Chapter

Antioxidants at Newborns

Melinda Matyas and Gabriela Zaharie

Abstract

Humans possess defense mechanisms against free radicals: enzymatic and non-enzymatic antioxidants. Antioxidant defense is deficient in newborns and can be enhanced by the action of reactive oxygen species, generated by perinatal diseases such as respiratory distress or asphyxia. Prematurity itself will be associated with deficient antioxidant mechanisms, which are primarily enzymatic, but also non-enzymatic. Under oxidative stress conditions, antioxidant defense is overcome and thus, low-molecular weight free iron is released, which is not bound to transferrin and will play a role in Fenton's reaction, catalyzing lipid peroxidation. The generated ROS will in turn influence antioxidant defense mechanisms, stimulating their synthesis, as an adaptation mechanism of the body in response to the presence of increased ROS levels.

Keywords: antioxidants, newborn, oxidative stress

1. Aim

The aim of the current chapter is to review the antioxidant status particularities newborn, to present the antioxidant evaluation and current opinions on antioxidant treatment in newborns.

2. Introduction

The human body possesses defense mechanisms against free radicals, consisting of enzymatic and non-enzymatic antioxidants. Antioxidant defense is deficient in newborns and can be enhanced by the action of reactive oxygen species, generated by perinatal diseases such as neonatal respiratory distress or birth asphyxia. Prematurity itself will be associated with deficient antioxidant mechanisms, which are primarily enzymatic, but also non-enzymatic. Antioxidant defenses, especially enzymatic ones, develop during the last trimester of pregnancy. Consequently, premature newborns will not have sufficient antioxidant defense. Under oxidative stress conditions, antioxidant defense is overcome and thus, low-molecular weight free iron is released, which is not bound to transferrin and will play a role in Fenton's reaction, catalyzing lipid peroxidation [1, 9]. Reactive oxygen species (ROS) production occurs through various mechanisms, of which the most common are hyperoxia, reperfusion, and inflammation. The generated ROS will in turn influence antioxidant defense mechanisms, stimulating their synthesis, as an adaptation mechanism in response to the presence of increased ROS levels. In neonatology, a "free radical disease" is described, which includes a number of disorders:

bronchopulmonary dysplasia, retinopathy of prematurity, necrotizing enterocolitis, and periventricular leukomalacia [1, 8, 17].

In the case of perinatal asphyxia, ROS will exert a considerable harmful effect on the brain because antioxidant levels are low and there is an increased oxygen consumption during transition from fetal life to neonatal life [14, 15, 25]. Randomized studies on relatively large numbers of term newborns with asphyxia have demonstrated the importance of resuscitation with atmospheric air in limiting injury and improving the survival rate [13, 26].

3. Antioxidants classification

Antioxidants are most commonly classified into enzymatic and non-enzymatic systems. Depending on their solubility, non-enzymatic antioxidants are divided into water-soluble and lipid-soluble antioxidants.

The main enzymatic antioxidant systems are:

- *superoxide dismutase* (SOD)—an enzyme that detoxifies the superoxide anion;
- *catalase* (CAT)—detoxifies oxygenated water and has a protective antitumor role;
- *peroxidases*—myeloperoxidase (MPO), lipid peroxidase, glutathione peroxidase (GSH-Px)—mainly protect the liver;
- *glutathione peroxidase (GPx) intracellular selen-protein that reduces hydrogen peroxide to glutathione disulfide and water*;
- *the system of cytochrome oxidases*, which reduce oxygen; they play a role in reducing the amount of oxidant or potentially oxidant substances; they can be released into the blood and extracellular fluid.

The main non-enzymatic antioxidant systems are represented by:

- the reduced-oxidized glutathione redox cycle;
- vitamin E—which intercepts the peroxyl radical;
- vitamin C;
- carotenoids—alpha-carotene, a precursor of vitamin A, is 10 times more effective than beta-carotene;
- selenium;
- uric acid and urates;
- bilirubin;
- cysteine-rich metallothioneins;
- metal-binding proteins: albumin, transferrin, ferritin, lactoferrin, and ceruloplasmin;

- amino acids such as histidine, taurine, cysteine which ensures protection against toxic aldehydes present in cigarette smoke, methionine which protects the colon;

- Heme proteins and heme-binding proteins—hemopexin, haptoglobin, porphyrin, carnosine, estrogens, coenzyme Q10, polyamines, saturated fatty acids, flavonoids which stabilize the cell membrane and are used in eye diseases, phenols, and polyphenols. Ceruloplasmin is an extracellular copper-transport protein.

3.1 Antioxidant enzymes

The most important antioxidant enzymes in newborns are: superoxide dismutase, catalase, and glutathione peroxidase.

Superoxide dismutase has three forms: MnSOD located in mitochondria, copper-zinc superoxide dismutase (Cu/ZnSOD) in the cytoplasm, and extracellular superoxide dismutase (EC-SOD). In newborns, the last one is located intracellularly in the cytoplasm, unlike in adults, where it is located extracellularly, as indicated by its name [23, 27].

Superoxide dismutase has the role of converting the highly toxic superoxide radical to hydrogen peroxide and water. Catalase and glutathione peroxidase convert hydrogen peroxide to water.

In the absence of catalase, a cascade reaction is triggered with the formation of hydroxyl radicals, which requires the presence of iron metal ions (Fe^{2+}) and copper Cu^{2+}, known as the Haber-Weiss reaction:

$$H_2O_2 + Fe^{2+} \rightarrow OH^{\bullet} + OH^{-} + Fe^{3+} \quad (1)$$

The hydroxyl radical resulting from this reaction will attack the structures of the cell, causing its destruction.

In the intrauterine period, there is an interaction between the fetus, placenta, and uterus, which requires a redox signal with a role in maintaining the balance of this interaction and allowing the development of antioxidant systems in the fetal period.

The decrease in lipid peroxidation in the placenta with the evolution of pregnancy is an indirect marker of the development of antioxidant mechanisms with the increase of gestational age [18].

Normal vascular development is conditioned by the activity of nitric oxide controlled by nitric oxide synthase. Nitric oxide plays a role in regulating the activity of antioxidant enzymes.

The protective role of SOD was demonstrated in experimental groups of animals—rats—at the Physiology Department of the University of Medicine, Cluj-Napoca, Romania [16]. The authors studied lipid peroxides as oxidative stress parameters by measuring malondialdehyde (MDA) and ceruloplasmin using the Ravin test [16].

The animals exposed to hypobaric hypoxia had, immediately after SOD administration, significantly increased malondialdehyde (MDA) values, which were close to the values found in unprotected animals exposed to hypobaric hypoxia. At 24 hours after SOD administration, in animals exposed to hypoxia, the values of MDA as a marker of lipid peroxidation were significantly decreased, being lower than those of the control group. In the case of ceruloplasmin, values were significantly lower in protected compared to unprotected animals [16].

The preterm neonate is born before the antioxidant systems capable of neutralizing ROS are formed. Birth itself is an oxidative stress-inducing factor, which will cause, in conjunction with other factors mentioned before such as hypoxia, hyperoxia, reperfusion, or inflammation, the rapid exhaustion of impaired defense mechanisms in the premature newborn. Transplacental nutrient supply has an important role in the formation of antioxidant defense mechanisms. However, this supply is limited in the case of preterm neonates. Chorioamnionitis present in a relatively great number of premature births is an induction factor for MnSOD mRNA in fetal membranes. Antenatal corticosteroids, in addition to their role in early lung, brain, and intestinal maturation, influence stimulation of the activity of antioxidant enzymes: SOD, catalase, and glutathione transferase [25, 29].

The endogenous surfactant has SOD and catalase in its composition. Their antioxidant role in the surfactant is to prevent surfactant lipid peroxidation and inactivation following the oxidative attack of ROS. These enzymes with antioxidant effects are not found in similar amounts in the exogenous surfactant used for the treatment of respiratory distress [30].

It is important to identify newborns at risk for oxidative stress in order to initiate early antioxidant therapy with a view to limiting oxidative stress progression. Since oxidative stress can frequently start during the intrauterine period, finding antioxidant therapies for the mother with an impact on the newborn is essential.

3.2 Non-enzymatic antioxidants

Vitamins have an antioxidant role. Among water-soluble vitamins, vitamin C is the most studied. The most extensively studied lipid-soluble vitamins in neonates are vitamins A and E.

Vitamin A acts on retinol-binding proteins and on retinoic acid receptors. The main actions of retinol consist of maintaining epithelial integrity, regulating growth and proliferation, and modulating the levels of ceruloplasmin, a protein with antioxidant effects [2, 21]. Vitamin A levels are decreased in preterm newborns, proportionally to the degree of prematurity. The benefits of vitamin A in limiting the incidence of bronchopulmonary dysplasia have been described in many studies. Its beneficial effect in reducing the incidence of the disease could not be demonstrated. Also, the fact that it requires intramuscular administration and relatively high doses to exert its antioxidant effects is a major disadvantage [15, 22].

Regarding vitamins E and C, their beneficial effect in preventing the teratogenic effect of maternal diabetes has been studied by a number of authors [19].

In the category of water-soluble vitamins, other vitamins besides vitamin C have an antioxidant role: riboflavin, pyridoxine, and niacin, which maintain GSH activity.

Vitamin E is the antioxidant that is present in the highest amount in the human body. It is a lipophilic vitamin, which accumulates in lipid-rich cell membranes. It is an important lipid peroxyl scavenger [15].

Carotenoids are also lipid-soluble and have a characteristic color. Lutein plays a role in ROS elimination. In umbilical cord blood, studies have evidenced higher lutein levels in preterm compared to term newborns [29].

Ceruloplasmin is an extracellular antioxidant that acts like a ferroxidase enzyme, catalyzing the oxidation reaction of Fe^{2+} to Fe^{3+}, thus limiting Haber-Weiss and Fenton reaction.

$$LOH + Fe^{2+} \rightarrow L\text{—}O^{\bullet} + OH^{\bullet} + Fe^{3+} \quad (2)$$

Uric acid is a non-enzymatic antioxidant resulting from purine metabolism. It is a scavenger of many ROS, but in certain situations, in excessive amounts, it has a

cytokine-mediated pro-inflammatory effect, playing a role in the pathogenesis of diseases such as diabetes [15, 30].

4. Evaluation of antioxidants in neonates

Antioxidant defense in neonates can be evaluated by measuring enzymatic and non-enzymatic systems. Among enzymatic systems, glutathione reductase, peroxidase, transferase, the oxidized/reduced glutathione ratio, superoxide dismutase, as well as other antioxidants such as ceruloplasmin, transferring are the most frequently measured.

The non-enzymatic antioxidant systems that can be measured in newborns are vitamins A, E, and C. Vitamin A and E values measured in newborns are presented in many studies. Shah et al. describe a correlation between hepatic vitamin A reserves and gestational age, as well as between nutritional status and maternal vitamin A levels. Vitamin A has an important role in the development of visual acuity, and also in lung development and surfactant synthesis [1]. Vitamin A levels are significantly lower in preterm compared to term neonates. Antenatal corticoid administration has a beneficial effect on vitamin A levels in premature babies. Thus, in preterm newborns benefiting from antenatal corticosteroids, the levels of these vitamins with antioxidant effect are higher than in preterm babies without antenatal treatment. The mechanism of corticosteroids in increasing vitamin synthesis is unknown. It seems that these act by increasing the plasma levels of retinol-binding proteins, stimulating the hepatic synthesis of these proteins [2].

Vitamin E, another important non-enzymatic antioxidant, with a role in stabilizing cell membranes, also has lower values in preterm compared to term neonates. Vitamin E has been used in many studies for its antioxidant effect in preventing retinopathy and bronchopulmonary dysplasia. However, in a 2003 Cochrane analysis, Brion et al. demonstrated that vitamin E plays a role in reducing the incidence of ROP and IVH, but increases the incidence of neonatal sepsis [3]. Allopurinol, melatonin, and acetylcysteine have been used in studies for their antioxidant effect, mainly as neuroprotective agents. Melatonin and acetylcysteine were used in the studies of Gitto, and subsequently Barceló, to reduce the incidence of NEC in premature neonates [4, 5]. However, there is no consensus regarding their use for the treatment of NEC in neonates or for the treatment of other conditions associated with hypoxia-ischemia. Nevertheless, it should be taken into consideration that exogenous antioxidant therapy with high doses of vitamin C and beta-carotene in particular will have a pro-oxidant effect.

For the evaluation of antioxidant defense in newborns, the levels of ceruloplasmin were measured in our service. This non-enzymatic antioxidant defense marker proved to be deficient in preterm compared to term neonates. Ceruloplasmin is a peroxyl radical scavenger. Free oxygen radical excess caused by certain oxidative stress-inducing situations will put a strain on the impaired defense mechanisms of the premature newborn. Antioxidant values will be lower compared to those of full-term newborns. Ceruloplasmin determined by spectrophotometry had lower values in preterm neonates with respiratory distress. Also, ceruloplasmin levels decreased with the decrease in gestational age. Determinations evidenced lower ceruloplasmin values on the first day compared to the third day of life (**Table 1**).

Exposure to asphyxia at birth results in decreased ceruloplasmin levels. Under these oxidative stress-inducing conditions, the measurements performed evidenced lower ceruloplasmin values in preterm newborns with asphyxia compared to term newborns with asphyxia. Asphyxia is followed by a diminution of antioxidant levels and an increase in transferrin saturation. Current data confirm the fact that in

	N	T	Z	p-Level
FiO_2—DOL_1 & FiO_2—DOL_3	59	52,5000	6,149,591	0.000000
pH—DOL_1 & pH—DOL_3	60	175,5000	4,346,968	0.000014
pCO_2—DOL_1 & pCO_2—DOL_3	60	412,5000	3,429,860	0.000604
pO_2—DOL_1 & pO_2—DOL_3	60	573,0000	2,014,110	0.043999
SaO_2—DOL_1 & SaO_2—DOL_3	60	208,5000	3,761,957	0.000169
CP—DOL_1 & CP—DOL_3	60	492,0000	2,814,343	0.004888

FiO_2-oxygen concentration; pH-value.

pCO_2-CO_2 partial pressure; pO_2-oxygen partial pressure.

SaO_2-oxygen saturation; CP-ceruloplasmin.
p-test significance; Z = test parameter.

Table 1.
Evolution of ceruloplasmin on 1st vs 3rd day of life (DOL).

neonatal asphyxia and in the post-asphyxic period, ROS are generated particularly during the re-oxygenation phase after perinatal asphyxia [10]. The brain is the most susceptible to oxidative injury, for the following reasons:

- Neuronal membranes are rich in polyunsaturated fatty acids, an important source of free oxygen radicals.
- The activity of antioxidant enzymes (catalase and SOD) is significantly diminished in the brain.
- Some brain areas are rich in iron [10]. The increase in CP in mild and severe asphyxia cases can represent a form of adaptation of the organism to the action of oxidative stress [15].

Ceruloplasmin was measured by Lindeman [23], who evidenced the fact that in premature newborns, its levels are constantly low until the age of 3–6 weeks. Its deficiency in premature newborns increases the risk of oxidative stress under conditions of exposure to the oxidative attack of ROS.

Another marker of antioxidant defense is represented by hydrogen donors. Like total antioxidant activity, these assess several natural non-enzymatic antioxidants: cysteine, glutathione, ascorbic acid, tocopherol, polyphenols, aromatic amines, and sulfhydryl protein groups. In the case of measurements performed with 1,1-diphenyl-picrylhydrazyl in neonates admitted to our service, we found a correlation of hydrogen donor values with the severity of respiratory distress. The presence of respiratory distress was a triggering factor for hydrogen donors, stimulating their antioxidant activity in a group of patients with impaired enzymatic antioxidant defense (**Table 2**).

Hydrogen donor levels in healthy, late preterm newborns are higher compared to those of preterm newborns with oxidative stress-inducing conditions such as respiratory distress or asphyxia at birth. Non-enzymatic antioxidant defense assessed by hydrogen donor values improves with time; our determinations showed significantly higher values on the third day compared to the first day ($p < 0.05$) (**Table 3**).

The enzymatic antioxidants studied in neonates are: catalase (CAT), superoxide dismutase (SOD), and glutathione peroxidase (GSH-Px). These are endogenous antioxidants and have the following antioxidant action mechanisms: superoxide dismutase catalyzes superoxide radical dismutation, resulting in hydrogen peroxide.

	1st day	3rd day	Stat (p-value)
Mild Stat (p-value)*b	42.20 (39.80-45.30) −3.11 (0.0019)	46.65 (41.53-52.05) −2.09 (0.0369)	2.42 (0.0157)
Moderate Stat (p-value)*b	62.70 (59.40-64.20) 1.55 (0.1218)	61.50 (60.43-64.35) 1.68 (0.0926)	0.00 (0.9999)
Severe Stat (p-value)*b	48.30 (46.48-51.31) −1.02 (0.3082)	49.60 (45.30-54.00) −0.91 (0.3650)	0.0 (0.9999)

b median (Q1-Q3), Q = quartile, Wilcoxon Matched Test
** as compared to control*

Table 2.
Hydrogen donors by severity of respiratory distress and comparisons with the controls.

	Group	n	Mean±Stdev	Std. Error Mean	t-value (p-value)
HD 1	Case	24	45.82 ± 10.36	2.12	−2.64 (0.0124)
	Control	13	54.38 ± 7.33	2.03	
HD 2	Case	24	49.03 ± 11.97	2.44	−1.47 (0.1514)
	Control	13	54.38 ± 7.33	2.03	

Table 3.
Hydrogen donors (HD) by groups.

Glutathione peroxidase and catalase catalyze hydrogen peroxide reduction to water and oxygen. Thus, they exert a protective effect against oxidative injury (**Figure 1**).

The levels of these enzymes decrease with the decrease in gestational age. Another factor that influences enzymatic antioxidant mechanisms is neonatal development. In neonates with intrauterine growth restriction, the antioxidant enzymes SOD, CAT, and GSH-Px have lower values than in term AGA neonates [12, 13].

In our study, for the assessment of enzymatic antioxidant defense capacity, erythrocyte SOD was measured using the Winterbourn method. Hemoglobin concentration was determined in K3 EDTA samples by the Drabkin method.

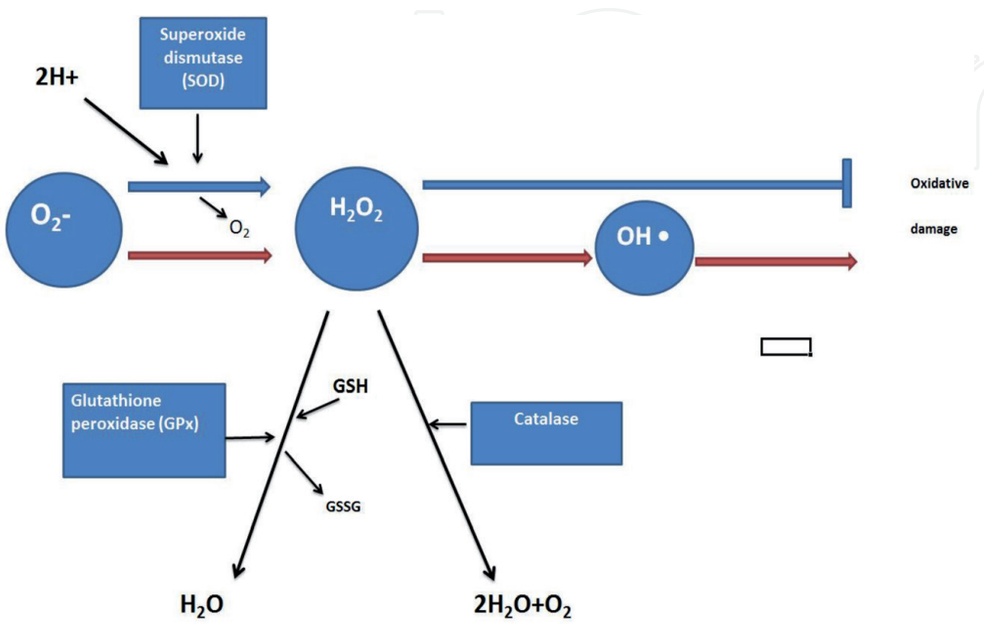

Figure 1.
Enzymatic antioxidant mechanism.

Determinations in the study group of preterm neonates compared to the values of the control group including full-term newborns evidenced a statistically significant difference, SOD values being higher in term newborns compared to the group of premature babies [6]. The same results were obtained in the case of SOD measurement using Ransod kits (Cat. No. SD 125, Randox Labs, UK). SOD activity was expressed as the amount of proteins leading to inhibition of 90% formazan (505 nm) using xanthine oxidase to generate superoxide radicals [7].

Other studies, as well as our findings show the fact that antioxidant defense is impaired in neonates. This impairment increases with the decrease in gestational age, but is also influenced by the association of oxidative stress-inducing factors that put a strain on the defective defense mechanisms of the newborn.

5. Antioxidant treatment

5.1 Enzymatic therapies

Animal studies have demonstrated the beneficial effects of SOD on ROS. SOD administration as aerosols in animals improved alveolar development in the case of bronchopulmonary dysplasia induced by the common action of multiple factors: prematurity, hyperoxia, and mechanical ventilation.

Cysteine, which has glutathione stimulating effects, was studied in premature babies. Glutathione is an important antioxidant and a cofactor for GPx. However, studies failed to demonstrate its beneficial effect in reducing oxidative stress, since the harmful effects of ROS could not be prevented by cysteine administration. Glutathione levels were significantly higher after cysteine administration. Administration of recombinant CuZnSOD to preterm babies during the intubation period led to a decrease in the incidence of wheezing episodes, but did not reduce the incidence of BPD compared to preterm babies who received placebo during the same period [20]. The incidence of ROP in preterm babies receiving this treatment also decreased [11].

5.2 Non-enzymatic therapies

The beneficial effects of vitamin E have been studied by different authors. Randomized controlled trials could not demonstrate the effect of vitamin E in preventing BPD. There are studies that evidence the beneficial effects of vitamin E in reducing the incidence of cerebral hemorrhage, while increasing the risk of neonatal sepsis; consequently, the risk exceeds the benefits provided by the antioxidant effect.

A Cochrane analysis of vitamin A describes its role in preventing BPD, but neurological and respiratory development at 18–22 months is not superior in babies receiving vitamin A [15, 21].

Regarding vitamin C, studies have demonstrated that in addition to its antioxidant effect, in certain situations, after a significant oxidative attack, vitamin C can act as a pro-oxidant and will cause additional injuries [13, 15].

High vitamin C concentrations will inhibit ceruloplasmin and will induce oxidation of Fe^{2+}, which will have a catalytic action in lipid peroxidation and thus will generate new free radicals [23].

Excess of protein-unbound iron has a pro-oxidant effect, resulting in the production of free radicals with harmful effects. Lactoferrin has a key role in limiting the pro-oxidant action of free iron, its presence in milk formulas being particularly important [22, 28].

5.3 Other antioxidant therapies

Resveratrol is known for its antioxidant effect in astrocytes. Its role is important after asphyxia episodes. It acts by stimulating glutamate synthase activity and increases GSH levels in hippocampal astrocytes. The increase in glutamate synthase activity counters the toxic effect of glutamate.

Melatonin is a substance studied for its antioxidant effect. It has a role in repairing leukomalacia lesions, but its beneficial action has been described when it is administered early, in the first 2 hours after injury. Animal studies have demonstrated beneficial effects of enteral arginine and glutamine in preventing NEC [4, 5, 28].

Human milk feeding has a number of benefits over formulas. Studies demonstrate the antioxidant effect of breast milk, which contributes to ROS elimination. Higher amounts of oxidative stress metabolites are eliminated in the urine of preterm babies fed with formula compared to those fed with breast milk. Oxidative stress is increased in premature neonates fed with formula. The antioxidant capacity of breast milk is higher than that of neonatal blood [24].

Author details

Melinda Matyas* and Gabriela Zaharie
University of Medicine and Pharmacy, Cluj-Napoca, Romania

*Address all correspondence to: melimatyas@yahoo.com

References

[1] Saugstad OD. Optimal oxygenation at birth and in the neonatal period. Neonatology. 2007;**91**:319-322

[2] Biesalski HK, Nohr I. Importance of vitamin-A for lung function and development. Molecular Aspects of Medicine. 2003;**24**:431-440

[3] Brion LP, Bell EF, Raghuveer TS. Vitamin E supplementation for prevention of morbidity and mortality in preterm infants. Cochrane Database of Systematic Reviews. 2003;**4**: CD003665

[4] Gitto E, Karbownik M, Reiter RJ, et al. Effects of melatonin treatment in septic newborns. Pediatric Research. 2001;**50**(6):756-760

[5] Sánchez-Barceló EJ, Mediavilla MD, Tan DX, Reiter RJ. Clinical uses of melatonin: Evaluation of human trials. Current Medicinal Chemistry. 2010;**17**(19):2070-2095

[6] Matyas M, Zaharie G, Craciun C, Blaga L. Evaluation of superoxide dismutase in preterm newborns. Obsterica Ginecologia. 2012;**LX**:267-271

[7] Matyas M, Craciun C, Popescu A, Popa M. The activity of erythrocytes superoxide dismutase in premature and mature infants-the relationship with gestational age. Physiology. 2007;**17, 1**(53):25-28

[8] Gitto E, Reiter RJ, Xian-Tan D, Barberi I. Respiratory distress syndrome in the newborn: Role of oxidative stress. Intensive Care Medicine. 2001;**27**:1116-1123

[9] Allen RG, Tresini M. Oxidative stress and gene regulation. Free Radical Biology & Medicine. 2000;**28**:463-499

[10] Sola A, Rodigo MR, Deulofeut R. Oxygen as a neonatal health hazard: Call for détente in clinical practice. Acta Paediatrica. 2007;**96**(6):801-812

[11] Ozsurekci Y, Aykac K. Oxidative stress related diseases in newborns. Oxidative Medicine and Cellular Longevity. 2016;**15**:1-9

[12] Gupta BP, Narang S, Banerjee BD. Oxidative stress in term small for gestational age neonates born to undernourished mothers: A case control study. BMC Pediatrics. 2004;**4**:14. DOI: 10.1186/1471-2431-4-14

[13] Shoji H, Koletzko B. Oxidative stress and antioxidant protection in the perinatal period. Current Opinion in Clinical Nutrition and Metabolic Care. 2007;**10**(3):324-328

[14] Martin A, Camille F, Debevec T, Rytz C, Millet G, Pialoux V. Preterm birth and oxidative stress: Effects of acute physical exercise and hypoxia physiological responses. Redox Biology. 2018;**17**:315-322

[15] Buonocore G, Groenendaal F. Anti-oxidant strategies. Seminars in Fetal & Neonatal Medicine. 2007;**12**:287e295

[16] Muresan A. Reactive Oxygen Species in Clinical Pathology. Romania: Editura Dacia; 1997:24-30. ISBN: 35-0703-2

[17] Matyas M, Zaharie G. Particularities of oxidative stress in newborns in Novel Propsects in Oxidative and Nitrosative Stress by Pinar Atukeren, IntechOpen: Rijeka 2018; 93-109

[18] Quango S, Mukherjea M. Ontogenic profile of some antioxidants and lipid peroxidation in human placental and fetal tissue. Molecular and Cellular Biochemistry. 2000;**215**(1-2):11-19

[19] Dheen ST, Tay SS, Boran J, et al. Recemnt studies on neural tube defects in embryos of diabetic pregnancy: An

overview. Current Medicinal Chemistry. 2009;**16**:2345-2354

[20] Davis JM, Parad R, Michele T, Allred E, Price A, Rosenfeld W. Pulmonary outcome at 1 year corrected age in premature infants treated at birth with recombinant human CuZn SOD dismutase. Pediatrics. 2003;**111**:469-476

[21] Ambalavanan N, Tyson JE, Kennedy KA, et al. Vitamin A supplementation for extremely low birth weight infants: Outcome at 18-22 months. Pediatrics. 2005;**115**:249-254

[22] Collard KJ. Iron homeostasis in the neonate. Pediatrics. 2009;**123**:1208-1216

[23] Lindeman JH, Lentjes EG, van Zoeren-Grobben D, Berger HM. Postnatal changes in plasma ceruloplasmin and transferrin antioxidant activities in preterm babies. Biology of the Neonate. 2000;**78**:73-76

[24] Ledo A, Arduini A, Asensi MA, et al. Human milk enhances antioxidant defenses against hydroxyl radical aggression in preterm infants. The American Journal of Clinical Nutrition. 2009;**89**:210-215

[25] Sahni PV, Zhang J, Sosunov S, Galkin A, Niatsetskaya Z, Starkov A, et al. Krebs cycle metabolites and preferential succinate oxidation following neonatal hypoxic-ischemic brain injury in mice. Pediatric Research. 2018;**83**:491-497

[26] Perlman JM, Wyllie J, Kattwinkel J, Wyckoff MH, Aziz K, Guinsburg R, et al. Part 7: Neonatal resuscitation: 2015 International consensus on cardiopulmonary resuscitation and emergency cardiovascular care science with treatment recommendations. Pediatrics; **2015**(Suppl 2):136, S120-S166

[27] Kuligowski J, Aguar M, Rook D, Lliso I, Torres-Cuevas I, Escobar J, et al. Urinary lipid peroxidation byproducts: Are they relevant for redicting neonatal morbidity in preterm infants? Antioxidants & Redox Signaling. 2015;**23**:178-184

[28] Sánchez-Illana Á, Thayyil S, Montaldo P, Jenkins D, Quintás G, Oger C, et al. Novel free-radical mediated lipid peroxidation biomarkers in newborn plasma. Analytica Chimica Acta. 2017;**996**:88-97

[29] Picone S, Ritieni A, Fabiano A, Troise AD, Graziani G, Paolillo P, et al. Arterial cord blood lutein levels in preterm and term healthy newborns are sex and gestational age dependent. Clinical Biochemistry. 2012;**45**:1558-1563. DOI: 10.1016/j.clinbiochem.2012.07.109

[30] Davis JM, Auten RL. Maturation of the antioxidant system and effects on preterm birth. Seminars in Fetal & Neonatal Medicine. 2010;**15**:191-195