT₁, and GSTM₁ metabolic gene polymorphisms in modulating the association between pregnancy smoking exposure and fetal growth restriction. Smokers with the variant CYP1A₁ "aa" genotype had babies with lower mean birth-weight than non-smokers with the same genotype. Risk of fetal growth restriction in mothers who smoked during pregnancy was modulated by maternal metabolic gene polymorphisms. The genetic control of the conversion of toxic metabolites of tobacco smoke to less damaging substances is important for maternal and fetal health. [9]

Placental and systemic oxidative stress with an imbalance in the oxidant/antioxidant activity seems to play a central role in the pathogenesis of pre-eclampsia. The aim of Rosta K. and colab. [22] study was to examine whether two missense polymorphisms of the extracellular superoxide dismutase (SOD₃) gene (Arg213Gly and Ala40Thr) are associated with pre-eclampsia in a Caucasian population from Hungary. The SOD₃ Arg213Gly and Ala40Thr genotypes were determined using the polymerase chain reaction-restriction length polymorphism (PCR-RFLP) and allele-specific amplification methods. The Arg213Gly variant was not detected in their population. There were no significant differences in the genotype and allele frequencies of the SOD₃ Ala40Thr polymorphism between pre-eclamptic patients and control subjects. However, the mutant allele carriers of this polymorphism showed an increased risk for severe fetal growth restriction-complicated pre-eclampsia, which was independent of maternal age, prepregnancy BMI, primiparity and smoking status. Their results suggest a role of SOD₃ Ala40Thr single nucleotide polymorphism in the risk of severe fetal growth restriction-complicated pre-eclampsia. [22]

Environmental tobacco smoking (ETS) is known to be associated with adverse pregnancy outcomes. The purpose of Park E. and colab. [20] study was to investigate the relationship between maternal exposure to ETS and oxidative stress for neonates, as well as the effect of maternal genetic polymorphisms, glutathione-S-transferase M₁ (GSTM₁) and GSTT₁, on this relationship. They used the radioimmunoassay to measure the urinary concentration of cotinine in 266 pregnant women who denied smoking cigarettes during pregnancy and in their singleton babies. In addition, the urinary concentration of malondialdehyde (MDA) and 8-hydroxy-2-deoxyguanosine (8-OH-dG) were assessed using high-performance liquid chromatography and enzyme-linked immunosorbent assay, respectively. They also extracted DNA from whole blood obtained from the mothers and then conducted polymerase chain reaction (PCR) on the samples to determine the GSTM₁ and GSTT₁ genotypes. The maternal cotinine concentration was found to be significantly associated with the fetal cotinine concentration, particularly for mothers whose urine cotinine concentrations were more 120 microg/gcr. The fetal urine cotinine concentration was also found to be significantly associated with the fetal urine MDA concentration. When the null type maternal GSTM₁ or the wild type GSTT₁ was present, the maternal oxidative stress level increased significantly as the maternal cotinine concentration increased. The fetal MDA levels increased significantly as fetal cotinine levels increased. These results suggest that the maternal exposure to ETS affects the fetal urine cotinine concentration and induces production of maternal oxidative stress. In addition, maternal genetic

polymorphisms of GSTM₁ and GSTT₁ may modify the oxidative stress by maternal exposure to ETS. [20]

A prospective cohort study was conducted Sasaki S. and colab. [23] among 460 pregnant women who delivered live singletons in Sapporo, Japan, from 2002 to 2005. Multiple linear regression models were used to estimate associations of maternal smoking and polymorphisms in two genes encoding N-nitrosamine-metabolizing enzymes-NAD(P)H: quinone oxidoreductase 1 (NQO₁) and cytochrome P₄₅₀ 2E1 (CYP2E1) - with birth size. Among infants born to smokers with the NQO₁ homozygous wild-type allele, birth weight, birth length, and birth head circumference were significantly reduced. For the homozygous wild-type CYP2E1 allele, birth weight was lower by an estimated 195g among smokers. These genotypes did not confer adverse effects among women who had never smoked or who quit smoking during the first trimester. The adverse effects of maternal smoking on infant birth size may be modified by maternal genetic polymorphisms in N-nitrosamine-metabolizing enzymes among Japanese subjects. Sasaki S. et al. results may help in directing smoking cessation interventions during pregnancy, especially among susceptible women. [23]

Hsieh C. and colab. [14] study was to explore the modification effect of metabolic gene polymorphisms to cord blood cotinine on children's neurodevelopment at the 2 years of age. This study is one investigation of the Taiwan Birth Panel Study and a total of 145 pregnant women and their neonates were recruited between April 2004 and January 2005. Cotinine in umbilical cord blood as an indicator of environmental tobacco smoke was analyzed by using HPLC-MS/MS. Four metabolic genes, CYP1A1 MspI, CYP1A1 Ile462Val, GSTT₁ and GSTM₁ were identified. Cotinine levels were significantly negatively associated with developmental quotients (DQs) of the whole test, and cognitive, language, fine-motor and social subtests. Lower cognitive and language DQs were found in exposed group with absent type of GSTT₁. In addition, the lowest scores in fine-motor and whole test DQs were detected in exposed group with CYP1A1 Ile462Val variant type and GSTT₁ absent type. It can be concluded that CYP1A1 Ile462Val and GSTT₁ metabolic genes can modify the effect of cord blood cotinine on early child neurodevelopment especially for language and fine motor development. [14]

Maternal smoking has been suggested as a source of oxidant stress in pregnant women and in newborns exposed in utero. The aim of Orhon F. and colab. [18] study was to determine the influence of maternal smoking on oxidant status and antioxidant vitamins of mother-infant pairs. Milk alpha-tocopherol levels of smoking mothers were lower than those of non-smoking mothers. In smokers, there were no correlations between maternal vitamin A intakes and milk levels of retinol, and between maternal plasma levels and milk levels of beta-carotene. Maternal smoking may lead to decreased milk levels of vitamin E, as a result of making use of this antioxidant in order to limit lipid peroxidation, as well as may lead to a possible limitation on the transfer of lipophilic antioxidants including vitamin A from blood plasma to milk. [18]

Oxidative stress in smoking pregnant women is assumed to be enhanced by oxidants and free radicals of tobacco smoke. Inactivation and removal of reactive oxygen species depend on reactions involving in the antioxidant defense system. Chelchowska M. and colab. [6] measured activities of superoxide dismutase (SOD), glutathione peroxidase (GPx) and catalase (CAT) in red blood cells. During pregnancy activity of SOD increased and was higher by 20% in III in comparison to the first trimester. In smoking pregnant women activity of SOD was higher than in tobacco abstinent, however decreased and was 15% lower in the late pregnancy than in I trimester. At the beginning of pregnancy activity of GPx was higher in smoking group than in non-smoking one. In both studied groups glutathione peroxidase decreased during pregnancy and was lower in III trimester by 10% and 30% in tobacco abstinent and smoking women respectively. In non-smoking women activity of CAT increased on the course of pregnancy and was higher by 20% in III in comparison to the first trimester. In smoking pregnant women activity of SOD was significantly correlated with concentration of cotinine both in serum and in urine. The similar correlation was observed between activity of GPx and level of cotinine in urine. Chelchowska M. et al. results indicate that smoking during pregnancy modifies

antioxidant defense system in red parameters may have a negative effect on antioxidant protection systems in neonates.[6]

In pregnancy complicated by cigarette smoking prooxidant-antioxidant imbalance may have a pathomorphological and pathophysiological effect in fetus. Efficient enzymatic antioxidant systems are natural factors protecting cells from damaging by free oxygen species. Chelchowska M. and colab. [2] estimated the effect of tobacco smoking during pregnancy on activities of superoxide dismutase, catalase, glutathione peroxidase and glutathione reductase in umbilical cord blood of newborns. They observed that, in umbilical cord blood from newborns of smoking women activities of catalase, glutathione peroxidase and glutathione reductase were lower by 30%, 15% and 37% respectively than in non-smoking. Activity of superoxide dismutase was similar in both studied group. In erythrocytes of newborns from smoking mothers activity of superoxide dismutase was significantly correlated with concentration of cotinine. The similar correlation was not observed in red blood cells of non-smoking ones. Their results indicate that tobacco smoking during pregnancy may have a negative effect on enzymatic antioxidant systems in umbilical cord blood. [2]

Indicative markers of oxidative stress and changes in antioxidant defense system were assayed in the erythrocytes of healthy pregnant and women with preeclampsia Dordević N. at al. [10]. Results of their work indicated high concentration of hydrogen peroxide, nitrite, peroxynitrite and lipid peroxides in preeclampsia compared to healthy pregnant women. Concentration of superoxide anion was lower in preeclamptic women. There were no differences in concentrations of vitamin E, reduced glutathione and oxidized glutathione. Activity of glutathione-S-transferase (GST) was higher while activities of superoxide dismutase (SOD), catalase (CAT) and glutathione reductase (GR) were lower in preeclamptic women. These results suggest that preeclampsia was characterized by oxidative stress and alteration of antioxidative defense system by imbalance in oxidative/antioxidative status of erythrocytes. [10]

Increased lipid peroxidation (LPO) and reduced antioxidant activity may contribute to the development of complications in pregnancy. Orhan H. and colab. [17] discussed the possibility of LPO and antioxidant activity in both maternal and umbilical cord blood as an indicator of oxygen radical activity. Erythrocyte GST activity was significantly increased in insulin-dependent diabetic pregnancy (IDDP) when compared to the control. Erythrocyte Se-GPx activity was found to be significantly increased in hypertensive preeclamptic pregnancy (HPP) and in IDDP. Alterations in enzyme activities were accompanied by a simultaneous significant increase in the levels of TBARs in plasma samples of HPP and IDDP. Enzyme activities were found to be significantly lower in cord blood samples than the maternal values, except GST. Cord blood erythrocyte and plasma Se-GPx and CAT activities were decreased significantly in the HPP group when compared to the maternal value. Cord blood erythrocyte CAT activity was significantly decreased in the HPP group compared to the control. Cord blood TBARs levels were significantly lower than the before deliveries maternal value in the HPP group. The results of the present study suggest that oxidative stress and subsequent lipid peroxidation accompany the complications of hypertension, preeclampsia and diabetes mellitus in pregnancy. Maternal erythrocyte GST activity seems to be a sensitive indicator of oxidative stress in IDDP before delivery. The same enzyme can be used in cord blood as a biomarker of oxidative stress upon a sudden increase in oxygenation during delivery. Orhan H. et al. wrote that these multiparameter biomarkers can also be used in monitoring the efficiency of antioxidant supplementation in complicated pregnant women, as has recently been suggested for diabetic and preeclamptic pregnancies. [17]

Bilodeau J. and colab. [1] wrote that preeclampsia is a leading cause of maternal and neonatal mortality and morbidity. It is a complex syndrome of undetermined etiologic origin, usually diagnosed during the second half of pregnancy, with clinical features of hypertension, proteinuria, and edema. No cure for preeclampsia exists, except premature delivery. There is increasing evidence that oxidative stress is an important contributing factor to the pathogenesis of preeclampsia. Oxidative stress is defined as an imbalance between reactive oxygen species

(ROS), such as nitric oxide (NO*), superoxide anion (O₂*-), and hydrogen peroxide (H₂O₂), and antioxidants, favouring an overabundance of ROS. The consequence of an overproduction of ROS can be observed as increased levels of markers of oxidative stress, such as lipid peroxides. Pregnant women affected by preeclampsia may have abnormal ROS production, particularly NO* and O₂*-, abnormal levels of antioxidant defenses, and increased placental lipid peroxidation. Several observations suggest that decreased bioavailability of endothelium-derived NO*, due to oxidative destruction of NO* by ROS, might contribute to the impaired endothelium-dependent vasodilatory responses and multisystemic pathology of preeclampsia, a phenomenon in which antioxidant vitamins may play a beneficial role. Review of Bilodeau J. and colab. [1] is focused on the rationale for vitamins C and E supplementation toward prevention of preeclampsia, with an emphasis on the limit of our scientific knowledge concerning the deleterious oxidative events taking place in this pathology.

Chelchowska M. et al. [5] studied the effect of cigarette smoking during pregnancy on plasma total radical trapping antioxidants parameters (TRAP) in mothers and their babies. Pregnant women were selected into the groups according to concentration of cotinine in serum. The plasma concentration of TRAP was lower in smoking pregnant women than in tobacco abstinent group. Value of TRAP in umbilical cord blood from newborns of smoking mothers was significantly lower and amounted only 74% of that observed in non-smoking ones. Plasma level of TRAP was significantly correlated with serum concentration of cotinine both in smoking pregnant women and in umbilical cord blood of their children. Results indicated that smoking depletes plasma TRAP in mothers and their babies. Decreased level of total plasma antioxidants parameters may have a negative effect on antioxidant protection systems in neonates.

Smoking during pregnancy leads to decreased pulmonary function and increased respiratory illness in offspring. Proskocil B. and colab. [21] reported that vitamin C supplementation can prevent some of the effects of maternal nicotine exposure on pulmonary function of offspring. Vitamin C supplementation also prevented the nicotine-induced increases in surfactant apoprotein-B protein. Prenatal nicotine exposure significantly decreased levels of elastin content in the lungs of offspring, and these effects were slightly attenuated by vitamin C. These findings nutrients suggest that vitamin C supplementation may potentially be clinically useful to limit the deleterious effects of maternal smoking during pregnancy on offspring's lung function.

The level of nicotine in fetal tissues was found to be equal to or greater than the plasma nicotine level in the mothers. [11] The oxidative stress induced by nicotine has been increasingly postulated as a major contributor to endothelial dysfunction. A large body of research has investigated the potential role of antioxidant in the prevention of endothelial dysfunction in women. Gallo C. and colab. [11] study was undertaken to assess the potential benefit of antioxidant supplementation on markers of placental oxidative stress in an *in vitro* model of endothelial dysfunction induced by nicotine, since it was previously found that nicotine is able to trigger the placental secretion of stress molecules. In this regard, they evaluated the effects of vitamin C, vitamin E and N-acetylcysteine (NAC), alone or in combination, in placental *villi culture* after exposure to nicotine. The effect of antioxidant nutrients on trophoblast cells proliferation and vitality was also evaluated. The results obtained suggest that in a pathophysiological condition, such as endothelial dysfunction induced by nicotine, the deleterious effect of reactive oxygen species may be counteracted by an antioxidant therapy, and there is the need to investigate the optimum dosing and timing of antioxidants administration, since an inappropriate antioxidant treatment in pregnant women may have deleterious consequences, reducing placental cells proliferation until to cell death.

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Summary

Recurrent respiratory infection children

Children with recurrent respiratory infection (RRI-Children) are prone to frequent respiratory infections. Frequent and especially severe acute respiratory infections (ARI) can affect physical and neuro-psychic development of children, and consequently lead to decrease of functional activity of immunity and to development of chronic inflammatory processes of the respiratory system.

RRI children present the problem which needs a complex approach for its solving. It defines a current interest and common efforts of physicians, families and the state that would contribute to performance of both therapeutic, rehabilitation and prophylaxis programs.

Rezumat

Infecțiile acute respiratorii (IAR) sunt cele mai frecvente maladii infecțioase la copii. Infecțiile acute respiratorii frecvente sau cele cu evoluție gravă pot provoca la copii dereglări de dezvoltare fizică și neuro-psihică, favorizând diminuarea activității imune funcționale și formarea focarelor de inflamare cronică al organelor respiratorii. Frecvențele IRA la copii este o problemă ce necesită o abordare complexă pentru a fi rezolvată, definește actualitatea și necesitatea integrării forțelor medicilor, a familiei și statului spre realizarea nu numai a programelor terapeutice, reabilitaționale, ci și a celor profilactice.

Copil frecvent bolnav (CFB) - este un termen, ce determină grupul de copii, detectați la evidența dispanserica, care se caracterizează printr-un nivel mai sporit de morbiditate cu infecții respiratorii. În acest grup sunt incluși copiii, la care recurențele respiratorii nu sunt determinate de stările patologice permanente congenitale sau dobândite. [24,25,26].